

*A Special issue on*

**“EXPLORING AND ADVANCING HEALTHCARE SYSTEM  
THROUGH NOVEL STRATEGIES IN PHARMACY FIELD”**

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## About this Special Issue

### “Exploring and Advancing Healthcare System through Novel Strategies in Pharmacy field”

The oral route of drugs administration is the most important method for administering drugs for systemic effects to produce the desired pharmacological actions. Tablets (one of the oral dosage form) are unit solid dosage form containing a drug or drugs with or without additives or excipients and generally prepared by compression method. The objective of the design and manufacture of the compressed tablet is to deliver orally the correct amount of drug or drugs in the desired location and to have its chemical integrity protected to the point. Synthesis and Analytical methods for the drugs are also required to characterize drug substances and drug product composition during all phases of pharmaceutical development. Initial methods must support changes in synthetic routes and dosage form and elucidate the levels of impurities and structures. In later phases, aim change to the development of rapid and robust methods for the stability evaluation and release.

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## SP-1

# STUDIES ON THE SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF SOME NEW HETEROCYCLIC MOITIES CONTAINING 1, 2, 4-TRIAZOLES

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## ABSTRACT

The development of new pharmaceuticals is critically dependent on a molecular-level understanding of biological processes and mechanisms of drug action. In current era, drugs are developed in special design for specific target sites. Chemists are doing research on drug design, development, synthesis and testing of drugs. To develop one drug moiety it takes an average of 10 to 15 years and \$800 million to more than \$1 billion. Developed drug should be safe and effective and it should have optimized dose, for which optimization study of formulation are also carried out. Progress in the field now depends on the design and synthesis of new molecules using tools such as structure activity relationships, combinatorial chemistry and computer-aided drug design. The objective of current study is Synthesis, Characterization and Biological Activities of Some New Heterocyclic Moieties Containing 1, 2, 4-Triazoles. Biological activities namely antibacterial and antifungal activities of Heterocyclic Moieties Containing 1, 2, 4-Triazoles were performed. For this study, the entire chemicals used were procured from Qualingens, Himedia and Loba-chemicals. Purity of compounds was checked on "Silica Gel G" coated on laboratory micro slides prepared by dipping method or precoated plates. The FT-IR spectra of the synthesized compounds have been obtained from BLDE College of Pharmacy, Bijapur. The HNMR spectra of the selected compounds have been obtained from Astra Zeneca Pharma India Ltd, Bangalore. For both Antibacterial and Antifungal activity determination, cup plate method was followed. The Antibacterial activity against E.Coli, P.Aurugenosa, S.Aureus and B.Subtilis was performed. The antifungal activity against Candida albicans and Aspergillus niger was done.

**KEYWORDS:** *Synthesis, Characterization, Antibacterial activity, Antifungal activity, 1,2,4-Triazoles.*

## 1. INTRODUCTION

Pharmaceutical Chemistry is the discipline that emphasizes the chemistry of development and drug design, action of drug, transport of drug, drug delivery, and drug targeting. The development of new pharmaceutical substance is critically dependent on a molecular-level understanding of biological processes and mechanisms of action of drug.<sup>1</sup> Progress in the field now depends on the design and synthesis of new drug molecules using tools such as structure activity relationships, combinatorial chemistry and computer-aided drug design. In current era, rational design of drugs tuned to specific target sites is becoming a reality due to concurrent advances in chemistry and biology, including elucidation of the human genome. Chemists continue to be at the forefront of drug design, synthesis, testing, and development.<sup>2</sup> Discovering and bringing one new drug molecule to the public typically costs a pharmaceutical or biotechnology company from \$800 million to more than \$1 billion and takes an average of 10 to 15 years. The drug discovery and development process is designed to ensure that only those pharmaceutical products that are both safe and effective are brought to market. New drug molecules begin in the laboratory with scientists, including

chemists and pharmacologists, who identify cellular and genetic factors that play a role in specific diseases. They search for chemical and biological substances that target these biological markers and are likely to have drug-like effects.<sup>3-4</sup>

## 2. MATERIAL AND METHODS

- a) The entire chemicals utilized for experiment, were procured from Qualingens, Himedia and Loba-chemicals. Purity of starting materials used for reaction was confirmed by checking their boiling point or melting point and by thin layer chromatography.
- b) Purity of compounds was checked on "Silica Gel G" coated on laboratory micro slides prepared by dipping method or precoated plates, eluent was the mixture of different polar and non-polar solvents in varying proportions and detection was done either by observing in UV (ultra-violet) light or exposure to iodine vapors as required. Appearance of new TLC spot at different  $R_f$  value and absence of TLC spots for starting materials ensured the completion of reaction.
- c) Melting points were determined in open capillary tube using precision melting point apparatus and uncorrected.
- d) The FT-IR spectra of the synthesized compounds have been obtained from BLDE College of Pharmacy, Bijapur. The IR spectra were recorded on SHIMADZU PERKIN EKMER 8201 PC IR SPECTROMETER using a thin film on potassium bromide pellets.<sup>4-6</sup>

### 2.1 ANTIMICROBIAL ACTIVITY

In general, any compound or drug which inhibits the growth or causes the death of micro-organisms is known as antimicrobial agent. Any drug which inhibits the growth of bacteria or fungi, it is said to possess bacteriostatic and fungi static activity respectively. If it kills the bacteria or fungi, it is called as bactericide and fungicide. In-vitro tests are used as screening procedure for new agents and to test the susceptibility of individual isolates from infections to determine which of the available drug might be useful therapeutically. Important factors for the antimicrobial activity and size of the inoculums, metabolic state of organisms, pH, temperature, duration of interaction, concentration of the inhibitors and presence of interfering substance. Sensitivity testing is done for determining the range of microorganisms that are susceptible to the compound under specified conditions. It can be performed by cup-plate method. This method is suitable for the organisms that grow well overnight such as most of the common aerobes and facultative anaerobes and fungi which grow rapidly. Several forms of disk diffusion methods have been advocated. Biological evaluation involves testing of microbial susceptibility to chemotherapeutic agents. Antimicrobial effectiveness determination against pathogens is essential for therapy. Testing can show the efficiency of antimicrobial against a pathogen and give an estimate of proper therapeutic dose. The concept of the effectiveness of a chemotherapeutic agent against a specific pathogen can be obtained from the minimum inhibitory concentration (MIC). The MIC is the lowest concentration of the drug that can prevent the growth of the pathogen. The important factors to be considered in the testing of the antimicrobial activity are as follows: a) Type of test organism b) Temperature and time of incubation c) Composition and pH of culture d) Inoculums concentration. Formazan derivatives are known for their antimicrobial activity which is described in the literature. Hence, in the present study, substituted formazan derivatives synthesized were screened for their antibacterial as well as antifungal activity using various bacterial strains as well as fungal strains.

#### 2.1.1 EVALUATION OF ANTIBACTERIAL ACTIVITY

Determination of Antibacterial activity was based on the *in vitro* activity in pure cultures. The cup plate method was used for *in vitro* susceptibility test. The antibacterial activity of formazan derivatives was evaluated by cup-plate method against the strains of common pathogens; *Pseudomonas aeruginosa*, gram negative organisms *Escherichia coli*, and Gram positive organisms *Staphylococcus aureus* *Bacillus subtilis*. Ciprofloxacin is used as a standard drug.<sup>7-8</sup>

#### Test organisms (bacteria)

*Bacillus subtilis*                      Gram positive bacteria

*Staphylococcus aureus* Gram positive bacteria

*Escherichia coli* Gram negative bacteria

*Pseudomonas aeruginosa* Gram negative bacteria

All the synthesized compounds were screened for antibacterial activity against the above mentioned strains by cup-plate method. The following materials were used for the testing.

1. Nutrient agar.
2. Sterilized petridish, beakers and pipettes.
3. Sterilized tuberculin syringes.
4. 18-24 hr old growth culture in nutrient broth.
5. Sterilized test tubes containing solution of test compounds in desired concentration

#### ***Preparation of Nutrient agar media***

Nutrient agar (40g), beef extract (5g), bacteriological peptone (1g) and sodium chloride (5g) were dissolved in distilled water (1000 ml). The pH of the solution was adjusted to 7 to 7.4 by using sodium hydroxide solution (40%, approximately 0.25 ml for 100 ml of nutrient broth) and then sterilized for 30 min. at 15 lbs pressure in an autoclave.

#### ***Preparation of sub culture***

One day prior to test the microorganisms were inoculated into the sterilized nutrient broth and incubated at 37°C for 24 hr on the day of testing the organisms were sub-cultured into sterile nutrient broth. After incubating for 3 hr, the growth thus obtained was used as inoculums for the test.

#### ***Sterilization of media and glass wares***

The media used in the present study, nutrient broth and nutrient agar were sterilized in a conical flask of suitable capacity by autoclaving the same at 15 lbs pressure for 20 min. The test tubes, petridishes and pipettes were sterilized by using hot air oven at 160 °C for 1 hr.

#### ***Preparation of solution of test compound***

The test compound (10 mg each) was dissolved in freshly distilled DMF (10 ml) in serially labeled sterile test tubes, thus giving a final concentration of 50 µg/0.1 ml, 100 µg/0.1 ml.

#### ***Preparation of standard solution***

The standard drug ciprofloxacin (10 mg) was dissolved in freshly distilled DMF (10 ml) in serially labeled sterile test tubes, thus it gives a final concentration of 50 µg/0.1 ml and 100 µg/0.1 ml.

## **METHOD OF TESTING**

### ***Cup-plate Method***

The cup plate method done by the diffusion of an antibacterial agent from a cavity through the solidified agar layer in a petridish to an extent such that growth of the added microorganisms is prevented entirely in a circular area or zone around the cavity containing a solution of test compounds. Molten nutrient agar about 15-20 ml was poured into each of the sterile petridishes. The cups were made by scooping out nutrient agar with a sterile cork borer. The agar plates so prepared were divided into different sets and each set of the plates were inoculated with the suspension of particular organism by spread plate technique. The cups of inoculated plates were filled with 0.1 ml of the test solution; the plates were then incubated at 37°C for 24 hours. The zone of inhibition (diameter in mm) if developed, then measured for the particular compound with each organism. The solvent DMF was used as negative-control to know the activity of the solvent. The results of antibacterial testing are summarized in the following Table-1. The antibacterial activity of the tested compounds are then compared with that of standard drug used i.e. Ciprofloxacin.<sup>9</sup>

### **2.1.2 ANTIFUNGAL ACTIVITY**

Cup plate method was used to determine the antifungal activity of formazan derivatives and compared with antifungal drug Clotrimazole. *Candida albicans* and *Aspergillus niger* were used as fungi cultures.



**Cup-plate method**

By using disc-diffusion method antifungal activity of the test compounds was assessed against the above strains of fungi. The following materials were used:

1. Sabourauds agar and tuberculin syringes with needles.
2. Sterilized petri-dishes and pipettes of **0.10.2 ml**.
3. 16-18 hr old cultures grown in Sabourauds broth.
4. Sterilized test tubes for preparation of solution of the test compounds in desired concentration.

**Preparation of media****Sabourauds agar**

Bacteriological peptone (**1 g**) and glucose (**4 g**) were dissolved in distilled water (**100 ml**) and filtered. Agar powder (**2 g**) was added and sterilized for 30 min at 15 lbs pressure.

**Preparation of sub cultures**

One day prior to the test, inoculation of the microorganisms (*Aspergillus niger* and *Candida albicans*) was made in sabourauds broth and incubated at **37°C** for **18 hr**.

**Sterilization of media and glass wares**

The media used in the present study was sterilized by using autoclave at 15 lbs pressure for about 20 min. The test tubes, petridish, and pipettes were sterilized in hot air oven at 160°C for one hour.

**Preparation of solution**

- 1. Compounds:** 10 mg of each test compounds was dissolved in 10 ml of DMF in serially and suitably labeled in sterile test tubes; it gives a final concentration of 50µg/0.1ml, 100µg/0.1ml.
- 2. Clotrimazole:** 10 mg of the clotrimazole was dissolved in 10 ml of DMF (dimethyl formamide) to get a concentration of 50µg/0.1ml, 100µg/0.1ml.

**METHOD OF TESTING****Cup-plate Method**

This method performed by the diffusion of an antibacterial from a cavity through the solidified agar layer in a petridish. Molten nutrient agar about 15-20 ml was poured into each of the sterile petridishes. With a sterile cork borer the cups were made by scooping out nutrient agar. The agar plates so prepared were divided into different set and each set of the plates were inoculated with the suspension of particular organism by spread plate technique. The cups of inoculated plates were then filled with 0.1 ml of the test solution; the plates were then incubated at 37°C for 24 hours. The zone of inhibition (diameter in mm) if developed, was then measured for the particular compound with each organism. The solvent DMF was used as negative-control to know the activity of the solvent. The results of antifungal testing are summarized in the following Table-2. The anti-fungal activities of the tested compounds are then compared with that of standard drug used i.e. Clotrimazole.<sup>10</sup>

**3. RESULTS AND DISCUSSION<sup>5-7,11-15</sup>**

**Table 1: Antibacterial activity of 1-(4-(isonicotinamido)-5-(phenoxyethyl)-4H-1,2,4-triazol-3-yl)-3,5-diphenylformazan(8a-8j):**

| Sl.No. | Comp. code | Diameter of zone inhibition (mm) |          |          |          |          |                        |          |          |          |          |                       |          |          |          |          |                   |          |          |          |          |
|--------|------------|----------------------------------|----------|----------|----------|----------|------------------------|----------|----------|----------|----------|-----------------------|----------|----------|----------|----------|-------------------|----------|----------|----------|----------|
|        |            | Escherichia coli                 |          |          |          |          | Pseudomonas aeruginosa |          |          |          |          | Staphylococcus aureus |          |          |          |          | Bacillus subtilis |          |          |          |          |
|        | -          | 5 µg/ml                          | 10 µg/ml | 25 µg/ml | 50 µg/ml | 75 µg/ml | 5 µg/ml                | 10 µg/ml | 25 µg/ml | 50 µg/ml | 75 µg/ml | 5 µg/ml               | 10 µg/ml | 25 µg/ml | 50 µg/ml | 75 µg/ml | 5 µg/ml           | 10 µg/ml | 25 µg/ml | 50 µg/ml | 75 µg/ml |
| 1      | 8a         | R                                | R        | 10       | 20       | 25       | R                      | R        | 9        | 19       | 26       | 10                    | 11       | 14       | 18       | 21       | R                 | 9        | 11       | 13       | 20       |
| 2      | 8b         | R                                | R        | R        | R        | 10       | R                      | R        | R        | 9        | 11       | R                     | R        | 10       | 13       | 14       | R                 | R        | 9        | 11       | 14       |
| 3      | 8c         | R                                | R        | R        | R        | R        | R                      | R        | R        | R        | 9        | R                     | 10       | 13       | 15       | 18       | R                 | 11       | 14       | 16       | 19       |

|    |               |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|----|---------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| 4  | 8d            | R  | R  | R  | 9  | 11 | R  | R  | R  | 10 | 12 | R  | R  | R  | R  | 10 | R  | R  | R  | R  | 9  |
| 5  | 8e            | R  | R  | R  | R  | 11 | R  | R  | R  | R  | 9  | R  | R  | R  | 9  | 12 | R  | R  | R  | 10 | 13 |
| 6  | 8f            | R  | R  | R  | 8  | 10 | R  | R  | R  | 9  | 11 | R  | R  | R  | R  | 10 | R  | R  | R  | R  | 8  |
| 7  | 8g            | R  | R  | R  | 10 | 11 | R  | R  | R  | 10 | 12 | R  | R  | 7  | 9  | 10 | R  | R  | 8  | 10 | 13 |
| 8  | 8h            | R  | R  | 9  | 11 | 15 | R  | R  | R  | 10 | 14 | R  | 8  | 15 | 18 | 20 | R  | R  | 9  | 11 | 13 |
| 9  | 8i            | R  | R  | R  | 10 | 12 | R  | R  | R  | 9  | 12 | R  | R  | R  | R  | 10 | R  | R  | R  | R  | 9  |
| 10 | 8j            | 8  | 11 | 13 | 16 | 17 | R  | 9  | 11 | 14 | 16 | 13 | 15 | 16 | 18 | 21 | R  | 9  | 11 | 13 | 20 |
| 11 | Ciprofloxacin | 23 | 26 | 30 | 35 | 37 | 23 | 30 | 34 | 36 | 38 | 23 | 26 | 29 | 33 | 35 | 14 | 23 | 28 | 30 | 34 |
| 12 | Control       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |

**Table 2: Antifungal activity of 1-(4-(isonicotinamido)-5-(phenoxyethyl)-4H-1,2,4-triazol-3-yl)-3,5-diphenylformazan(8a-8j)**

| SI No. | Comp. Code   | Diameter of zone inhibition (mm) |                 |                 |                 |                 |                   |                 |                 |                 |                 |
|--------|--------------|----------------------------------|-----------------|-----------------|-----------------|-----------------|-------------------|-----------------|-----------------|-----------------|-----------------|
|        |              | Candida albicans                 |                 |                 |                 |                 | Aspergillus niger |                 |                 |                 |                 |
|        | -            | 5<br>µg/<br>ml                   | 10<br>µg/<br>ml | 25<br>µg/<br>ml | 50<br>µg/<br>ml | 75<br>µg/<br>ml | 5<br>µg/<br>ml    | 10<br>µg/<br>ml | 25<br>µg/<br>ml | 50<br>µg/<br>ml | 75<br>µg/<br>ml |
| 1      | 8a           | 12                               | 14              | 15              | 17              | 25              | 10                | 13              | 16              | 20              | 27              |
| 2      | 8b           | 10                               | 13              | 16              | 18              | 22              | R                 | 15              | 20              | 23              | 26              |
| 3      | 8c           | 10                               | 15              | 19              | 20              | 23              | R                 | R               | 20              | 21              | 26              |
| 4      | 8d           | 10                               | 12              | 13              | 16              | 18              | 12                | 13              | 15              | 18              | 22              |
| 5      | 8e           | 8                                | 10              | 15              | 16              | 10              | 13                | 15              | 18              | 20              | 24              |
| 6      | 8f           | 8                                | 9               | 13              | 15              | 17              | R                 | 12              | 15              | 16              | 23              |
| 7      | 8g           | 8                                | 10              | 13              | 16              | 18              | 13                | 14              | 17              | 20              | 25              |
| 8      | 8h           | 15                               | 16              | 20              | 23              | 25              | 10                | 13              | 16              | 18              | 23              |
| 9      | 8i           | 8                                | 10              | 11              | 12              | 16              | 12                | 14              | 17              | 20              | 22              |
| 10     | 8j           | 16                               | 17              | 22              | 23              | 27              | 21                | 23              | 25              | 31              | >40             |
| 11     | clotrimazole | 24                               | 26              | 30              | 35              | 37              | 23                | 26              | 29              | 33              | 35              |
| 12     | Control      | -                                | -               | -               | -               | -               | -                 | -               | -               | -               | -               |

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## SP-2

## OPTIMIZATION OF NIFEDIPINE 10 MG MOUTH DISSOLVE TABLET BY USING VARIOUS DISINTEGRANT

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### ABSTRACT

The most common preferred route is oral route of administration. Today oro-dispersible tablet from novel drug delivery system gain importance from patient. This tablet is administered to the patient to control the attack of angina or hypertension, but for immediate control, Oro-dispersible tablet is oral solid dosage form in which the tablet gets dispersed in oral cavity in absence of water. Various manufacture are formulated this formulation by various method. The advantage of this formulation are masking of taste of drugs. Generally oro-dispersible tablet are prepared by direct compression method. Wet granulation, dry granulation, Spray drying is the various methods for preparation of oro-dispersible tablet. Oro-dispersible tablet generally contains filler, glidant, anti-adherent super disintegrate, sweetener and resins. Evaluation parameter includes hardness, friability, moisture uptake, disintegration test, wetting time, and dissolution test. Disintegration time, Wetting time, and Dissolution test is directly proportional to the hydrophobic ingredient added for lubrication, anti-adherent, Glidant action. These hydrophobic ingredients are Magnesium Stearate. To oppose the action of magnesium stearate, hydrophilic additives are incorporated viz Sodium lauryl sulphate. The concept of Mouth Dissolve Drug Delivery System emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate or dissolve to release a drug as soon as they come in contact with saliva in oral cavity, thus obviating the need for water during administration, an attribute that makes them highly attractive for paediatric and geriatric patients. Elderly patients may face difficulty in administration to maintain healthy life. Children may also have difficulty in swallowing because of their under developed muscular nervous system. The problem of swallowing tablets is also evident in travelling patients who may not have ready access to water. Aforementioned problems can be resolved by means of Mouth Dissolving Tablets. Some tablets are designed to dissolve in saliva within few seconds, and are true fast-dissolving tablets.

**KEYWORDS:** *Oro dispersible Table Nifedipine 10 mg, cross Carmillose Sodium, Sodium starch glycolate, Cross povidone*

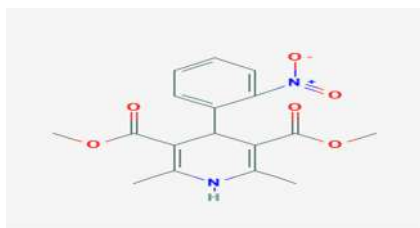
### 1. INTRODUCTION

Qualities are built in the pharmaceutical formulation by designing the formulation of drugs. The total quality in the product is known as Total Quality Management. To gain this goal of optimized quality product, the knowledge obtained from pharmaceutical development studies and manufacturing provides the scientific background. Although it is based on different pharmaceutical studies, but it has its aim that it minimizes the end product testing and increases the chances of regulatory acceptance by different pharmaceutical governing bodies. The aim and objective of the present study is to develop and evaluate oro dispersible tablet of Nifedipine and enhance the onset of action of Nifedipine and also to study the

influence of excipients on the physical characteristics of the tablets by applying two level three factor factorial designs taking Nifedipine as model drug. It is used in the treatment of the High blood pressure, cardiac arrhythmia and Angina Pectoris. The study of this formulation to select the best possible excipient combination of semi synthetic & natural and artificial additives to develop formulation. Super disintegrants namely Cross carmilllose sodium, cross povidone sodium starch glycolate are added to formulate the dispersible tablets among all the diluents and finally the effect of the various super disintegrants on the Disintegration time and dissolution properties of the tablet were also determined.<sup>1-5</sup>

## 2. MATERIAL AND METHOD

|               |                        |
|---------------|------------------------|
| Formula       | : $C_{17}H_{18}N_2O_6$ |
| Molar mass    | : 345.335 g/mol        |
| Melting point | : 172 to 174 °C        |



Nifedipine was patented in 1967 and approved in 1981 in the United States of America for marketing. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system for various cardiac diseases. It is available as a generic medication in various dosage forms and various formulation ranges from 5 mg to 20 mg. Nifedipine is odourless, yellow crystalline tasteless Powder. Nifedipine is water insoluble. Chemically Nifedipine is a Dihydropyridine Calcium Channel Blocker. The mechanism of action of Nifedipine on heart is as a Calcium Channel Antagonist. The chemical classification of Nifedipine is Dihydropyridine. Nifedipine act as calcium channel blocker to treat hypertension and angina pectoris and other cardiovascular diseases. Nifedipine therapy is associated with a low rate of serum enzyme elevations and has been linked to several instances of clinically apparent acute liver injury. Nifedipine is a potent vasodilator agent with calcium antagonistic action.<sup>6-10, 13-14</sup>

## 3. MATERIAL AND THEIR USE WITH OBTAINED SOURCES<sup>15</sup>

**Table 1: Materials with their uses and sources**

| S. No. | Material                        | Use of ingredients | Sources  |
|--------|---------------------------------|--------------------|--|
| 1      | Nifedipine                      | Active Ingredients | J.B. chemicals. Anklashwar   |
| 2      | Lactose                         | Diluents           | Pacific India.<br><br>A Pharmaceutical exporter, Village-Dhana, Bagbania Nalagarh, Solan, (H.P.) |
| 3      | Microcrystalline cellulose      | Diluents           |  |
| 4      | Sodium starch Glycolate         | Disintegrants      |  |
| 5      | Cross Carmillose sodium         | Disintegrants      |  |
| 6      | Cross povidone                  | Disintegrants      |  |
| 7      | Aspartame                       | Sweetener          |  |
| 8      | Methyl Paraben & Propyl paraben | Preservative       |  |
| 9      | Mannitol                        | Diluents/Sweetener |  |
| 10     | Starch Direct compressible      | Antiadhrants       |  |
| 11     | Magnesium stearate              | Glidant            |  |
| 12     | Talc                            | Lubricants         |  |

#### 4. PREPARATION OF NIFEDIPINE 10 MG ORO DISPERSIBLE TABLET BY DIRECT COMPRESSION METHOD<sup>16</sup>

**Table 2: Preparation of Nifedipine 10 Mg oro Dispersible Tablet by Direct Compression Method**

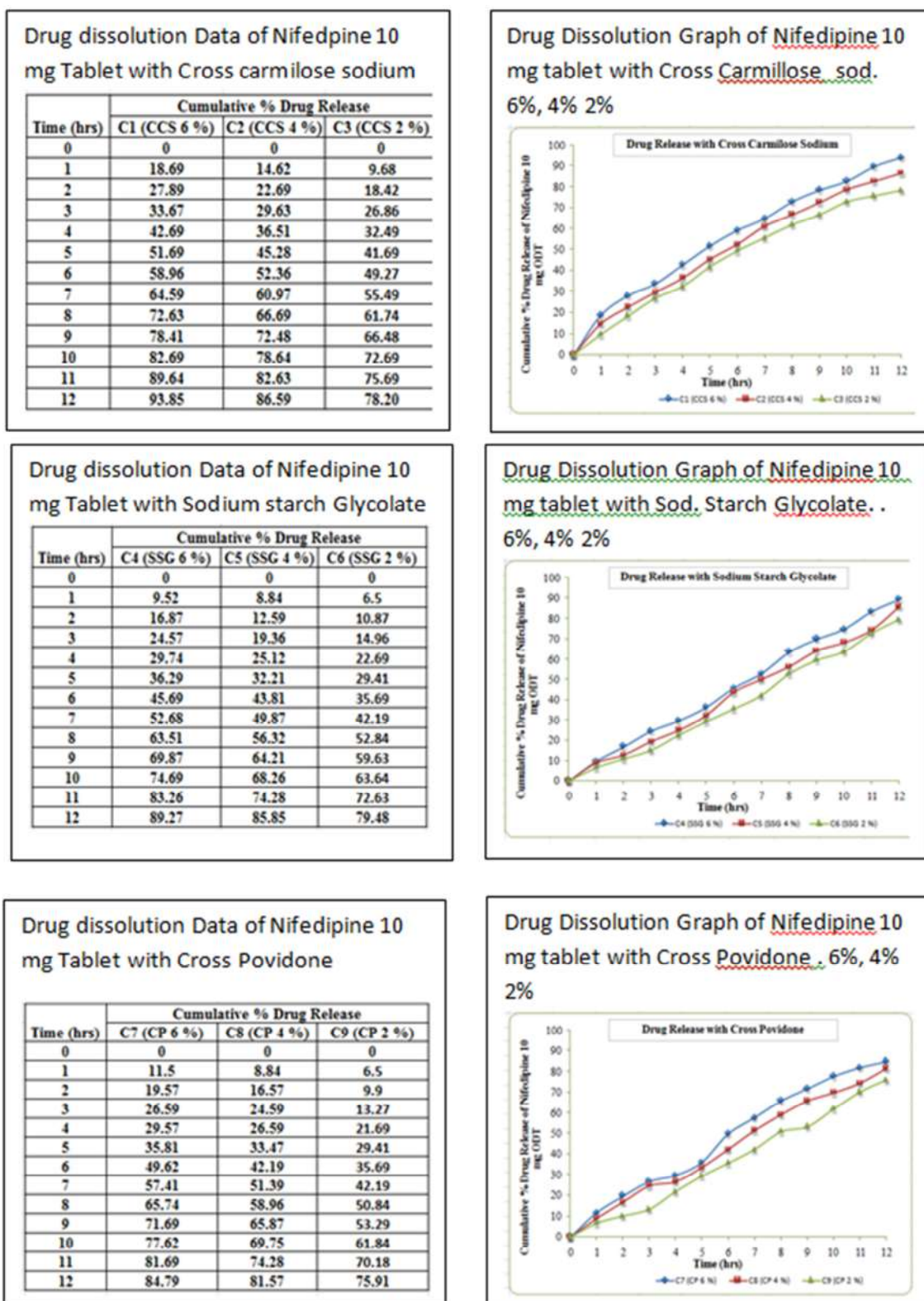
| s. No | Ingredients             | C1 (mg)    | C2 (mg)    | C3 (mg)    | C4 (mg)    | C5 (mg)    | C6 (mg)    | C7 (mg)    | C8 (mg)    | C9 (mg)    |
|-------|-------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| 1     | Nifedipine              | 10         | 10         | 10         | 10         | 10         | 10         | 10         | 10         | 10         |
| 2     | Cross Carmillose Sod.   | 24 (6%)    | 16 (4%)    | 8 (2%)     | ---        | ---        | ---        | ---        | ---        | ---        |
| 3     | Sodium starch Glycolate | ---        | ---        | ---        | 24 (6%)    | 16 (4%)    | 4 (2%)     | ---        | ---        | ---        |
| 4     | Cross povidone          | ---        | ---        | ---        | ---        | ---        | ---        | 24 (6%)    | 16 (4%)    | 4 (2%)     |
| 5     | Lactose                 | 90         | 98         | 106        | 90         | 98         | 106        | 90         | 98         | 106        |
| 6     | Aspartame               | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         |
| 7     | Methyl Paraben          | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          |
| 8     | Propyl Paraben          | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 1          |
| 9     | Mannitol                | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         |
| 10    | Starch DC grade         | 105        | 105        | 105        | 105        | 105        | 105        | 105        | 105        | 105        |
| 11    | Micro crystalline ce.   | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         |
| 12    | Magnesium stearate      | 8          | 8          | 8          | 8          | 8          | 8          | 8          | 8          | 8          |
| 13    | Talc                    | 8          | 8          | 8          | 8          | 8          | 8          | 8          | 8          | 8          |
|       | <b>Total</b>            | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> |

All the ingredients of formulation i.e. Active ingredients and additives were passed through 60 # sieve separately, Magnesium stearate and talc through 40 #, The ingredient were mixed by geometrical mixing and Tablet were compressed on 9.5 mm sizes of flat round punch to get tablet by using Rimeck Single rotary compression machine.

#### 5. RESULT AND DISCUSSION<sup>11,12</sup>

##### POST COMPRESSION PARAMETER AND STUDIES

| Formulation code | Assay of Drug (%) | Disintegration Time (Sec) | Dissolution (%) | Hardness (Kg/cm2) | Friability (%) | Thickness (mm) |
|------------------|-------------------|---------------------------|-----------------|-------------------|----------------|----------------|
| C1 (CCS 6 %)     | 99.32             | 4-7                       | 93.85           | 3.60              | 0.62           | 4.05           |
| C2 (CCS 4 %)     | 98.82             | 8-11                      | 86.59           | 3.30              | 0.52           | 4.07           |
| C3 (CCS 2 %)     | 98.41             | 11-16                     | 78.20           | 3.20              | 0.86           | 3.92           |
| C4 (SSG 6 %)     | 98.52             | 13-16                     | 89.27           | 3.40              | 0.49           | 4.00           |
| C5 (SSG 4 %)     | 98.78             | 16-21                     | 85.85           | 3.30              | 0.71           | 3.96           |
| C6 (SSG 2%)      | 98.50             | 19-24                     | 79.48           | 3.20              | 0.60           | 3.94           |
| C7 (CP 6 %)      | 98.62             | 18-23                     | 84.59           | 3.40              | 0.71           | 3.96           |
| C8 (CP 4 %)      | 98.38             | 20-25                     | 81.57           | 3.00              | 0.64           | 4.04           |
| C9 (CP 2 %)      | 98.32             | 23-27                     | 75.91           | 3.90              | 0.57           | 4.06           |



**Fig 1. Drug Dissolution data of Nifedipine 10 mg Tablet with different Additives**

## 6. CONCLUSION

After completion of this experiment the results obtained and conclude that Optimization of oro dispersible tablet of Nifedipine 10 mg formulation by using various super disintegrants i.e. Cross Carmillose sodium, cross Povidone, Sodium starch glycolate gives results are mentioned below:

1. Fast Disintegrating tablets of Nifedipine 10 mg were successfully prepared by direct compression method.
2. The hardness of compressed tablet by direct compression method found in the rage of 3.0 to 3.9 kg/cm<sup>2</sup>.
3. The Thickness of the prepared tablets of all 5 formulations was found between 3.92 mm. to 4.07 mm.



4. The Friability of the compressed tablet found within the range i.e. less than 1%. Maximum Friability for C3 contains 2 % Cross Carmilose sodium is 0.86 %
5. The in vitro disintegration studies are found to be in 4 to 27 seconds. Formulation C1 contains 6 % CCS show in vitro disintegration time i.e. 4-7 seconds.
6. Formulation C1 with 6 % CCS on the basis of disintegration time facilitate the faster disintegration in the mouth. The *in-vitro* % drug releases from fast dissolving tablets of Nifedipine 10 mg prepared by direct compression method were found to be in the range of 99.32 %. Hence, it is concluded that the prepared oro dispersible tablets of Nifedipine 10 mg is potential candidate for effective fast disintegrating tablet dosage form.

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## SP-3

## HPLC METHOD VALIDATION FOR THE DETERMINATION OF CAFFEINE IN BULK AND TABLET DOSAGE FORM AS PER USP

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### ABSTRACT

High Performance liquid chromatography is nowadays a common and important method for validation of different drugs in the form of Active pharmaceutical ingredients and different formulations. HPLC is a type of liquid chromatography in which solvent which is a mobile phase runs through the column. Column acts as a stationary phase. Affinity every molecule is different with stationary phase, on this basis we can identify the substance. Molecules that interact strongly with the stationary phase will move slowly through the column, while the molecules that interact less strongly will move rapidly through the column. In present study, a new HPLC method has been validated with different parameters for Caffeine in Bulk and Tablet dosage form. Caffeine is a natural stimulant most commonly found in cocoa plants, tea and coffee. Caffeine acts by stimulating the brain and central nervous system. Caffeine blocks the effects of adenosine, which is a neurotransmitter that relaxes the brain and makes you feel tired. The chromatograms were developed using a mobile phase of Methanol: Glacial acetic acid: Water (28:3:69). The flow rate of mobile phase was 2 ml/min. C18 Column of 4.6 x 10 cm dimension was used as a stationary phase, particle size 5µm. The detection was carried out at 275 nm wavelength. The method was validated according to ICH guidelines for precision (Intraday & Interday), Accuracy, linearity, Repeatability and Robustness. The response was found to be linear in concentration range of 11.25-33.75 mcg/ml for Caffeine. The validated method was accurate, simple, precise and reproducible and therefore suitable for analysis of drugs in tablet dosage form.

**KEYWORDS:** *HPLC; Caffeine; USP; Validation; Tablet.*

### 1. INTRODUCTION

HPLC is a liquid chromatographic technique used to separate the complex mixture of molecules encountered in chemical and biological systems, in order to understand better the role of individual molecules. In liquid chromatography, a mixture of molecules dissolved in a solution (mobile phase) is separated into its constituent parts by passing through a column of tightly packed solid particles (stationary phase). The separation occurs due to interaction with the stationary phase. Molecules that interact strongly with the stationary phase will move slowly through the column, while the molecules that interact less strongly will move rapidly through the column. This different rate of movement of component facilitates the separation of the molecules. HPLC method is utilized for the determination of Caffeine in Bulk and Tablet dosage form as per USP. Caffeine [Chemical Name- Guanine Methylxanthine 1,3,7-Trimethylxanthine Theine] is a natural stimulant most commonly found in cocoa plants, tea and coffee. Caffeine acts by stimulating the brain and central nervous system; it helps to stay alert and reduce tiredness. Caffeine blocks the effects of adenosine, which is a neurotransmitter that relaxes the brain and makes you feel tired.<sup>1-5</sup>

## 2. EXPERIMENTAL<sup>6-7</sup>

**Table 1: Name of API and Suppliers**

| Sr. No | Name of API | Supplier                                       |
|--------|-------------|--|
| 1      | Caffeine    | Medley Pharmaceuticals,<br>Daman Unit, Gujarat |

### 2.1 Marketed Tablet Formulation

**Table 2: Marketed Tablet Formulation**

|                        |                    |
|------------------------|--------------------|
| <b>Sr. no.</b>         | 1                  |
| <b>Brand Name</b>      | Micropyrin         |
| <b>Strength</b>        | Caffeine- 30 mg    |
| <b>Name of company</b> | Abbott Health care |
| <b>Batch no.</b>       | V 000 19           |
| <b>Mfg. Date</b>       | March 2012         |
| <b>Exp. Date</b>       | Feb. 2015          |
|                        |                    |

### 2.2 Reagents and Chemicals

**Table 3: List of Reagents and Chemicals**

| Sr. No | Name of Chemical              | Supplied by                             |
|--------|-------------------------------|---|
| 1      | Methanol, HPLC Grade          | Research Lab Fine Chem Industry, Mumbai |
| 2      | Water, HPLC Grade             | Rankem Industry                         |
| 3      | Glacial Acetic Acid, AR Grade | Research Lab Fine Chem Industry, Mumbai |
| 4      | Benzoic Acid, AR Grade        | Research Lab Fine Chem Industry, Mumbai |

### 2.3 Preparation Of Standard Solution

#### 2.3.1 Preparation Of Mobile Phase

The mobile phase is prepared by dissolving 15 ml of glacial acetic acid and 140 ml of methanol in 345 ml of water. 2 ml/min was flow rate of mobile phase.

##### 2.3.1.1 Preparation Of Internal Standard Solution

The standard solution was prepared by dissolving 1.2 gm of benzoic acid in 20 ml of methanol.

##### 2.3.1.2 Preparation Of Solvent mixture

The solvent mixture was prepared by dissolving 15 ml of glacial acetic acid in 285 ml of methanol.

##### 2.3.1.3 Preparation Of Standard Stock Solution

Sufficient quantity of caffeine was weighed and dissolved in solvent mixture to obtain 0.25 mg/ml of caffeine.

**2.3.1.4 Standard Preparation**

3 ml of internal standard solution and 20 ml of standard stock solution was mixed with solvent mixture to get 50 ml standard preparation.

**2.3.1.5 Assay Preparation**

20 Tablets of Caffeine were weighed and powdered; powder equivalent to 250 mg is transferred into 100 ml volumetric flask. 75 ml solvent is added in the flask and shaken for 30 minutes. Diluted with solvent upto 100 ml mark. 2 ml of this solution and 3 ml of internal standard solution is mixed in another 50 ml flask and diluted with solvent upto the mark.

**2.3.1.6 Preparation of stock solution for Caffeine**

Dissolve 10 mg of Caffeine in 100 ml flask containing diluent. This becomes a 100 ppm solution. Take 1 ml from above solution and make volume upto 10 ml with diluent in 10 ml flask. This becomes 10 ppm solution.

**Preparation of solution**

Pipette out 0.75 ml, 1.12 ml, 1.5ml, 1.87 ml and 2.25 ml in different volumetric flask to get 50%, 75%, 100%, 125% and 150% solution of Caffeine.

**2.4 ANALYTICAL METHOD VALIDATION OF CAFFEINE TABLET AS PER USP<sup>8-11</sup>****1) Linearity**

Linearity of the method was studied by preparing concentration of drugs in linear range and injecting each concentrations of the drug prepared in the Methanol, Water and Glacial Acetic Acid in the range of 11.25 - 33.75 µg/ml for Caffeine into the HPLC system. The injection volume was 10µg/ml. The peak areas were plotted against the corresponding concentrations to obtain the calibration graphs.

**2) Accuracy (Recovery Study)**

To study the suitability and reliability of standard method, recovery experiments were carried out. A known amount of solution of Caffeine Tablet was subjected to the analysis. If value of relative standard deviation is lower, then it indicates the accuracy of the method. To determine the accuracy of standard method, at 80%, 100% and 120% of the label claim, the recovery studies were performed.

**3) Precision**

It was considered at three levels: 1) repeatability, 2) intermediate precision and 3) reproducibility.

**3.1 Repeatability**

It was measured by multiple injections of a homogenous test sample; it indicates the performance of the HPLC instrument under chromatographic conditions.

**3.2 Interday Precision**

This method is performed by injecting multiple sample of homogenous standard solution on different days under same operating condition.

**3.3 Intraday Precision**

The intraday precision of the standard method was evaluated by analyzing samples of different concentrations of Caffeine three times on the same day and % RSD was calculated.

**4) Robustness**

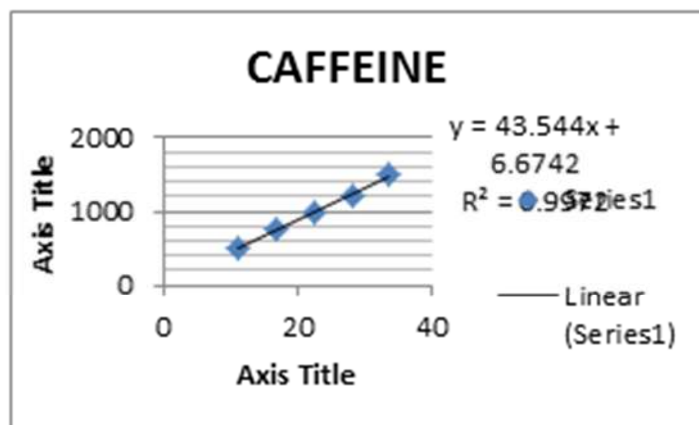
For this study the possible variation parameters were identified and they are willfully changed. The method parameters for HPLC include the variation in flow rate, mobile phase composition, pH, temperature, different column of same lot or same suppliers. The robustness of the system was determined by deliberate change in Mobile phase concentration, flow rate, PH and temperature.

**5) System Suitability Test**

System suitability parameters like theoretical plates, tailing factor, relative standard deviation and Resolution should be within limit.

**6) Range**

The range of an analytical method is the interval from the upper to the lower level.

**3. RESULTS<sup>12-15</sup>**

**Figure 1: Calibration Curve of Caffeine**

**Table 4: Result of % Accuracy Study of Caffeine**

| Conc  | Drug Added (µg/ml) |     | Area Found | % Recovery | Analysis of % Recovery   |
|-------|--------------------|-----|------------|------------|--------------------------|
|       | Pure               | Tab |            |            |                          |
| 80 1  | 12                 | 15  | 795.59     | 99.67      | Mean:99.96<br>%RSD:0.32  |
| 80 2  | 12                 | 15  | 800.76     | 100.32     |                          |
| 80 3  | 12                 | 15  | 797.39     | 99.89      |                          |
| 100 1 | 15                 | 15  | 990.77     | 99.30      | Mean:100.06<br>%RSD:1.00 |
| 100 2 | 15                 | 15  | 994.74     | 99.69      |                          |
| 100 3 | 15                 | 15  | 1009.74    | 101.20     |                          |
| 120 1 | 18                 | 15  | 1186.12    | 99.06      | Mean:100.06<br>%RSD:0.98 |
| 120 2 | 18                 | 15  | 1209.69    | 101.03     |                          |
| 120 3 | 18                 | 15  | 1198.50    | 100.10     |                          |

**Table 5: Inter Day Precision of Caffeine**

| Day | Conc. Level | Mean Area | %RSD   |
|-----|-------------|-----------|--------|
| 1   | 50%         | 498.135   | 1.286  |
| 2   | 100%        | 1008.746  | 0.552  |
| 3   | 150%        | 1497.640  | 1.1657 |

**Table 6: Intra Day Precision of Caffeine**

| Conc. | Mean Area | %RSD  |
|-------|-----------|-------|
| 50%   | 496.63    | 0.708 |
| 100%  | 997.755   | 0.656 |
| 150%  | 1492.145  | 0.901 |

**Table 7: Robustness for Caffeine**

| Chromatographic Condition | Area    | SD    | %RSD |
|---------------------------|---------|-------|------|
| <b>1) Flow Rate</b>       |         |       |      |
| 1.8                       | 1058.34 | 19.76 | 0.63 |
| 2.0                       | 1008.32 | 8.99  | 0.89 |
| 2.2                       | 950.83  | 23.70 | 0.85 |
| <b>2) Mobile Phase</b>    |         |       |      |
| 67:29:4                   | 996.75  | 25.41 | 1.01 |
| 69:28:3                   | 997.64  | 7.96  | 0.79 |
| 71:27:2                   | 997.08  | 33.97 | 1.05 |

**Table8: System Suitability Test Parameters**

| Ret. Time | Theor. Plate | Resolutn | %RSD |
|-----------|--------------|----------|------|
| 7.28      | 7115         | 18.64    | 0.82 |

**Table9: Range for Caffeine**

| Sr. No    | 50%    | 150%    |
|-----------|--------|---------|
| Mean Area | 500.99 | 1500.07 |
| %RSD      | 1.13   | 0.35    |

**Table 10: Assay of Marketed Formulation**

| Drug in Tablet (mg) | Drug taken (mg) | Drug found (mg) | %Amount found(mg) |
|---------------------|-----------------|-----------------|-------------------|
| 30                  | 15              | 14.95           | 99.69             |

#### 4. CONCLUSION

The main goal of this work is based on to select the more suitable, accurate, precise, validated and reliable method for the determination of Caffeine tablet which are given in standard Pharmacopoeial book like USP. Assay of Caffeine tablet is reported in IP, BP and USP. This study helps to find out the problem during the analysis and solve the problem by finding alternative and validated method. This study is designed to make a comparative and comprehensive analysis of Caffeine tablet. From the chromatographic study, I concluded that USP method is more accurate, precise, reliable and reproducible for analysis purpose. So one can perform assay as per USP.

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## SP-4

# NATURAL GUM (POLYMER) USED IN FORMULATION OF MATRIX TABLET FOUND IN KHANDESH REGION, MAHARASHTRA, INDIA

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## ABSTRACT

Natural gums (gums obtained from plants) are hydrophilic carbohydrate polymers of high molecular weights, commonly composed of monosaccharide units joined by glucosidic bonds. Synthetic gums used in pharmaceutical industries possess problems of toxic effects and health problems. To avoid drawbacks of synthetic gums and reduce import expenses, alternative natural gums are to be explored. Gums achieve from plants were used in India as excipients in food, pharmaceutical and cosmetic industries. India is the hub of medicinal plants and these are not commercially abused much. Indian industries depend on the imported gums. Since common man will be involved in collecting the gums the society will be benefited. Present article focus on natural gums which are found in khandesh region, Maharashtra, India used for formulation of matrix tablet. Natural gums are ecological, biocompatible, patient tolerance, low cost, environmental friendly. These are the advantages of Natural gums. And disadvantages are- there may be chances of microbial contamination, batch to batch variation and uncontrolled rate of hydration. Gum Arabic, Gum Ghati and Gum Karaya are some commercially important gums produced in India. These are used as in sweetmeats, dairy products, beverages, as emulsifier in food products, petroleum and for oil-well-acidizing purpose in the industry. Annually around 5,000 tons of plant based gums produced in India. These are used as in sweetmeats, dairy products, beverages, as emulsifier in food products, petroleum and for oil-well- acidizing purpose in the industry. Synthetic gums used in pharmaceutical industries possess problems of toxic effects and health problems. Natural gums are currently being imported by India from other countries such as Sudan (56 %), Chad (29 %) and Nigeria (10 %). To avoid drawbacks of synthetic gums and reduce import expenses, alternative natural gums are to be explored.

**KEYWORDS:** *Natural gum. Khandesh region, Karaya gum, Acacia gum, Guar gum.*

## 1. INTRODUCTION

### NATURAL GUM

Gums are manufactured from woody plants either naturally from exudations from cracks in the bark or damage to the bark by insects or animals. Gum flow is also artificially induced by incisions in the bark. The viscous, brittle nodule, which forms, can simply be removed by the hand. Gums are nothing but complex carbohydrate derivatives of a polysaccharide nature and are whichever soluble in water, as in the case of gum arable, or form mucilage's by the absorption of large amounts of water<sup>1</sup>. Uses of gums for native ingestion and for sale to earn some cash are very common among the forest residence communities, particularly tribes in India. Annually around 5,000 tons of plant based gums produced in India. Gum Arabic, Gum Ghati and Gum Karaya are some commercially important gums produced in India. These are used as in sweetmeats, dairy products, beverages, as emulsifier in food products, petroleum and for oil-well- acidizing

purpose in the industry. Constant research support is needed for processing, value addition and product development to meet the changing demand of domestic and international consumers<sup>2-5</sup>. Natural gums (gums obtained from plants) are hydrophilic carbohydrate polymers of high molecular weights, commonly composed of monosaccharide units joined by glucosidic bonds. They are normally insoluble in oils or organic solvents such as hydrocarbons, ether, or alcohols. Gums are either water-soluble or absorb water and swell up or disperse in cold water to give a viscous solution or jelly. On hydrolysis they yield arabinose, galactose, mannose and glucuronic acid. Gums are typical products of broadleaved trees and shrubs. They are complex carbohydrate derivatives of a polysaccharide nature and are either soluble in water, as in the case of gum arabic, or form mucilage's by the absorption of large amounts of water. Their primary use is in foodstuffs by nature of their ability to impart favorite qualities to foods by influencing their viscosity, body and texture: most regularly in sweetmeat food, flavoring and soft drinks<sup>6-9</sup>. They also have pharmaceutical applications as demulcents, adhesives in pill manufacture and as emulsifying agents. Industrial uses are for adhesives, lithography, paints and inks. Uses of gums for local consumption and for sale to earn some cash are very common among the forest residence communities, particularly tribes in India. Millions of forest and sub-forest dwellers in the central and western Indian states depend on gums as a viable income source. Majority of NTFPs are available only for short period while gums, which can be collected around six to eight months in a year, provides a steady source of income to the dependent gum collectors<sup>10-14</sup>. Nearly 5,000 tons of plant based gums formed in India annually (except guar gum – a seed based gum and annual production approximately 2,10,000 tons). The major gum producing states in India are Andhra Pradesh, Madhya Pradesh, Chhattisgarh, Orissa, Maharashtra, Gujarat, Rajasthan, etc. The export of plant-based gums from India during 2006-07 was 1,730.24 tons valued Rs. 2,218.27 lakh. Due to mandate India also imports gums and import of gums in India during 2006-07 was 19,464.08 tons values Rs. 5,879.14 lakh. Gum Arabic, Gum Ghatti and Gum Karaya are commercially important gums produced in India. Gum Tragacanth from *Astragalus* spp. of Asia Minor is even more valuable. It is a natural emulsifier in food products such as mayonnaise but is now being replaced, because of its high cost, by synthetic fermentation type products. Gums of commercial interest are also obtained from the fruit of the carob (*Ceratonia siliqua*), Gum Mesquite (*Prosopis latifolia*) and Indian Squill from *Urginea indica*<sup>15-18</sup>.

## 2. ADVANTAGES OF NATURAL GUMS

Advantages of natural gums and in pharmaceutical sciences.

The following are a number of the advantages of natural plant-based materials.

- Ecological
- Biocompatible and non-toxic
- Low cost
- Environmental-friendly processing
- Local availability
- Well patient tolerance as well as public acceptance
- In the food industry they are used as thickening agents, gelling agents, emulsifying agents and stabilizers.
- In other industries, they are also used as adhesives, binding agents, crystal inhibitors, clarifying agents, encapsulating agents, flocculating agents, swelling agents, foam stabilizers, etc. Most often these are botanical gums, found in the woody elements of plants or in seed coatings<sup>19</sup>.

## 3. DISADVANTAGES OF NATURAL GUMS

- Contamination by microbes
- Batch to batch variation
- Uncontrolled rate of hydration and Reduced viscosity on storage

## d. CLASSIFICATION OF GUMS

The different available gums can be classified as follows:

### According to the charge

A. **Non-ionic seed gums:** Tamarind, Xanthan, Amylose, Guar, Locust Bean, Arabinans, Cellulose, Galactomannans.

**B. Anionic gums:** Gellan, Agar, Algin, Carrageenans, Arabic, Karaya, Tragacanth, and Pectic Acid.

#### According to the source

**A. Marine origin/algal (seaweed) gums:** Alginic acid, Laminarin Agar, Carrageenans.

**B. Plant origin:** Shrubs/tree exudates—Gum arabica, 23elatinatti, Gum karaya, Gum tragacanth, khaya and Albizia gums. Seed gums—Guar gum, Locust bean gum, starch, Amylose, cellulose..

**C. Animal origin:** Chitin and Chitosan, Chondroitin sulfate, Hyaluronic acid.

**D. Microbial origin** (bacterial and fungal): Xanthan, Dextran, Curdian, Pullulan, Zanflo, Emulsan, Baker's yeast glycan, Schizophyllan, Lentinan, Krestin, Scleroglucan.

#### Semi-synthetic

**A. Starch derivatives**—Starch phosphates, Hetastarch, Starch acetate.

**B. Cellulose derivatives**—Carboxy Methyl Cellulose (CMC), Hydroxy Ethylcellulose, Hydroxypropyl Methylcellulose (HPMC), Methylcellulose (MC), Microcrystalline Cellulose (MCC).

#### According to shape

**A. Linear:** Algins, Amylose, Cellulose, Pectins.

**B. Branched:** a. Short branches—Xanthan, Xylan, Galactomanan. B. Branch-on-branch—Amylopectin, Gum Arabic, Tragacanth.

#### According to monomeric units in chemical structure

**A. Homoglycans**—Amylose, Arabinanas, Cellulose;

**B. Diheteroglycans**—Algins, Carragennans, Galactomannans;

**C. Tri-heteroglycans**—Arabinoxylans, Gellan, Xanthan;

**D. Tetra-heteroglycans**—Gum Arabic, Psyllium seed gum;

**E. Penta-heteroglycans**—Ghatti gum, Tragacanth

#### d. REASONS FOR DEVELOPMENT OF NEW NATURAL GUM (POLYMER)

Synthetic gums used in pharmaceutical industries possess problems of toxic effects and health problems. Natural gums are currently being imported by India from other countries such as Sudan (56 %), Chad (29 %) and Nigeria (10 %). To avoid drawbacks of synthetic gums and reduce import expences, alternative natural gums are to be explored. Gums achieve from plants were used in India as excipients in food, pharmaceutical and cosmetic industries. India is the hub of medicinal plants and these are not commercially abused much. Indian industries depend on the imported gums. Since common man will be involved in collecting the gums the society will be benefited.<sup>5</sup>

#### d. KHANDESH REGION

Khandesh (Marathi: खानदेश) is a geographic area in Central India, which forms the northwestern portion of Maharashtra state. Khandesh main cities in Central India on the northwestern corner of the Deccan Plateau, in the valley of the Tapi River. It is limited to the north by the Satpura Range, to the east by the Berar (Vidarbha) region, to the south by the Hills of Ajanta (belonging to the Marathwada region of Maharashtra), and to the west by the northernmost ranges of the Western Ghats. The principal natural feature is the Tapi River. Disparate the rest of the Deccan, whose rivers rise in the Western Ghats and flow eastward to the Bay of Bengal, the Tapi flows westward from headwaters in southern Madhya Pradesh to blank into the Arabian Sea. The Tapi receives thirteen principal tributaries in its course through Khandesh. None of these rivers is navigable, and the Tapi flows in a deep bed which historically made it difficult to use for irrigation. Most of Khandesh lies south of the Tapi and is tired by its tributaries: the Girna, Bori and Panjhra. The alluvial plain north of the Tapi contains some of the richest tracts in Khandesh, and the land rises towards the Satpuda hills. In the centre and east, the country is level, save for some low ranges of barren hills. To the north and west, the plain rises into rugged hills, thickly wooded, and inhabited by the tribal Bhil people.<sup>10</sup>

#### • Geographic elements Cities

✓ Jalgaon:

Jalgaon, Amalner, Bhadgaon, Bhusawal, Bodwad, Chalisgaon, Chopda, Erandol, Dharangaon, Faizpur, Jamner, Pachora, Parola, Raver, Savda, Yawal,

✓ Dhulia:

Dhule, Sakri, Sindkheda, Shirpur,

✓ Nashik:

Deola, Kalwan, Malegaon, Nampur, Tarahbad, Satana,

✓ Nandurbar:

Nandurbar, Prakasha, Shahada, Talode, Navapur, Akkalkuwa, Dhadgaon,

✓ General: Burhanpur (in Madhya Pradesh, capital of old Khandesh province)

Asirgarh (in Madhya Pradesh, part of old Khandesh province)

Khandesh District: is a former governmental division of British India, which included the presentday Jalgaon, Dhule and Nandurbar districts and a portion of Nashik District in Maharashtra.

#### d. GUMS IN KHANDESH REGION

• Gum found in Nandurbar and Dhule District:

• SterculiaUrens:

Local name: kadai, kadhay, kadoni, kewdi, kandul, kevda, kudal

• TerminaliaCrenulata:

Local name: Sadaba, Haijada, Sandadi

• GarugaPinnata:

Local name: kakad, kakada, kakod, kakado

• Boswelvia Serrate:

Local name: Dhupali, Salai, Goradu, Sal, Sayphal

• AzadirachtaIndica:

Local name: Neem, Kadu-Neem, Neemada

• Acacia Chandra:

Local name: Khair, Esa, Esan, Kati.

• Acacia NiloticaSpp.Indica:

Local name: Babhul, Telya-Babhul,

SadhaBabhul.

•BuchananialanzanSpreng: (Anacardiaceae)

Charoli.

•Pteriospermumsuberifolium.

• Buteamonosperma.

• Dalbergiasissoorob.

• Lanneacoromandelica

• Magniferaindicalinn

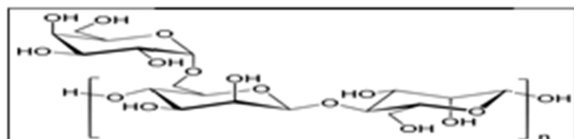
#### d. DESCRIPTION OF GUMS

##### 8.1 KARAYAGUM

**Synonyms** : Karaya, gum karaya, Sterculia,gumsterculia,Kadaya, Katilo, Kullo, Kuterra.

**Empirical Formula:** (C<sub>32</sub>H<sub>48</sub>O<sub>14</sub>)<sub>n</sub>

**Structural formula:**



**Functional Category:**Emulsifier, stabilizer, thickening agent.

**Description:**

Unground product: It occurs in tears of variable size and in broke irregular pieces having a characteristic semi-crystalline

**appearance;**pale yellow to pinkish brown;translucentand horny.

**Powdered product:** It occurs as pale grey to pinkish brown; a distinctive odour of acetic acid.

**Typical Properties:**

**Solubility:** Insoluble in ethanol, in water it swells to form a granular, stiff, slightly opalescent gel.

Loss on drying: Not more than 20% (105°C, 5 h).

Total ash: Not more than 8%

Acid insoluble ash: Not more than 1%

**Applications in Pharmaceutical Formulation or Technology**

Karaya gum is widely used in oral and topical pharmaceutical formulations, cosmetics and foods as a suspending and stabilizing agent. It is also used as a thickener and emulsifier. It is non toxic, compatible with most of the pharmaceuticals. Karayagum gels show pseudoplastic behavior, the shear thinning being directly proportional to the shear rate.

**Stability and Storage Conditions**

Karaya gum should be stored in a well closed container in a cool and dry place.

**Incompatibilities**

Karaya gum is an anionic material and is not usually compatible with cationic surfactants, polymers or preservatives, as precipitation occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of Karaya gum from a solution.

**Safety**

Karaya gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and food products, and is generally regarded as nontoxic and nonirritant at the levels employed as a pharmaceutical excipients. The estimated acceptable daily intake for Karaya gum has been set by the WHO at up to 10 mg/kg body weight.

**8.2 GUAR GUM**

**Nonproprietary Names:** BP: Guar Galactomannan

PhEur : Guar Galactomannan

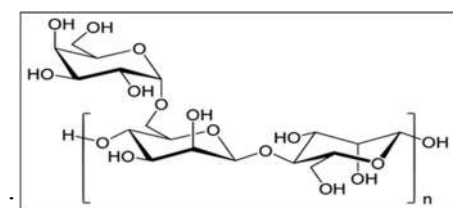
USP-NF : Guar Gum

**Synonyms** : Galactosol; guar flour; guar galactomannanum; jaguar gum;

**Empirical Formul** :  $(C_6H_{12}O_6)_n$

**Chemical name** : Galactomannan polysaccharide

**Structural Formula :**



**Functional Category:** Suspending agent; tablet binder; tablet disintegrant; viscosity enhancer.

**Description:** It occurs as odorless, yellowish-white granules with a bland taste.

**Typical Properties:** Acidity/alkalinity: pH = 5.0-7.0 (1% w/v aqueous dispersion)

Density: 1.492g/cm<sup>3</sup>. **Solubility:** Practically insoluble in organic solvents and in cold or hot water.

**Stability and Storage Conditions:** Guar gum granules should be stored in a well-closed container in a cool, dry place.

**Incompatibilities:** Guar gum is compatible with most other plant hydrocolloids such as tragacanth. It is incompatible with acetone, ethanol (95%), tannins, strong acids, and alkalis. Borate ions, if present in the dispersing water, will prevent the hydration of guar gum.

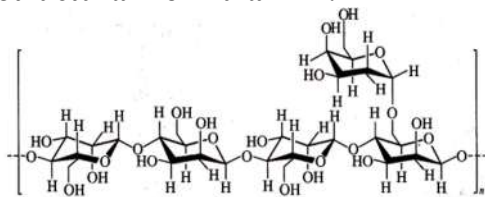
**Safety:** It is widely used in foods, and oral and topical pharmaceutical formulations. Excessive consumption may cause gastrointestinal disturbance such as flatulence, diarrhea or nausea.



### 8.3 ACACIA GUM

**Synonyms** : Senegal gum, Gum arabic

**Structural Formula** :



**IUPAC Name:** 17-acetyl-3,7-dihydroxy-4,4,10,13,14-pentamethyl-2,3,5,6,7,12,16,17 octahydro-1H-cyclopenta[a]phenanthrene-11,15-dione

**Molecular Formula** : C<sub>24</sub>H<sub>34</sub>O<sub>5</sub>

**CAS** : 97659-43-3

**Physical Description:** Solid

**Melting Point** : 280-283°C

**Molecular weight:** 402.531.g/ml

**Description** : Acaia, commonly known as the wattles or acacias, is a large genus of shrubs and trees in the subfamily Mimosoideae of the pea family Fabaceae. Initially it comprised a group of plant species native to Africa and Australia, with the first species *A. nilotica* described by Linnaeus. Acacia, also known as gum Arabic, is used in the pharmaceutical industry as an emulsifier, stabilizing agent, suspending agent, tablet binder, and viscosity- increasing agent.

### 8.4 MANGO GUM

Mango gum is a dried gummy exudates polysaccharide obtained from the bark of *Mangifera indica*, belongs to the family Anacardiaceae. Physical, thermal, sorption and functional properties of a mango gum were characterized. The results obtained in this study establish the fundamental characteristics of mango gum. Gum of *mangifera indica* (mango) as a tablet binder employing paracetamol as a model drug, resin of *mangifera indica* (mango) as a tablet retardant polymer in the formulation development of sustained release of drugs, employing diclofenac sodium as a model drug was studied. Mouth dissolving tablets of metformin hydrochloride was prepared using mango gum powder as disintegrant.

### 8.5 NEEM GUM

Neem gum is obtained from the trees of *Azadirachta indica* belongs to the family Meliaceae. Each and every part of the tree (bark, leaves, root and fruit) serves a certain purpose. Neem gum contains mannose, glucosamine, arabinose, galactose, fructose, xylose and glucose. In a study Neem gum used as a binder in pharmaceutical dosage forms. A sustained release matrix tablets of Nimesulide using the fruit mucilage of *Azadirachta indica* was studied<sup>76</sup>.

## 2. CONCLUSION

The present article conclude that natural gum are safe, effective, low cost, ecological and environmental processing which are widely used in food and pharmaceutical processing. In the food industry they are used as thickening agents, gelling agents, emulsifying agents, and stabilizers. In other industries, they are also used as adhesives, binding agents, crystal inhibitors, clarifying agents, encapsulating agents, flocculating agents, swelling agents, & foam stabilizers.

## 3. ACKNOWLEDGEMENT

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## PULSINCAP: A COMPREHENSIVE REVIEW

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### ABSTRACT

Pulsatile drug delivery systems are established to deliver drug according to circadian behavior of diseases. This means that these systems will deliver drug at time when disease show it's most morbid and mortal state within a circadian cycle (24 hrs.). The product follow a sigmoidal drug release profile characterized by a time period of no release followed by a rapid and complete drug release. Thus drug can be delivered at right time, in right amount and at right site of action by use of such method. The probable profits of chronotherapeutics have been inspected and recognized for number of diseases like asthma, arthritis, cancer, diabetes, epilepsy, hypertension, ulcer, hypercholesterolemia etc. Various capsular, osmotic, single and multiple unit systems that are modulated by soluble or erodible polymer coatings, rupturable membranes are available in market. These systems are advantageous for diseases showing chronopharmacological behavior where night time dosing is required or for the drugs having high first pass effect or having site specific absorption in GIT, or for drugs with high risk of toxicity or tolerance. These systems also increase patient compliance by decreasing dosing frequency. Present review article discussed the reasons for development of pulsatile drug delivery system, types of the disease in which pulsatile release is required, classification, evaluations, advantages, limitation, and future aspects of pulsatile drug delivery system.

**KEYWORDS:** *Pulsincap, pulsatile drug delivery system, Ritalin, chronopharmaceutic.*

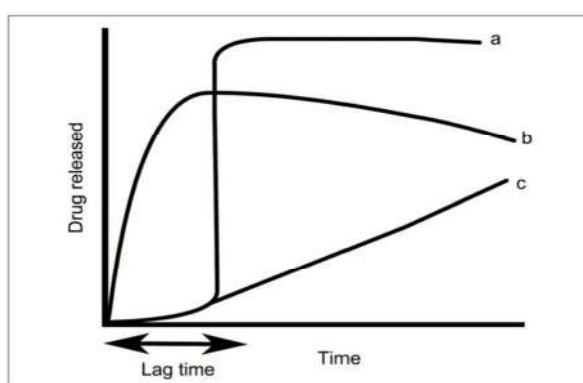
### 1. INTRODUCTION

#### PULSATILE DRUG DELIVERY SYSTEM

Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug molecules within a short time period instantly after a predetermined off-release period, i.e. Lag time. This delivery system goals to release the drug on programmed pattern i.e. at suitable time and at suitable site of action the pulsatile effect, i.e. the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time. Pulsatile systems are intended in a manner that the drug is available at the site of action at the right time in the right amount.<sup>1</sup> Pulsatile systems are reaching a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed based on the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. Products available as once-a-daily formulation based on Pulsatile release like Pulsincap, Ritalin, and Pulsys. In these systems, a most important and widely used pulsincap system is described here.<sup>2</sup> A pulsatile drug delivery

system that can be administered at night (before sleep) but that release drug in early morning would be a promising chronopharmaceutic system for the effective treatment of RA.<sup>3</sup> Circadian rhythm regulates many body functions in Circadian rhythm regulates many body functions in patterns, hormone production, etc. It has been reported that more shocks and heart attacks occur during morning hours. The level of cortisol is higher in the morning hours, and its release is reported to decline slowly during the day. Blood pressure is also reported to be high in the morning till late afternoon, and then drops off during night. Patients distress from osteoarthritis are pulsatile delivery systems are characterized by a reported to have less pain in the morning than night, programmed drug release, as constant blood levels of a while patients pain from rheumatoid arthritis feel more pain in the morning hours. The release of some drugs is chosen in pulses. A single dosage form offers an initial dose of drug followed by one release free interval, after which second dose of drug is released, which is followed by additional release-free interval and pulse of drug release the pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time. Such systems are also called time-controlled as the drug released is independent of the environment.<sup>4</sup>

**Fig 1. Drug release profiles. a) Sigmoidal release b) extended release c) extended release after lag time**



## 2. ADVANTAGES

1. Prolonged daytime or night time activity.
2. Reduced side effects
3. Dosage frequency.
4. Decrease in dose size.
5. Enhanced patient compliance.
6. Lower daily cost to patient due to fewer dosage units are essential by the patient.
7. Drug adapts to suit circadian rhythms of body functions or diseases.
8. Drug targeting to specific sites like colon.
9. Protection of mucosa from irritating drugs.
10. Drug loss is prevented by extensive first pass metabolism.

## 3. DISADVANTAGES

1. Absence of manufacturing reproducibility and efficacy.
2. Huge number of process variables.
3. Multiple formulation steps.
4. Advanced cost of production.
5. Essential of advanced technology.<sup>5</sup>

### d. CLASSIFICATION OF PDDS

Pulsatile drug delivery system can be broadly classified into three classes;

- d. Time controlled pulsatile drug delivery
- II. Stimuli induced pulsatile drug delivery

### III. Externally regulated pulsatile drug delivery

#### I. Time controlled pulsatile drug delivery

##### A. Single unit pulsatile system

1. Capsule based systems
    - E.g. Pulsincap system
  2. Capsular system based on Osmosis
    - a. 'PORT' System
    - b. System based on expandable orifice
    - c. Delivery by series of stops.
    - d. Pulsatile delivery by solubility modulation
  3. Pulsatile system with Erodible or soluble barrier coatings.
    - a. The chronotropic system
    - b. 'TIME CLOCK' System.
      - c. Compressed tablets
      - d. Multi-layered Tablets
  4. Pulsatile system with reputable coating
- ##### B. Multiparticulate / Multiple unit systems:
1. Pulsatile system with reputable coating
- E.g. Time –controlled Explosion system (TCES)
2. Osmotic based reputable coating system
    - E.g. Permeability controlled system
  3. Pulsatile delivery by change in membrane permeability E.g. Sigmoidal release system.

### II. Stimuli induced pulsatile drug delivery

1. Temperature-induced pulsatile release:
2. Chemical stimuli-induced pulsatile release:
  - Glucose-responsive insulin release devices
  - Inflammation-induced pulsatile release
  - Drug release from intelligent gels responding to antibody concentration.
  - Electric stimuli-responsive pulsatile release:

### III. Externally regulated pulsatile drug delivery:<sup>6</sup>

#### I. Time controlled pulsatile drug delivery

##### A. Single unit pulsatile system

1. Capsule based systems E.g. Pulsincap system

## 5. PULSINCAP SYSTEM

R. R. Scherer International Corporation, Michigan, US developed Pulsincap. This system covers of a water-insoluble capsule enclosing the drug reservoir. Seal the drug contents into the capsule body, a swell able hydrogel plug was used. It swelled, when this capsule came in contact with the dissolution fluid and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug.<sup>7</sup>

## 6. DEFINITION

Pulsincap is an oral drug delivery device which is intended to release the drug in a pulsed fashion at a predetermine time in the gastrointestinal tract or predetermine site in the body.<sup>8</sup>

Single-unit systems are mostly established in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a "Pulse" from the insoluble capsule body.<sup>9</sup>

## 7. PULSINCAP SYSTEM

### 7.1 PARTS OF PULSINCAP

1. Water Soluble Body
2. Water Soluble Cap

3. Acid Insoluble Cap
4. Hydrogel Plug
5. Drug Formulation.<sup>10</sup>

## 7.2 ADVANTAGES OF PULSINCAP

1. These are easy to handle and carry
2. They are beautiful in appearance
3. Pulsincap are made from gelatin and 31elatinehey are therapeutically inert
4. The drug having unpleasant odour and taste can be administered by enclosing these method
5. They are economical.<sup>11</sup>

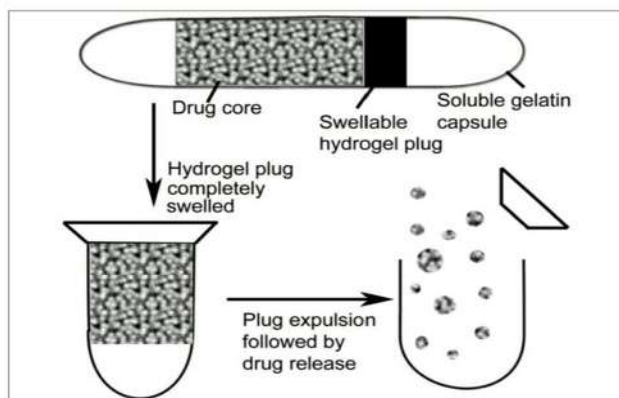
## 7.3 DISADVANTAGES

1. Hard to swallow in case of children and older people.
2. The concentrated solution which essential previous dilution are unstable for capsule because administered as such lead to irritation in to stomach
3. Costly
4. Not useful for efflorescent or deliquescent material
5. Hygroscopic drug cannot be filled in capsule
6. Less or no flexibility of dose.<sup>12</sup>

## 7.4 APPLICATION OF PULSINCAP

There are number of disease in which pulsincap drug are used. They are,

1. Rheumatoid Arthritis
2. Asthma
3. CVS Disease
4. Diabetes Mellitus
5. Peptic Ulcer
6. Cancer
7. Colonoc Delivery
8. CNS disorder



### *Rheumatoid arthritis*

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder. The cardinal symbols of rheumatoid arthritis are stiffness, swelling and pain of one or more joints of the body normally most severe in the morning. Rheumatoid arthritis shows a marked circadian difference in its symptoms. A group of British volunteers self-assessed the pain and stiffness of affected finger joints every 2 to 3 h daily for several sequential days. They also measured the boundary of the arthritic joints to gauge the amount of their swelling, and they performed grip strength tests to determine the effect of the arthritic condition on the hands. Ratings of the severity of joint pain swelling and stiffness were about 3 times higher between 08:00 and 11:00 am than at bedtime. In similarity, hand strength was lower by as much as 30% in the morning than at night. This is classic of rheumatoid arthritis sufferers. The symptoms of rheumatoid arthritis are always poorer in the morning. The danger of severe side effects from these medications increases when they are taken more than 8 to 9 h after the customary time of awakening, after 15:00 pm for most people. The later in

the day these medications are taken, the greater the risk of side effects. If the relief from the morning symptoms of rheumatoid arthritis sufferers is not attained by a once-day morning schedule, an increase in the morning dose is recommended. The results of one study suggest an early afternoon once-a-day treatment schedule might be beneficial for those people who fail to get significant relief from the morning pain and stiffness of rheumatoid arthritis when taking medicine in the morning.<sup>13</sup>

### ***Osteoarthritis***

The circadian rhythm of pain and stiffness in osteoarthritis varies from that of rheumatoid arthritis. Osteoarthritis is a degenerative disease of the joints and is the commonest of all joint diseases, affecting nearly everyone at least to some degree by age 70. The weight bearing joints of the hip, knee, back, toes and fingers are mostly affected. The pain of osteoarthritis sufferers is typically less powerful in the morning than in the afternoon or evening. This is illustrated by the findings of a Canadian study of 20 persons anxious with osteoarthritis of the knee. Participants did pain self-ratings 10 times daily for 7 repeated days. For the group as a whole, pain intensity was rated about 40 percent higher on average between 20:00 pm and midnight than between 06:00 and 10:00 am. However, the precise nature of the 24 h pattern of pain differed from person to person. In 40 percent, pain was greatest between 14:00 and 20:00 pm, and in 25%, it was highest between 20:00 pm and midnight. In 15 %, it peaked at two different times of the day, and in 20 %, the level of pain exhibited no day-night variation whatsoever. The successful treatment of osteoarthritis requires that medications be taken at the right time.

### ***Asthma***

The chronotherapy of asthma has been broadly studied. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases increasingly at night in asthmatic patients. Circadian changes are seen in normal lung function, the later reaches a low point in the early morning hours. This dip is particularly noticeable in people with asthma. Because bronchoconstriction and exacerbation of symptoms vary in a circadian fashion, asthma is well suited for chronotherapy. Chronotherapies have been studied for asthma with oral corticosteroids, theophylline, and B2-agonists.

### ***CVS disease***

In cardiovascular disease capillary resistance and vascular reactivity are greater in the morning and decreases latter in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Because of this reason the frequencies of myocardial infarction and of sudden cardiac death are more during a period from morning to noon. Ambulatory blood pressure measurements show important circadian variation to characterize blood pressure. This variation is affected by a variety of external factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, hematological and renal variables. Increased heart rate, blood pressure, imbalanced autonomic tone, circulating level of catecholamine controlling the cardiac arrhythmias show important circadian variation and trigger the genesis of the circadian pattern of cardiac arrhythmias. Atrial arrhythmias appear to exhibit circadian pattern usually with a higher frequency in the daytime and lower frequency in the night time with the abnormal foci under the same long-term autonomic regulation as normal pacemaker tissue.

### ***Diabetes mellitus***

There circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type 1 diabetes has been well recognized. The aim of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion. Providing basal insulin exogenously to patients with diabetes inhibits hepatic glucose production. Exogenous administration of mealtime doses promotes peripheral glucose uptake (i.e. it prevents postprandial increases in blood glucose concentration) as well as reducing hepatic glucose release.

### ***Cancer***

Human and animal studies propose that chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal tissue. The rhythmic circadian changes in tumor blood flow and cancer growth are related both when



tumors are small and growing most rapidly and when they are larger and growing more slowly. The blood flow to tumors and tumor growth rate are each up to threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. Clinical studies indicating whether circadian chemotherapy timing meaningfully affects drug toxicity patterns and severity, maximum tolerated dose, average dose intensity, tumor response quality and frequency and the survival of patients with cancer, have been indicated since the pioneer work of Haus et al. on leukemic mice.

## 7.5 METHOD OF PREPARATION OF PULSINCAP

### POLYMER USED IN PULSINCAP

#### ***Guar Gum***

##### ***Category:***

1. Stabilizing agent
2. Suspending agent
3. Tablet binder and disintegrant

##### ***Uses:***

1. In colonic drug delivery
2. Used in cosmetic, food and pharmaceutical formulations.

#### ***Maltodextrin***

##### ***Category:***

1. Stabilizing agent
2. Tablet binder
3. Viscosity enhancer

##### ***Uses:***

1. Tablet film former in aqueous film coating
2. Carrier to increase the viscosity of solution
3. Osmolarity regulator for solutions.

#### ***PVP k30***

##### ***Category***

1. Stabilizing agent
2. Tablet binder and disintegrant
3. Dissolution enhancer
4. Suspending agent

##### ***Uses***

1. Solubilizer
2. Coating agent

## 7.6 EXCIPIENT USED IN PULSINCAP

### HPMC K100 M

##### ***Category***

1. Controlled release agent
2. Film former
3. Suspend agent
4. Viscosity enhancer
5. Sustained release agent

##### ***Uses :***

1. Emulsifier
2. Used in oral, ophthalmic, nasal and topical pharmaceutical formulations.
3. Suspend agent in topical gels and ointments.

#### ***Sodium Starch Glycolate***

##### ***Category***

Tablet and capsule disintegrant

##### ***Uses***

Super disintegrant

### **Lactose**

**Category** 1.Dry powder inhaler 2.Carrier

**Uses-** Tablet and capsule diluent.

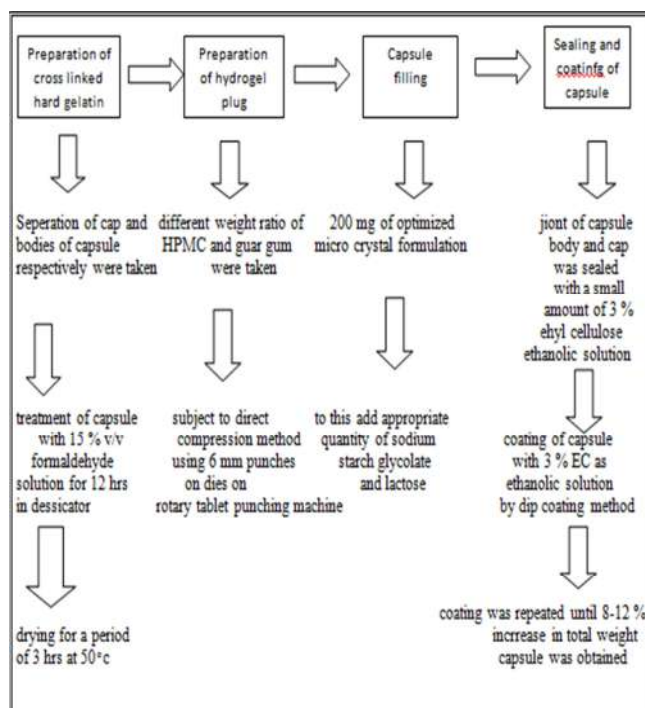
## **7.7 COMPOSITION OF PULSINACP**

1. Microcrystal
2. Sodium starch glycolate
3. Lactose

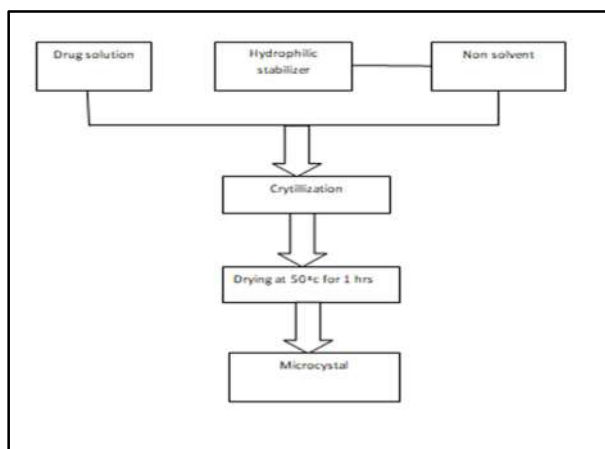
## **COMPOSITION OF HYDROGEL PLUG**

1. HPMC
2. Guar gum

### **a. PREPARATION**



## **PREPARATION OF MICROCRYSTAL BY RAPID SOLVENT CHANGE METHOD**



## **7.9 EVALUATION PARAMETER OF PULSINACP:**

1. Solubility studies
2. Disintegration test
3. In vitro drug release studies

4. Evaluation of hydrogel plugs
  - a. Thickness test
  - b. Friability test
  - c. Weight variation test
  - d. Hardness test
5. Evaluation of microcrystal
  - a. Percentage crystal yield
  - b. Percentage drug content
  - c. In vitro drug release studies
  - d. Particle size distribution.

### **Solubility Studies**

Solubility is defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response.

Therapeutic effectiveness of drug depends upon the bioavailability and ultimately upon the solubility of drug molecules.

### ***Techniques of solubility enhancement***

- a. Particle size reduction
- b. Modification of crystal habit
- c. Drug dispersion in carrier
- d. Complexation
- e. Solubilization by surfactants

### ***Application***

1. Solubility is a fundamental importance in a large number of scientific disciplines and practical applications to the use of medicines.
2. Solubility is representing a fundamental concept in field of research such as chemistry, physics. Pharmaceutical and biological science.

### ***d. Disintegration Test***

Solution is break down of the tablet into smaller particles or granules, a process called granulation. The U.S.P disintegration test apparatus use for disintegration determination. To test for disintegration time one tablet is placed in each tube and the basket rack is positioned in a 1-Litre beaker of water. Simulated gastric fluid or simulated intestinal fluid at  $37 \pm 2^\circ\text{C}$  such that the tablets remain 2.5 cm below the surface liquid on their upward movement and not closer than 2.5 cm from the bottom of beaker in their downward movement. Move the basket containing tablet up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of tablet can be prevented by placing perforated plastic disc on each tablet of the beaker.

### ***In Vitro Drug Release Studies***

Performed outside a living organism are used to study the transport of drugs through different types of membranes or biological membranes or biological materials.

Such experiment may utilized

1. Diffusion cells
2. Laboratory animal
3. Cell culture.

### ***Evaluation of Hydrogel Plugs.***

- a. Thickness test
- b. Friability test
- c. Weight variation test
- d. Hardness test

**Thickness test**

Thickness testing to determine the material thickness and to measure the thickness of coating or lining

Ex. Ultrasonic testing.

**Friability test**

(The condition of being friable)

Friability testing is a method ,which is employed to determine physical strength of uncoated tablets upon mechanical shock and attrition.

Ex. Rochefribilitor.

**Weight variation test**

Weight uniformity was carried out to ensure that each of tablet contains the proper amount of drug. The test carried out by using tablet.

Ex. Digital balance.

**Hardness test**

The purpose of hardness testing is to determine the suitability of a material, or the particular treatment to which the material has been subjected.

Ex. Pfizer hardness tester.

**5. MARKETED FORMULATION**

**Table 1: Marketed Formulation**

| TECHNOLOGY                 | PROPRIETARY NAME AND DOSAGE FORM | MECHANISM                   | API                            | DISEASE      |
|----------------------------|----------------------------------|-----------------------------|--------------------------------|--------------|
| Three dimentional printing | Their Form                       | Externally regulated system | Diclofenac sodium              | Inflammation |
| PulsincapTM                | PulsincapTM                      | Rupturable system           | Dofetilide                     | Hypertension |
| DIFFUCAPS                  | Innopran                         | Multiparticulate system     | Verapamil HCL, propranolol HCL | Hypertension |
| OROS                       | Covera-H5                        | Osmotic mechanism           | Verapamil HCL                  | Hypertension |

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## SP-6

# FORMULATION, EVALUATION AND OPTIMIZATION OF ORODISPERSIBLE TABLETS OF NAPROXEN SODIUM 100 MG BY USING VARIOUS SUPER DISINTEGRANT

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## ABSTRACT

Among the different type of route of administration oral route for drug administration is most common route in which Oro dispersible tablet is preferred for the patient which are unconscious, weak or for immediate control. The tablet gets dispersed in mouth cavity without water, present study deals with formulation of Naproxen sodium mouth dissolving tablets using super disintegrants. Naproxen sodium is analgesic and NSAID, used for the treatment of pain and inflammation caused by different condition such as osteoarthritis, rheumatoid arthritis and menstrual cramps. However gastric discomfort caused by naproxen sodium result in poor patient compliance associated with it conventional doses form but now days Naproxen sodium MDTs produces rapid onset of action and minimise gastric discomfort associated with it. Thus improves patient compliance, enhance bioavailability and reduces the dose of drug. MDTs are formulated by direct compression method using super disintegrants in different proportion. The powder blend is subjected to pre-compression evaluation parameters like bulk density, true density, and tapped density and angle of repose. Formulations are evaluated for weight variation, hardness, wetting time, water absorption time, disintegration time. And in vitro dissolution studies and all formulations complies Pharmacopoeias standards. The tablets are evaluated and result compared for all nine formulations the most efficacious super disintegrants for MDTs of Naproxen sodium as suggested by the dispersion time, disintegration time and drug dissolution profiles. The concept of Mouth Dissolve Drug Delivery System emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate or dissolve to release a drug as soon as they come in contact with saliva in oral cavity, thus obviating the need for water during administration, an attribute that makes them highly attractive for paediatric and geriatric patients.

**KEYWORDS:** Oro dispersible Tablet, Naproxen Sodium, cross Carmillose Sodium, Sodium starch glycolate, Cross povidone

## 1. INTRODUCTION

Among the all Analgesic drugs, Naproxen Sodium is a non-steroidal anti-inflammatory agent useful for the treatment of pain inflammation and fever caused by the conditions such as arthritis, migraine and menstrual cramps. It has a good solubility in water and saliva and inherent ability to permeate through oral mucosal tissue, drug moiety is weak acidic so remains in partially none ionised form at oral pH which favour pre gastric absorption. This parameter makes the drug ideal character for MTD.<sup>1,2</sup> These tablets display a fast and spontaneous de-aggregation in mouth, soon after the contact with saliva, the active agent can thus



rapidly dissolved in the saliva and be absorbed through whatever membrane it encounters, during deglutition, unless it is protected from pre-gastric absorption. To fulfil these requirements tablets must be highly porous, incorporating hydrophilic excipients, able to rapidly absorb water for a rapid de-aggregation of the matrix. Different technological techniques, such as freeze drying, moulding and direct compression currently employed to prepare the formulation of this type present in the pharmaceutical market. The aim and objective of the present study is to develop and evaluate oro dispersible or mouths dissolving tablet of Naproxen sodium and enhance the onset of action of Naproxen and also to study the influence of excipients on the physical characteristics of the tablets by applying two level three factor factorial designs taking Naproxen as model drug.<sup>3,14,15</sup>

## 2. MATERIAL AND METHOD

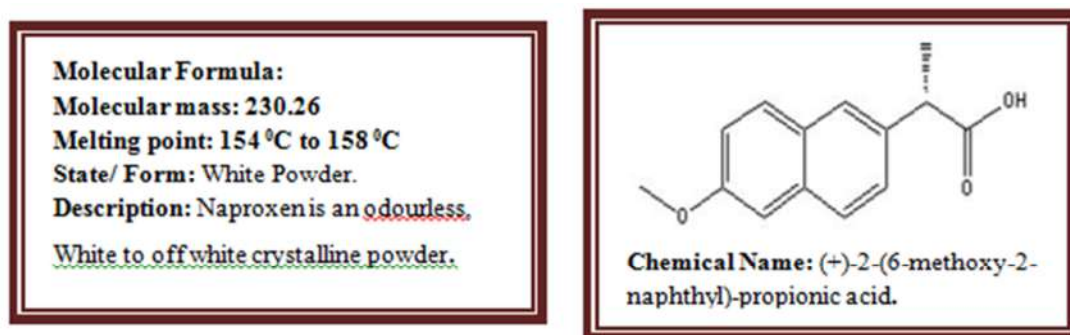


Fig. 1: Structure of Naproxen

## 3. MATERIAL AND THEIR USE WITH OBTAINED SOURCES<sup>4-6</sup>

Table 1: Materials with their Uses and Sources

| S. No. | Material                        | Use of ingredients | Sources  |
|--------|---------------------------------|--------------------|--|
| 1      | Naproxen Sodium                 | Active Ingredients | Iosis Pharma, Baddi, Solan H.P.  |
| 2      | Lactose                         | Diluents           | Pacific India.<br><br>A Pharmaceutical exporter, Village-Dhana, Bagbania Nalagarh, Solan, (H.P.) |
| 3      | Microcrystalline cellulose      | Diluents           |  |
| 4      | Sodium starch Glycolate         | Disintegrants      |  |
| 5      | Cross Carmillose sodium         | Disintegrants      |  |
| 6      | Cross povidone                  | Disintegrants      |  |
| 7      | Aspartame                       | Sweetener          |  |
| 8      | Methyl Paraben & Propyl paraben | Preservative       |  |
| 9      | Mannitol                        | Diluents/Sweetener |  |
| 10     | Starch Direct compressible      | Antiadhrants       |  |
| 11     | Magnesium stearate              | Glidant            |  |
| 12     | Talc                            | Lubricants         |  |

## 4. PREPARATION OF NAPROXEN 100 MG ORO DISPERSIBLE TABLETS BY DIRECT COMPRESSION METHOD<sup>7</sup>

Table 2: Preparation of Naproxen 100 mg oro dispersible Tablets by direct Compression Method

| s. N o | Ingredients     | C1 (mg) | C2 (mg) | C3 (mg) | C4 (mg) | C5 (mg) | C6 (mg) | C7 (mg) | C8 (mg) | C9 (mg) |
|--------|-----------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| 1      | Naproxen Sodium | 100     | 100     | 100     | 100     | 100     | 100     | 100     | 100     | 100     |

|    |                         |            |            |           |            |            |           |            |            |           |
|----|-------------------------|------------|------------|-----------|------------|------------|-----------|------------|------------|-----------|
| 2  | Cross Carmillose Sod.   | 30<br>(5%) | 18<br>(3%) | 6<br>(1%) | ---        | ---        | ---       | ---        | ---        | ---       |
| 3  | Sodium starch Glycolate | ---        | ---        | ---       | 30<br>(5%) | 18<br>(3%) | 6<br>(1%) | ---        | ---        | ---       |
| 4  | Cross povidone          | ---        | ---        | ---       | ---        | ---        | ---       | 30<br>(5%) | 18<br>(3%) | 6<br>(1%) |
| 5  | Lactose                 | 90         | 102        | 114       | 90         | 102        | 114       | 90         | 102        | 114       |
| 6  | Aspartame               | 50         | 50         | 50        | 50         | 50         | 50        | 50         | 50         | 50        |
| 7  | Methyl Paraben          | 5          | 5          | 5         | 5          | 5          | 5         | 5          | 5          | 5         |
| 8  | Propyl Paraben          | 1          | 1          | 1         | 1          | 1          | 1         | 1          | 1          | 1         |
| 9  | Mannitol                | 100        | 100        | 100       | 100        | 100        | 100       | 100        | 100        | 100       |
| 10 | Starch DC grade         | 100        | 100        | 100       | 100        | 100        | 100       | 100        | 100        | 100       |
| 11 | Micro crystalline ce.   | 100        | 100        | 100       | 100        | 100        | 100       | 100        | 100        | 100       |
| 12 | Magnesium stearate      | 12         | 12         | 12        | 12         | 12         | 12        | 12         | 12         | 12        |
| 13 | Talc                    | 12         | 12         | 12        | 12         | 12         | 12        | 12         | 12         | 12        |
|    | Total                   | 600        | 600        | 600       | 600        | 600        | 600       | 600        | 600        | 600       |

All the ingredients of formulation i.e. Active ingredients and additives were passed through 60 # sieve separately, Magnesium stearate and talc through 40 #, The ingredient were mixed by geometrical mixing and Tablet were compressed on 12 mm sizes of flat round punch to get tablet by using Rimeck Single rotary compression machine.<sup>13</sup>

#### 4. RESULT AND DISCUSSION:

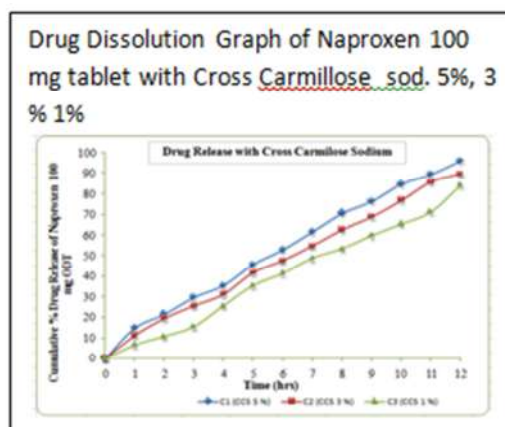
##### POST COMPRESSION PARAMETER AND STUDIES<sup>8-12</sup>

**Table 3: Post Compression Parameter and Studies**

| Formulation code | Assay of Drug (%) | Disintegration Time (Sec) | Dissolution (%) | Hardness (Kg/cm <sup>2</sup> ) | Friability (%) | Thickness (mm) |
|------------------|-------------------|---------------------------|-----------------|--------------------------------|----------------|----------------|
| C1 (CCS 5 %)     | 98.32             | 6-9                       | 95.85           | 4.60                           | 0.49           | 4.05           |
| C2 (CCS 3 %)     | 98.62             | 8-12                      | 89.59           | 4.30                           | 0.67           | 4.07           |
| C3 (CCS 1 %)     | 98.60             | 11-15                     | 84.20           | 4.20                           | 0.39           | 3.92           |
| C4 (SSG 5 %)     | 98.32             | 11-15                     | 91.27           | 4.40                           | 0.40           | 4.00           |
| C5 (SSG 3 %)     | 98.70             | 16-20                     | 87.85           | 4.30                           | 0.79           | 3.96           |
| C6 (SSG 1%)      | 98.59             | 19-24                     | 79.48           | 4.20                           | 0.68           | 3.94           |
| C7 (CP 5 %)      | 98.28             | 16-22                     | 86.59           | 4.40                           | 0.89           | 3.96           |
| C8 (CP 3 %)      | 98.38             | 20-24                     | 81.57           | 4.00                           | 0.70           | 4.04           |
| C9 (CP 1 %)      | 98.32             | 23-27                     | 75.91           | 3.90                           | 0.64           | 4.06           |

**Drug dissolution Data of Naproxen 100 mg Tablet with Cross carmillose sodium**

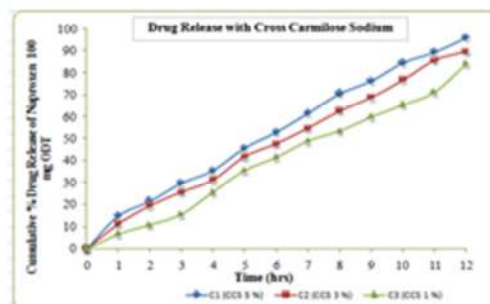
| Time (hrs) | C1 (CCS 5 %) | C2 (CCS 3 %) | C3 (CCS 1 %) |
|------------|--------------|--------------|--------------|
| 0          | 0            | 0            | 0            |
| 1          | 14.85        | 11.28        | 6.69         |
| 2          | 21.54        | 19.58        | 10.63        |
| 3          | 29.74        | 25.59        | 15.53        |
| 4          | 35.41        | 31.27        | 25.69        |
| 5          | 45.59        | 41.83        | 35.59        |
| 6          | 52.82        | 47.52        | 41.59        |
| 7          | 61.53        | 54.62        | 48.92        |
| 8          | 70.59        | 62.74        | 53.42        |
| 9          | 76.19        | 68.93        | 59.93        |
| 10         | 84.59        | 76.89        | 65.48        |
| 11         | 89.39        | 85.69        | 71.28        |
| 12         | 95.85        | 89.59        | 84.2         |



Drug dissolution Data of Naproxen 100 mg Tablet with Cross carmillose sodium

| Time (hrs) | Cumulative % Drug Release |              |              |
|------------|---------------------------|--------------|--------------|
|            | C1 (CCS 5 %)              | C2 (CCS 3 %) | C3 (CCS 1 %) |
| 0          | 0                         | 0            | 0            |
| 1          | 14.85                     | 11.28        | 6.69         |
| 2          | 21.54                     | 19.58        | 10.63        |
| 3          | 29.74                     | 25.59        | 15.53        |
| 4          | 35.41                     | 31.27        | 25.69        |
| 5          | 45.59                     | 41.83        | 35.59        |
| 6          | 52.82                     | 47.52        | 41.59        |
| 7          | 61.53                     | 54.62        | 48.92        |
| 8          | 70.59                     | 62.74        | 53.42        |
| 9          | 76.19                     | 68.93        | 59.93        |
| 10         | 84.59                     | 76.89        | 65.48        |
| 11         | 89.39                     | 85.69        | 71.28        |
| 12         | 95.85                     | 89.59        | 84.2         |

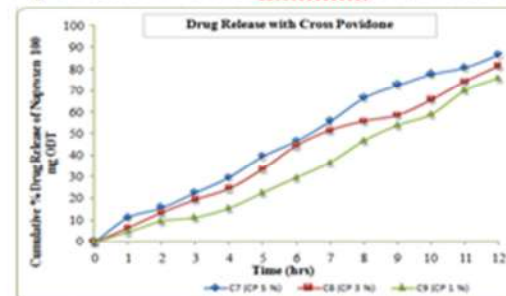
Drug Dissolution Graph of Naproxen 100 mg tablet with Cross Carmillose sod. 5%, 3 % 1%



Drug dissolution Data of Naproxen 100 mg Tablet with Cross Povidone

| Time (hrs) | Cumulative % Drug Release |             |             |
|------------|---------------------------|-------------|-------------|
|            | C7 (CP 5 %)               | C8 (CP 3 %) | C9 (CP 1 %) |
| 0          | 0                         | 0           | 0           |
| 1          | 11.22                     | 6.52        | 4.52        |
| 2          | 15.67                     | 13.52       | 9.57        |
| 3          | 22.69                     | 19.52       | 11.29       |
| 4          | 29.57                     | 24.59       | 15.59       |
| 5          | 39.58                     | 33.57       | 22.69       |
| 6          | 46.59                     | 44.59       | 29.48       |
| 7          | 55.69                     | 51.59       | 36.59       |
| 8          | 66.59                     | 55.82       | 46.81       |
| 9          | 72.61                     | 58.59       | 53.96       |
| 10         | 77.69                     | 65.89       | 58.96       |
| 11         | 80.59                     | 74.28       | 70.18       |
| 12         | 86.59                     | 81.57       | 75.91       |

Drug Dissolution Graph of Naproxen 100 mg tablet with Cross Povidone 5%, 3 % 1%



## 7. CONCLUSION

After completion of this experiment the results obtained and conclude that development of oro dispersible tablet of Naproxen sodium 100 mg formulation by using various super disintegrants i.e. Cross Carmillose sodium, cross Povidone, Sodium starch glycolate gives results are mentioned below:

1. Naproxen Sodium Active drug stable with different excipients.
2. Fast Disintegrating tablets of Naproxen Sodium 100 were successfully prepared by direct compression method.
3. The flow property of the granules of nine batches (C1, to C9) is observed and concludes C1 containing the CCS 5 % tablets is better.
4. The hardness of compressed tablet by direct compression method found in the rage of 3.9 to 4.6 kg/cm<sup>2</sup>.
5. The Thickness of the prepared tablets of all 5 formulations was found between 3.92 mm. to 4.06 mm.
6. The Friability of the compressed tablet found within the range i.e. less than 1%. Maximum Friability for C7 contains 5 % Cross Povidone is 0.89%.
7. The in vitro disintegration studies are found to be in 6 to 27 seconds. Formulation C1 contains 5 % CCS show in vitro disintegration time i.e. 6-9 seconds.
8. On the basis of disintegration time formulation C1 with 5 % CCS which facilitate the faster disintegration in the mouth. The *in-vitro* Percentage drug releases from fast dissolving tablets of Naproxen Sodium 100 mg prepared by direct compression method were found to be in the range of 98.32 %. Hence, finally it was concluded that the prepared oro dispersible tablets of Naproxen Sodium 100 mg may prove to be potential candidate for effective fast disintegrating tablet dosage form.

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## FORMULATION, EVALUATION AND OPTIMIZATION OF ORODISPERSIBLE TABLETS OF NAPROXEN SODIUM 250 MG BY USING VARIOUS SUPER DISINTEGRANT

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### ABSTRACT

Among the different type of route of administration oral route for drug administration is most common route in which Oro dispersible tablet is preferred for the patient which are unconscious, weak or for immediate control. The tablet gets dispersed in mouth cavity without water, present study deals with formulation of Naproxen sodium mouth dissolving tablets using super disintegrants. Naproxen sodium is analgesic and NSAID, used for the treatment of pain and inflammation caused by different condition such as osteoarthritis, rheumatoid arthritis and menstrual cramps. However gastric discomfort caused by naproxen sodium result in poor patient compliance associated with it conventional doses form but now days Naproxen sodium MDTs produces rapid onset of action and minimise gastric discomfort associated with it. Thus improves patient compliance, enhance bioavailability and reduces the dose of drug. MDTs are formulated by direct compression method using super disintegrants in different proportion. The powder blend is subjected to pre-compression evaluation parameters like bulk density, true density, and tapped density and angle of repose. Formulations are evaluated for weight variation, hardness, wetting time, water absorption time, disintegration time. And in vitro dissolution studies and all formulations complies Pharmacopoeias standards. The tablets are evaluated and result compared for all nine formulations the most efficacious super disintegrants for MDTs of Naproxen sodium as suggested by the dispersion time, disintegration time and drug dissolution profiles. The concept of Mouth Dissolve Drug Delivery System emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate or dissolve to release a drug as soon as they come in contact with saliva in oral cavity, thus obviating the need for water during administration, an attribute that makes them highly attractive for paediatric and geriatric patients. Difficulty in swallowing conventional tablets and capsules is common among all age groups especially on elderly and dysphasic patients. Elderly patients may find the administration of the conventional oral dosage forms difficult as they regularly require medicines to maintain healthy life. Children may also have difficulty in ingesting because of their under developed muscular nervous system. The problem of swallowing tablets is also evident in travelling patients who may not have ready access to water. Aforementioned problems can be resolved by means of Mouth Dissolving Tablets. Some tablets are designed to dissolve in saliva within few seconds, and are true fast- dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed as fast disintegrating tablets, as they may take about to disintegrate completely.



**KEYWORDS:** Oro dispersible Tablet, Naproxen Sodium, cross Carmillose Sodium, Sodium starch glycolate, Cross povidone.

## 1. INTRODUCTION

Among the all Analgesic drugs, Naproxen Sodium is a non-steroidal anti-inflammatory agent useful for the treatment of pain inflammation and fever caused by the conditions such as arthritis, migraine and menstrual cramps. It has a good solubility in water and saliva and inherent ability to permeate through oral mucosal tissue, drug moiety is weak acidic so remains in partially none ionised form at oral pH which favour pre gastric absorption.<sup>1</sup> This parameter makes the drug ideal character for MTD. These tablets display a fast and spontaneous de-aggregation in mouth, soon after the contact with saliva, the active agent can thus rapidly dissolved in the saliva and be absorbed through whatever membrane it encounters, during deglutition, unless it is protected from pre-gastric absorption. To fulfil these requirements tablets must be highly porous, incorporating hydrophilic excipients, able to rapidly absorb water for a rapid de-aggregation of the matrix.<sup>2</sup> Different technological techniques, such as freeze drying, moulding and direct compression currently employed to prepare the formulation of this type present in the pharmaceutical market. The aim and objective of the present study is to develop and evaluate oro dispersible or mouths dissolving tablet of Naproxen sodium and enhance the onset of action of Naproxen and also to study the influence of excipients on the physical characteristics of the tablets by applying two level three factor factorial designs taking Naproxen as model drug.<sup>3-5</sup>

## 2. MATERIAL AND METHOD<sup>6-7</sup>

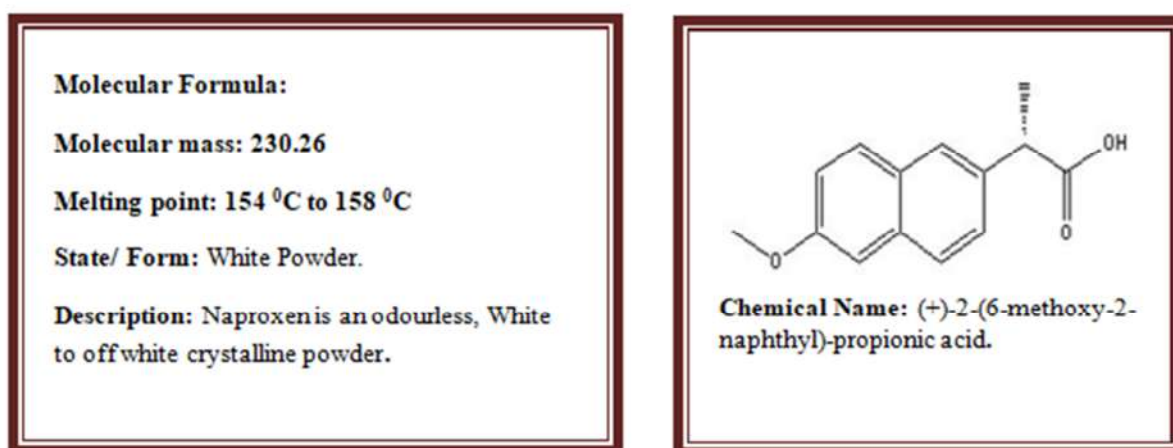


Fig. 1 Structure of Naproxen

## 2. MATERIAL AND THEIR USE WITH OBTAINED SOURCES:<sup>8</sup>

**Table 1: Materials with their Uses and Sources**

| S. No. | Material                        | Use of ingredients | Sources  |
|--------|---------------------------------|--------------------|--|
| 1      | Naproxen Sodium                 | Active Ingredients | Iosis Pharma, Baddi, Solan H.P.  |
| 2      | Lactose                         | Diluents           | Pacific India.<br><br>A Pharmaceutical exporter, Village-Dhana, Bagbania Nalagarh, Solan, (H.P.) |
| 3      | Microcrystalline cellulose      | Diluents           |  |
| 4      | Sodium starch Glycolate         | Disintegrants      |  |
| 5      | Cross Carmillose sodium         | Disintegrants      |  |
| 6      | Cross povidone                  | Disintegrants      |  |
| 7      | Aspartame                       | Sweetener          |  |
| 8      | Methyl Paraben & Propyl paraben | Preservative       |  |
| 9      | Mannitol                        | Diluents/Sweetener |  |



|    |                            |              |  |
|----|----------------------------|--------------|--|
| 10 | Starch Direct compressible | Antiadhrants |  |
| 11 | Magnesium stearate         | Glidant      |  |
| 12 | Talc                       | Lubricants   |  |

### 3. PREPARATION OF NAPROXEN TABLET BY DIRECT COMPRESSION METHOD:<sup>9-10</sup>

**Table 2: Preparation Of Naproxen Tablet by Direct Compression Method**

| Sr<br>·<br>N<br>o | Ingredients             | C1<br>(mg) | C2<br>(mg) | C3<br>(mg) | C4<br>(mg) | C5<br>(mg) | C6<br>(mg) | C7<br>(mg) | C8<br>(mg) | C9<br>(mg) |
|-------------------|-------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| 1                 | Naproxen Sodium         | 250        | 250        | 250        | 250        | 250        | 250        | 250        | 250        | 250        |
| 2                 | Cross Carmillose Sod.   | 30<br>(5%) | 18<br>(3%) | 6<br>(1%)  | ---        | ---        | ---        | ---        | ---        | ---        |
| 3                 | Sodium starch Glycolate | ---        | ---        | ---        | 30<br>(5%) | 18<br>(3%) | 6<br>(1%)  | ---        | ---        | ---        |
| 4                 | Cross povidone          | ---        | ---        | ---        | ---        | ---        | ---        | 30<br>(5%) | 18<br>(3%) | 6<br>(1%)  |
| 5                 | Lactose                 | 90         | 102        | 114        | 90         | 102        | 114        | 90         | 102        | 114        |
| 6                 | Aspartame               | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         |
| 7                 | Methyl Paraben          | 5          | 5          | 5          | 5          | 5          | 5          | 5          | 5          | 5          |
| 8                 | Propyl Paraben          | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 1          |
| 9                 | Mannitol                | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         |
| 10                | Starch DC grade         | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         |
| 11                | Micro crystalline ce.   | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         |
| 12                | Magnesium stearate      | 12         | 12         | 12         | 12         | 12         | 12         | 12         | 12         | 12         |
| 13                | Talc                    | 12         | 12         | 12         | 12         | 12         | 12         | 12         | 12         | 12         |
|                   | Total                   | 600        | 600        | 600        | 600        | 600        | 600        | 600        | 600        | 600        |

All the ingredients of formulation i.e. Active ingredients and additives were passed through 60 # sieve separately, Magnesium stearate and talc through 40 #, The ingredient were mixed by geometrical mixing and Tablet were compressed on 12 mm sizes of flat round punch to get tablet by using Rimeck Single rotary compression machine.

### 5. RESULT AND DISCUSSION: POST COMPRESSION PARAMETER AND STUDIES<sup>11-15</sup>

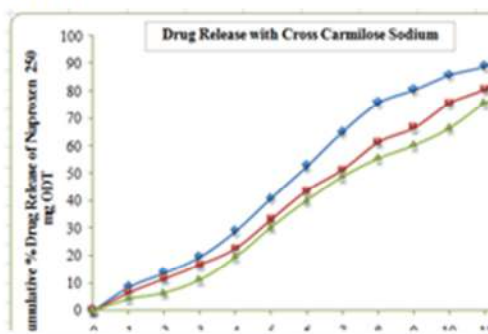
**Table 3: Post Compression Parameter and Studies**

| Formulation code | Assay of Drug (%) | Disintegration Time (Sec) | Dissolution (%) | Hardness (Kg/cm2) | Friability (%) | Thickness (mm) |
|------------------|-------------------|---------------------------|-----------------|-------------------|----------------|----------------|
| C1 (CCS 5 %)     | 98.88             | 8-11                      | 93.85           | 4.5               | 0.45           | 4.02           |
| C2 (CCS 3 %)     | 98.76             | 10-14                     | 88.59           | 4.4               | 0.62           | 4.05           |
| C3 (CCS 1 %)     | 98.62             | 16-21                     | 81.25           | 4.1               | 0.32           | 3.98           |
| C4 (SSG 5 %)     | 98.45             | 12-17                     | 89.12           | 4.3               | 0.48           | 4.01           |
| C5 (SSG 3 %)     | 98.76             | 15-21                     | 83.52           | 4.2               | 0.75           | 3.99           |
| C6 (SSG 1%)      | 98.56             | 19-27                     | 77.68           | 4.1               | 0.61           | 3.91           |
| C7 (CP 5 %)      | 98.42             | 16-21                     | 85.41           | 4.3               | 0.81           | 3.99           |
| C8 (CP 3 %)      | 98.24             | 22-27                     | 80.52           | 4.4               | 0.83           | 4.01           |
| C9 (CP 1 %)      | 98.45             | 29-33                     | 74.82           | 4.2               | 0.74           | 4.08           |

Drug dissolution Data of Naproxen 250 mg Tablet with Cross carmillose sodium

| Time (hrs) | Cumulative % Drug Release |              |              |
|------------|---------------------------|--------------|--------------|
|            | C1 (CCS 5 %)              | C2 (CCS 3 %) | C3 (CCS 1 %) |
| 0          | 0                         | 0            | 0            |
| 1          | 8.57                      | 6.51         | 4.32         |
| 2          | 13.59                     | 11.52        | 6.35         |
| 3          | 19.51                     | 16.57        | 11.21        |
| 4          | 28.93                     | 22.57        | 19.58        |
| 5          | 40.87                     | 33.28        | 30.5         |
| 6          | 52.61                     | 43.69        | 40.21        |
| 7          | 64.98                     | 51.27        | 48.81        |
| 8          | 75.62                     | 61.28        | 55.51        |
| 9          | 80.34                     | 66.59        | 60.21        |
| 10         | 85.68                     | 75.41        | 66.51        |
| 11         | 88.95                     | 80.59        | 75.51        |
| 12         | 93.85                     | 88.59        | 81.21        |

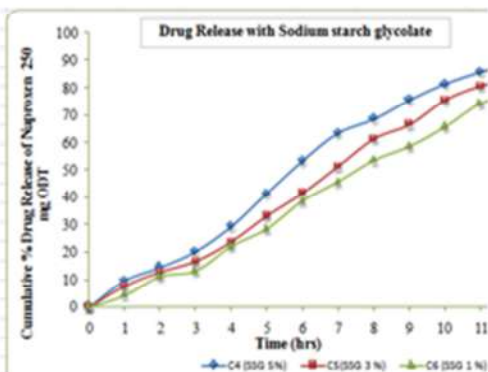
Drug Dissolution Graph of Naproxen 250 mg tablet with Cross Carmillose sod. 5%, 3 % 1%



Drug dissolution Data of Naproxen 250 mg Tablet with Sodium starch Glycolate

| Time (hrs) | Cumulative % Drug Release |              |             |
|------------|---------------------------|--------------|-------------|
|            | C4 (SSG 5%)               | C5 (SSG 3 %) | C6 (SSG 1%) |
| 0          | 0                         | 0            | 0           |
| 1          | 9.51                      | 7.59         | 4.32        |
| 2          | 14.52                     | 12.59        | 11.2        |
| 3          | 20.15                     | 16.57        | 13.2        |
| 4          | 29.28                     | 23.59        | 22.2        |
| 5          | 41.29                     | 33.28        | 28.5        |
| 6          | 53.2                      | 41.59        | 38.5        |
| 7          | 63.28                     | 51.27        | 45.5        |
| 8          | 68.59                     | 61.28        | 53.5        |
| 9          | 75.59                     | 66.59        | 58.5        |
| 10         | 81.29                     | 75.41        | 65.8        |
| 11         | 85.59                     | 80.59        | 74.2        |
| 12         | 89.12                     | 83.52        | 77.6        |

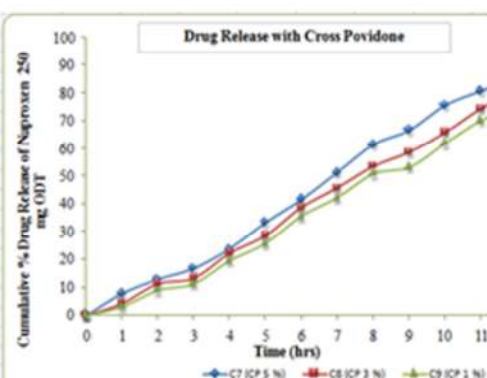
Drug Dissolution Graph of Naproxen 250 mg tablet with Sod. Starch Glycolate. 5%, 3 % 1%



Drug dissolution Data of Naproxen 250 mg Tablet with Cross Povidone

| Time (hrs) | Cumulative % Drug Release |             |            |
|------------|---------------------------|-------------|------------|
|            | C7 (CP 5 %)               | C8 (CP 3 %) | C9 (CP 1%) |
| 0          | 0                         | 0           | 0          |
| 1          | 7.59                      | 4.32        | 3.12       |
| 2          | 12.59                     | 11.29       | 8.9        |
| 3          | 16.57                     | 13.29       | 11.2       |
| 4          | 23.59                     | 22.29       | 19.5       |
| 5          | 33.28                     | 28.59       | 25.5       |
| 6          | 41.59                     | 38.57       | 35.4       |
| 7          | 51.27                     | 45.59       | 42.1       |
| 8          | 61.28                     | 53.59       | 50.8       |
| 9          | 66.59                     | 58.59       | 53.2       |
| 10         | 75.41                     | 65.89       | 61.8       |
| 11         | 80.59                     | 74.28       | 70.1       |
| 12         | 85.41                     | 80.52       | 74.8       |

Drug Dissolution Graph of Naproxen 250 mg tablet with Cross Povidone 5%, 3 % 1%



## 5. CONCLUSION

After completion of this experiment the results obtained and conclude that development of oro dispersible tablet of Naproxen sodium formulation by using various super disintegrants i.e. Cross Carmillose sodium, cross Povidone, Sodium starch glycolate gives results are mentioned below:

1. Naproxen Sodium Active drug stable with different excipients.
2. Fast Disintegrating tablets of Naproxen Sodium were successfully prepared by direct compression method.

3. The flow property of the granules of nine batches (C1, to C9) is observed and concludes C1 containing the CCS 5 % tablet is better.
4. The hardness of compressed tablet by direct compression method found in the range of 4.1 to 4.5 kg/cm<sup>2</sup>.
5. The Thickness of the prepared tablets of all 5 formulations was found between 3.91 mm. to 4.08 mm.
6. The Friability of the compressed tablet found within the range i.e. less than 1%. Maximum Friability for C8 contains 3 % Cross Povidone is 0.83 %.
7. The in vitro disintegration studies are found to be in 8 to 33 seconds. Formulation C1 contains 5 % CCS show in vitro disintegration time i.e. 8-11 seconds.
8. On the basis of disintegration time formulation C1 with 5 % CCS which facilitate the faster disintegration in the mouth. The *in-vitro* percentage drug releases from fast dissolving tablets of Naproxen Sodium 250 mg prepared by direct compression method were found to be in the range of 98.88 %. Hence, finally it was concluded that the prepared oro dispersible tablets of Naproxen Sodium 250 mg may prove to be potential candidate for effective fast disintegrating tablet dosage form.

## 7. REFERENCES

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## DEVELOPMENT AND EVALUATION OF A FORMULATED PATCH OF GRANISETRON FOR TRANSDERMAL DELIVERY

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### ABSTRACT

Skin is an important site to apply the drug for both local and systemic effects. The concept of transdermal drug delivery system (delivering drugs through skin) is old, as the use of it is reported back in 16th century B.C. In 1979, the first transdermal patch was approved by FDA. The first transdermal patch contained the drug scopolamine, it is used to treat motion sickness. The success of a drug applied on skin for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect. One patch design consists of four layers of thin, flexible membranes: an impermeable backing, a drug reservoir, a rate-controlling membrane, and an adhesive. When the patch is applied, the drug begins flowing through the skin into the bloodstream at a rate regulated by the membrane, pre-programmed to keep the drug at levels that provide effectiveness with acceptable adverse effects. Granisetron Hydrochloride is a 5-HT<sub>3</sub> antagonist (5-HT<sub>3</sub>-receptor antagonist) with antiemetic activity. It is used in the management of vomiting and nausea induced by cytotoxic chemotherapy and radiotherapy. The matrix-type transdermal patches containing Granisetron HCl were attempted to prepare using different ratios of Ethyl cellulose, hydroxy propyl methyl cellulose, Eudragit RLPO and RSPO as matrix materials. Six such formulations of Granisetron HCl transdermal patches were formulated using different polymeric ratios. The formulations were evaluated for physico-chemical parameters like weight variation, drug content, thickness, folding endurance, % moisture content, moisture uptake, flatness, water vapor transmission rate, and biopharmaceutical evaluation like in-vitro drug release study, in-vitro permeation study through dialysis membrane. Matrix patches show an initial burst effect to provide the loading dose of the drug, followed by sustained release, it indicates a potential of the granisetron hydrochloride matrix patches as an alternative to the conventional dosage form like tablets.

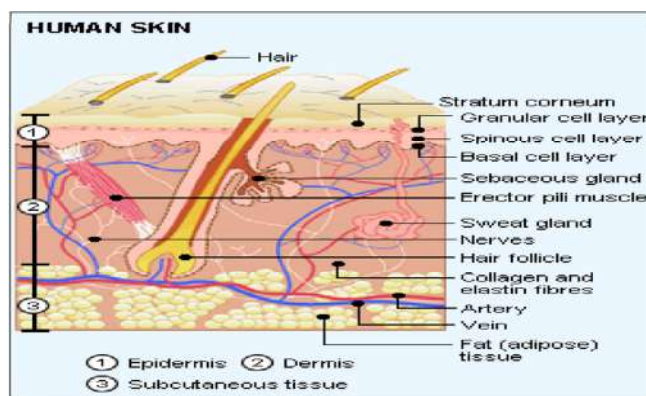
**KEYWORD:** *Granisetron, Transdermal drug delivery, evaluation, Vomiting, anti-emetic.*

### 1. INTRODUCTION

Skin is an important site of drug application for both local and systemic effects. The idea of transdermal drug delivery system (delivering drugs through skin) is old, as the use of it is reported back in 16th century B.C.<sup>1</sup> During the last years, developments in transdermal drug delivery have been incremented focusing mainly on overcoming problems associated with the skin barrier properties.<sup>2-3</sup> In skin, the stratum corneum is the main barrier for drug penetration. The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the



desired therapeutic effect. One patch design consists of four layers of thin, flexible membranes: an impermeable backing, a drug reservoir, a rate-controlling membrane, and an adhesive. When the patch is applied, the drug begins flowing through the skin into the bloodstream at a rate regulated by the membrane, pre-programmed to keep the drug at levels that provide effectiveness with acceptable adverse effects. Chemotherapy-induced nausea vomiting (CINV) is one of the most distressing side effects of chemotherapy; approximately 70 % of patients who receive chemotherapy will experience some level of CINV. CINV can cause significant discomfort and anxiety, dehydration, electrolyte imbalances, affect normal physical and mental function, and decrease quality of life. Hence, some patients may choose to give up the beneficial chemotherapy in the end due to its side effects. Although researchers are keep finding more effective therapy for CINV every Year, CINV still remains as an important issue. None of the therapies has completely solved the problem; in fact, up to 30 % of the patients experience refractory nausea vomiting and also delayed CINV, even with the best antiemetic treatment.<sup>3-5</sup>



**Fig 1: Diagrammatic representation of cross section of skin**

### ***Advantages of TDDS***

Transdermal drug delivery systems offer several important advantages over more traditional approaches, including:

- ✓ □ Duration of action is longer which reduce dosing frequency.
- ✓ Easy to administer drugs which would require frequent dosing.
- ✓ Bioavailability is improved.
- ✓ More uniform blood plasma levels.
- ✓ Improved therapy and reduce side effects due to maintenance of plasma level upto the end of dosing interval.

### ***Disadvantages of TDDS***

- ✓ May cause local irritation at the site of application.
- ✓ Local edema and erythema can be caused by the drugs or excipients.
- ✓ Increase in Transepidermal water loss (TEWL).

Granisetron Hydrochloride is a 5-HT<sub>3</sub> antagonist (5-HT<sub>3</sub>-receptor antagonist) with antiemetic activity. It is used in the management of vomiting and nausea induced by cytotoxic chemotherapy and radiotherapy. Granisetron Hydrochloride is also used for the prevention and treatment of postoperative nausea and vomiting. Furthermore, Granisetron Hydrochloride is used for the management of vomiting and nausea the important role of 5-HT<sub>3</sub> antagonists. As long term medication is required to prevent the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. So Granisetron HCl transdermal matrix patch may be alternative of oral drug delivery system of antiemetic drug. The objective of the present study is the formulation and evaluation of Granisetron HCl transdermal matrix patches using ethyl cellulose (EC), hydroxyl propyl methylcellulose (HPMC) Eudragit RLPO and RSPO as matrix materials by solvent evaporation technique by keeping the concentration of the drug constant.<sup>6-7</sup>

## 2. MATERIALS AND METHODS

Granisetron hydrochloride was obtained as a gift from Industry, India. Ethyl cellulose was received from S.D. Film Chemicals. HPMC was obtained as a gift from Ozone International Eudragit RLPO and RSPO purchased from EvonikRoehm Pharma Polymers. Methanol was received From LobaCheme Laboratories. Chloroform was received From Himedia lab Pvt Ltd., Mumbai. PEG600 was received From Thomas Baker Chemicals Pvt. Ltd. Glycerin was received From Wallis Pharmaceuticals All the solvents used were of analytical reagent grade.

Formulation of transdermal patches Drug-Excipient compatibility study was conducted with FTIR spectrum.

### *Preparation of matrix type transdermal patch*

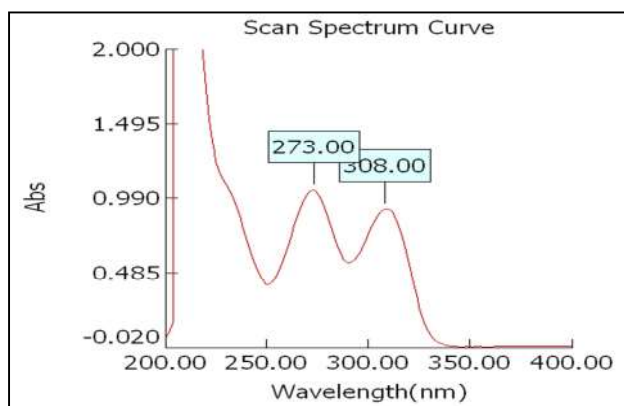
The matrix-type transdermal patches containing Granisetron HCl Patch were prepared using different ratios of ethyl cellulose, Hydroxy Propyl methyl cellulose Eudragit RLPO and RSPO and plasticizer. The polymers in different ratios were dissolved in the solvent (chloroform and Methanol). PEG600 was used as plasticizers. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. Then the solution was poured on the glass mold and dried at the room temperature. Then the patches were cut out from glass mold for evaluation.<sup>8-10</sup>

**Table 1: Formulation of Matrix-type transdermal patch containing Granisetron HCl**

| FormulationCode  | F1  | F2  | F3  | F4  | F5  | F6  |
|--|-----|-----|-----|-----|-----|-----|
| Drug (% w/w) of total polymer  | 10  | 10  | 10  | 10  | 10  | 10  |
| HPMC (mg)  | 400 | 300 | 200 | 400 | 300 | 200 |
| RLPO (mg)  | 50  | 100 | 150 | -   | -   | -   |
| RSPO (mg)  | -   | -   | -   | 50  | 100 | 150 |
| Ethylcellulose (mg)  | 50  | 100 | 150 | 50  | 100 | 150 |
| Total polymer weight (mg)  | 500 | 500 | 500 | 500 | 500 | 500 |
| Plasticizer % w/w of total polymer<br>PEG600 ml  | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Permeation Enhancer % w/w of<br>total polymer (CH <sub>3</sub> OH, CHCl <sub>3</sub> ) | 10  | 10  | 10  | 10  | 10  | 10  |

### *Evaluation of TDDS<sup>11-12</sup>*

Accurately weighed 10 mg of drug was dissolved in 100 ml of Phosphate buffer (7.4 pH) in 100 ml of volumetric flask and prepare suitable dilution to make it to a concentration of 100µg/ml make adequate of sample with concentration range of 0.5-2.5µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V spectrophotometer (LABINDIA UV 3000 +).



**Fig 2. Determination of  $\lambda_{\max}$  of Granisetron hydrochloride**



### 3.1) Thickness

The thickness of patches was measured at three different places using a Absolute Digimetic (Mitutoyo) from Medreich Lab, Bangalore.

### 3.2) Folding Endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance.



**Fig.3 Modified Folding Endurance Tester**

### 3.3) Tensile Strength

The instrument was designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds transdermal patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of and the other end of pulley was attached with movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. Three of patches were cut having 2cm length and 2cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation. The rate of change of stress was kept constant with the increment of 0.5g per 2minutes. The elongation was observed and the total weights taken were used for calculation. The tensile strength was calculated by using following formula

$$\text{Tensile stress (S)} = \frac{\text{Applied force}}{\text{Cross sectional area}} = \frac{m \times g}{b \times t}$$

Where, S = tensile stress in 980 dynes/cm<sup>2</sup>

m = mass in grams

g = acceleration due to gravity (980 dynes/cm<sup>2</sup>)

b = breadth of strip in centimeters

t = thickness of strip in centimeters

The strain is change resulting in size of strip after the force was applied to its original size. Therefore, the strain can be given as,

$$\text{Strain (E)} = \frac{\text{Total elongation}}{\text{Original length}} = \frac{L - L_0}{L_0}$$

Where, L = length after force was applied

L<sub>0</sub> = original length

### 3.4) Percentage of Moisture Content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

**3.5) Percentage of Moisture Uptake**

A weighed film kept in desiccators at room temperature for 24 hrs was taken out and exposed to 84% relative humidity (a saturated solution of aluminium chloride) in a Desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. [73]

**3.6) Water Vapor Transmission (WVT) Rate**

The film was fixed over the brim of a glass vial, containing 3 g of fused calcium chloride as desiccant, with an adhesive type. The vial was weighed and kept in desiccators containing saturated solution of potassium chloride to provide relative humidity of 84%. The vial was taken out and weighed at every 24 hrs intervals for a period of 72 hrs. The water vapor transmission rate was calculated from the plots of amount of water vapor transmitted versus time.

**3.7) Drug Content Analysis**

In 100 ml volumetric flask the patches (n=3) of specified area were taken and dissolved in methanol and volume was made up with phosphate buffer pH 7.4. Subsequent dilutions were made and analyzed by UV spectrophotometer at 242.0 nm.

**3.8) Scanning Electron Microscopy (SEM) Study**

By using a JEOL, JSM-6360 scanning electron microscope at 7 kv The surface morphologies of the patches (blank and drug containing patches) were investigated. Scanning Electron Microscopy (SEM) Study shows that blank patch is very clear and drug is uniformly distributed in the picture of SEM of drug containing patch.

**3.9) In Vitro Skin permeation study**

In vitro release studies were carried out using Franz diffusion cell (), where by a piece of the circular patches was mounted over the donor compartment. The backing membrane side of the patch was exposed to the atmosphere while the receptor compartment was filled with freshly prepared phosphate buffered saline (pH 7.4). Temperature was maintained at 32 °C by circulating water through the water jacket and stirring at 40 – 50 rpm. The patch was in contact with the receptor liquid surface. Samples (5 mL) were withdrawn at 1 h interval for 8 h and immediately replaced with the same volume of medium. Each sample was filtered, diluted suitably and analyzed spectrophotometrically at 302 nm [11]. The means of three readings was taken. In order to investigate drug release mechanism, the data were fitted to zero order, first order, Higuchi release models.<sup>13</sup>

**4. RESULTS AND DISCUSSION<sup>11-14</sup>**

Using different polymeric ratios six formulations of Granisetron HCl transdermal patches were formulated. The formulations were evaluated for physico-chemical parameters like drug content, folding endurance, thickness, weight variation, % moisture content, moisture uptake, water vapor transmission rate, and biopharmaceutical evaluation like in-vitro drug release study, in-vitro permeation study through Franz Cell Diffusion.

**4.1) Thickness of the patches**

By dial calipers the thickness of the patch was determined at different points of the patch. The value of thickness of the patches changes from 0.44 to 0.56 mm. The values obtained for all the formulations are given in table 2

**4.2) Weight variation of the patches**

The weight variation of the patches was in the range of  $350.67 \pm 10.12$  mg to  $406.28 \pm 11.67$  mg. As there was increasing EC, there is consistent increase in weight because of low water permeability nature of EC that prevent evaporation of water.

#### 4.3) Folding endurance of the patches

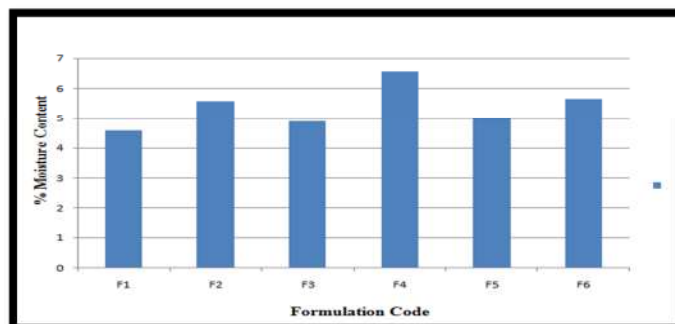
Folding endurance of all the formulation were found to be in the range of  $8.83 \pm 1.47$  to  $24 \pm 1.05$  and it is said to be satisfactory. The values for all five formulations are given in the table. The folding endurance value of all the patches was found satisfactory which ensures that patches prepared using plasticizer glycerol (40 % w/w of polymer) were having optimum flexibility and were not brittle.

**Table 2: Thicknesses and Folding Endurance of Different Formulations**

| S. No. | Formulation Code | Thickness ( $\mu\text{m}$ )* | Folding Endurance* |
|--------|------------------|------------------------------|--------------------|
| 1.     | F1               | $88 \pm 1.23$                | MT 250 $\pm$ 2     |
| 2.     | F2               | $90 \pm 0.89$                | MT 250 $\pm$ 3     |
| 3.     | F3               | $81 \pm 0.95$                | MT 250 $\pm$ 5     |
| 4.     | F4               | $83 \pm 1.10$                | MT 250 $\pm$ 6     |
| 5.     | F5               | $85 \pm 0.85$                | MT 250 $\pm$ 3     |
| 6.     | F6               | $82 \pm 1.05$                | MT 250 $\pm$ 3     |

#### 4.4) Moisture content of the patches

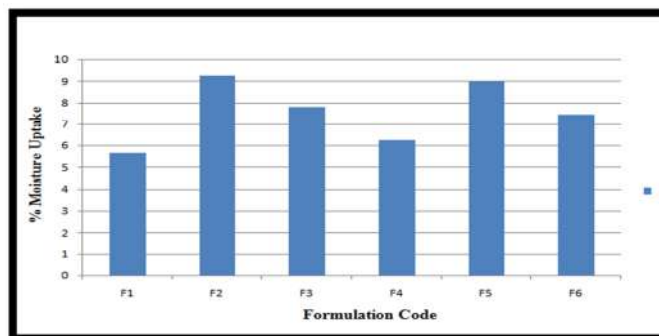
If hydrophilic polymer concentration increased the moisture content is increased and similarly decreased as hydrophobic concentration increased. Among all the patches GH 1 was found to highest moisture content ( $12.01 \pm 1.14$ ). The formulation GH 5 (Eudragit RLPO: RLSO) showed lowest percent moisture content than other formulations. This may be because of the low water permeability of ethyl cellulose polymer. Lower moisture content in formulations is reasonably good for a transdermal patch to prevent brittleness with 100% dryness, maintain stability. It is good for transdermal patch if moisture content is low, to prevent brittleness with 100% dryness and maintain stability. If moisture content is more, then there is a chance of microbial contamination.



**Fig 4: Moisture content of different transdermal patches of Granisetron HCl.**

#### 4.5) Moisture uptake of the patches

The % moisture uptake was calculated as the difference between final and initial weight with respect to initial weight. For different formulations the results of moisture uptake studies are shown in Table and Figure. The moisture uptake of F1 formulation was also low which could protect the formulation from microbial contamination reduce bulkiness.



**Fig 5. % Moisture Uptake of Formulations F1 to F6**

**Table 3. % Moisture Content and Moisture Uptake of Different formulations**

| S.No. | Formulation Code | %Moisture Content | % Moisture Uptake |
|-------|------------------|-------------------|-------------------|
| 1.    | F1               | 4.56              | 5.65              |
| 2.    | F2               | 5.56              | 9.23              |
| 3.    | F3               | 4.89              | 7.78              |
| 4.    | F4               | 6.56              | 6.23              |
| 5.    | F5               | 4.98              | 8.98              |
| 6.    | F6               | 5.65              | 7.45              |

#### 4.6) Water vapour transmission rate of the patches

The formulation GH 6 (Eudragit RLPO: RLPO) showed maximum water vapor transmission rate than other formulations due to the lesser concentration of HPMCE& with higher concentration of EC.

**Table 4. Physical parameters of formulations**

| S.No. | Physical Parameters                     | Observation   |
|-------|---|---|
| 1     | Colour, Odour, Taste                    | White to off white powder, Odourless, Tasteless                 |
| 2     | Solubility                              | Soluble in Water, Chloroform, Ethanol, Methanol, buffer, pH 7.4 |
| 3     | Melting Point                           | 219°C.  |
| 4     | Bulk density                            | 1.052g/cc   |
| 5     | Compressibility Index (%)               | 5.99%.  |
| 6     | Hausner ratio                           | 1.061   |
| 7     | Angle of Repose                         | 43.56 degree  |
| 8     | Moisture by Karl-Fischer Apparatus (KF) | 0.4 %.  |

#### 4.7) Determination of Drug content

Estimation of drug content is essential to check the content uniformity of different patches from a single batch. The drug content was found in the range of  $72 \pm 0.816\%$  and  $92 \pm 0.816\%$ . The drug content (DC) analysis of the patches has showed that the process employed to prepared patches was capable of giving uniform DC and minimum batch variability. The values for drug content of each formulation are given in the table.

**Table No: 5 Percentage Drug Content of all the Formulations**

| S.No | Formulation Code | % Drug Content   |
|------|------------------|------------------|
| 1    | F1               | $92 \pm 0.816$   |
| 2    | F2               | $87 \pm 3.74$    |
| 3    | F3               | $75.66 \pm 4.18$ |
| 4    | F4               | $87 \pm 0.816$   |
| 5    | F5               | $75 \pm 3.2$     |
| 6    | F6               | $72 \pm 0.816$   |

This test is essential to check the uniformity of drug content in different patches from a single batch. The drug content analysis of patch show that the process employed to prepared patch was capable of giving uniformity drug content and minimum batch variability. F1 is optimized formulation that shows the good result.

#### 4.8) SEM Analysis

SEM study help to investigate the surface morphology of patch. The picture of patch (F1 formulation) was clear and also show the drug was uniformly distributed in it was an optimized formulation.

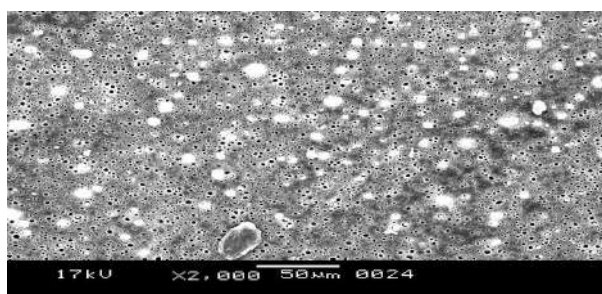


Fig 6. SEM Image of optimized formulation F-1

#### 4.9) In-vitro dissolution study

Conducting a drug release study of the patch is essential to ensure the drug concentration at the surface of stratum corneum is greater than the drug concentration in the body to achieve a constant rate of permeation through diffusion. Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage form. A number of mathematical model have been developed to describe the drug dissolution kinetics from controlled release drug delivery system e.g., Higuchi, First order, Zero order model. The dissolution data is fitted to these models and the best fit is obtained to describe the release mechanism of the drug. All the five formulations studied and data was fitted to mathematical model Zero order, First order, Higuchi to explain the release mechanism and pattern. The profiles are plotted between the cumulative amounts of drug released as a function of square root time which fits better with the linear regression than the other plots. The coefficient of correlation was calculated are shown in Table 4.

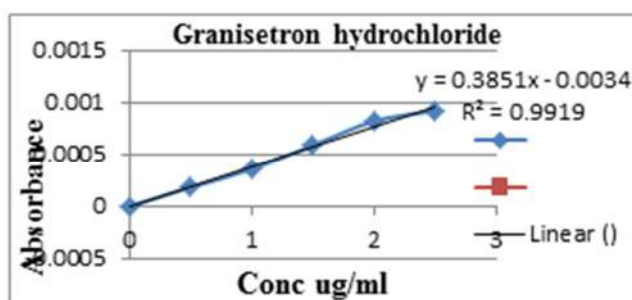


Fig 7. Calibration Curve of Granisetron Hydrochloride at 308.0 nm

#### 4.10) Stastical Data For Linearty

| S.No. | Parameter               | Remark        |
|-------|-------------------------|---------------|
| 1     | Linearty Range          | 0.5-2.5 µg/ml |
| 2     | Regression Equation     | 0.385+ 0.003  |
| 3     | Correlation Coefficient | 0.991         |

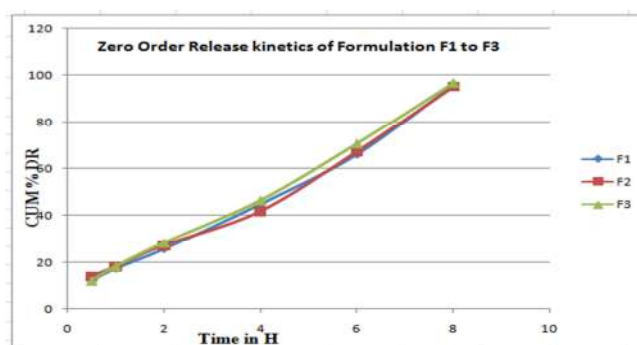
#### In Vitro % Permeation Profile of Granisetron Hydrochloride in Formulation F1-F6

| S.No. | Time (Hrs.) | % Drug Permeated |      |       |      |      |      |
|-------|-------------|------------------|------|-------|------|------|------|
|       |             | F1               | F2   | F3    | F4   | F5   | F6   |
| 1     | 0.5         | 12.19            | 13.9 | 12.04 | 13.6 | 12.9 | 13.9 |
| 2     | 1           | 17.4             | 18.0 | 18.2  | 19.6 | 19.3 | 18.3 |

|   |   |       |      |       |       |      |      |
|---|---|-------|------|-------|-------|------|------|
| 3 | 2 | 25.8  | 27.2 | 28.4  | 27.0  | 28.5 | 29.5 |
| 4 | 4 | 45.0  | 41.8 | 46.5  | 45.3  | 48.4 | 49.7 |
| 5 | 6 | 66.12 | 67.2 | 70.6  | 76.0  | 79.5 | 78.0 |
| 6 | 8 | 96.07 | 95.2 | 96.75 | 95.25 | 96.0 | 95.0 |

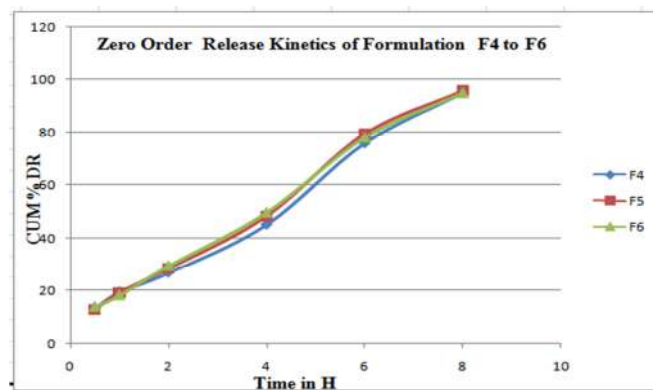
**Release Kinetics of Optimized Formulation****Table 6: Zero order release kinetic profile of Granisetron Hydrochloride Transdermal patches with RLPO ( F1-F3)**

| S.No | Time in H | % CUM Drug release |      |       |
|------|-----------|--------------------|------|-------|
|      |           | F1                 | F2   | F3    |
| 1    | 0.5       | 12.19              | 13.9 | 12.04 |
| 2    | 1         | 17.4               | 18.0 | 18.2  |
| 3    | 2         | 25.8               | 27.2 | 28.4  |
| 4    | 4         | 45.0               | 41.8 | 46.5  |
| 5    | 6         | 66.12              | 67.2 | 70.6  |
| 6    | 8         | 96.07              | 95.2 | 96.75 |

**Fig .No.8 Zero order release kinetic profile of Granisetron Hydrochloride Transdermal patches with RLPO ( F1-F3)****Table 7: Zero order release kinetic profile of Granisetron Hydrochloride Transdermal patches with RSPO ( F4-F6)**

| S.No | Time in H | % CUM Drug release |      |      |
|------|-----------|--------------------|------|------|
|      |           | F4                 | F5   | F6   |
| 1    | 0.5       | 13.6               | 12.9 | 13.9 |
| 2    | 1         | 19.6               | 19.3 | 18.3 |
| 3    | 2         | 27.0               | 28.5 | 29.5 |
| 4    | 4         | 45.3               | 48.4 | 49.7 |
| 5    | 6         | 76.0               | 79.5 | 78.0 |
| 6    | 8         | 95.25              | 96.0 | 95.0 |

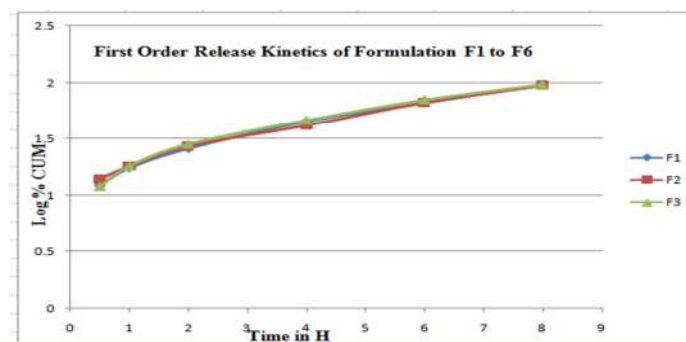




**Fig.9 Zero order release kinetic profile of Granisetron Hydrochloride Transdermal patches F4 to F6**

**Table 8: First order release kinetic profile of Granisetron Hydrochloride Transdermal patches F1 to F3**

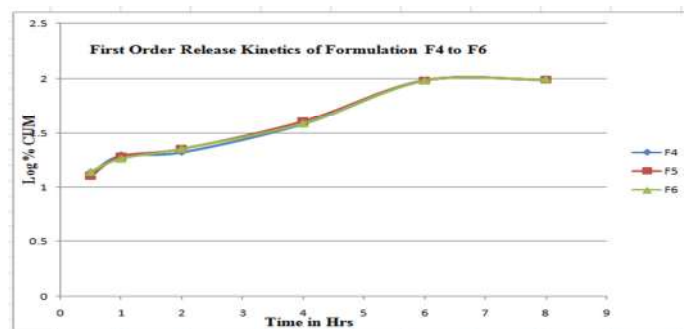
| S.No | Time in Hrs | Log Cum % Drug release |        |        |
|------|-------------|------------------------|--------|--------|
|      |             | F1                     | F2     | F3     |
| 1    | 0.5         | 1.0860                 | 1.1430 | 1.0806 |
| 2    | 1           | 1.2405                 | 1.2552 | 1.2600 |
| 3    | 2           | 1.4116                 | 1.4345 | 1.4533 |
| 4    | 4           | 1.6532                 | 1.6211 | 1.6674 |
| 5    | 6           | 1.8203                 | 1.8273 | 1.8488 |
| 6    | 8           | 1.9825                 | 1.9786 | 1.9856 |



**Fig. 7.13 First order release kinetic profile of Granisetron Hydrochloride Transdermal patches F1 to F6**

**Table 9: First order release kinetic profile of Granisetron Hydrochloride Transdermal patches F4 to F6**

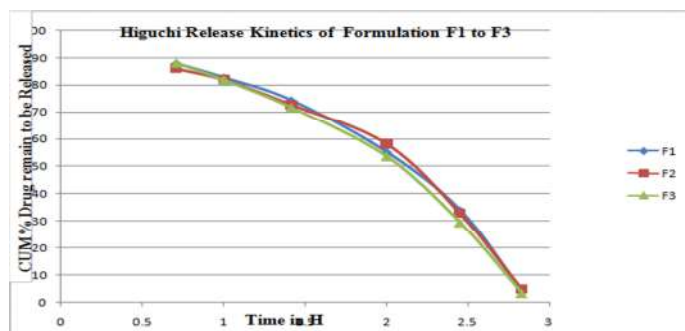
| S.No | Time in Hrs | Log Cum % Drug release |          |          |
|------|-------------|------------------------|----------|----------|
|      |             | F4                     | F5       | F6       |
| 1    | 0.5         | 1.133539               | 1.11059  | 1.143015 |
| 2    | 1           | 1.292256               | 1.285557 | 1.262451 |
| 3    | 2           | 1.322219               | 1.352183 | 1.352183 |
| 4    | 4           | 1.583199               | 1.606381 | 1.587711 |
| 5    | 6           | 1.982271               | 1.984527 | 1.983175 |
| 6    | 8           | 1.992333               | 1.989005 | 1.995635 |



**Fig.No.11 First order release kinetic profile of Granisetron Hydrochloride Transdermal patches F4 to F6**

**Table 10: Higuchi Release Kinetics Data of Granisetron Hydrochloride Transdermal Patch with RLPO ( F1 to F3 )**

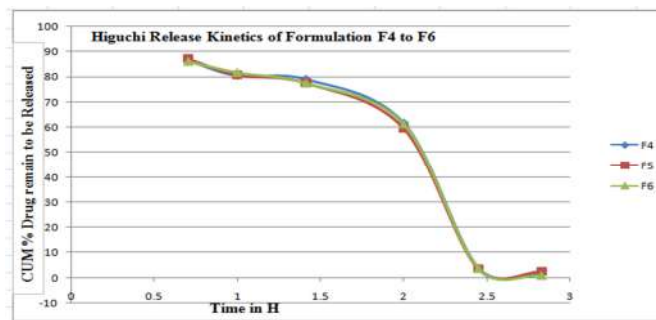
| S. No | Root Time | % CUM Drug Release |      |       |
|-------|-----------|--------------------|------|-------|
|       |           | F1                 | F2   | F3    |
| 1     | 0.707107  | 87.81              | 86.1 | 87.96 |
| 2     | 1         | 82.6               | 83   | 81.8  |
| 3     | 1.414214  | 74.2               | 73.8 | 78.6  |
| 4     | 2         | 69.2               | 68.2 | 67.5  |
| 5     | 2.44949   | 3.88               | 2.8  | 19.4  |
| 6     | 2.828427  | 1.93               | 1.8  | 2.25  |



**Fig.No.12 Higuchi Release Kinetics Data of Granisetron Hydrochloride Transdermal Patch with RLPO (F1 to F3)**

**Table 11: Higuchi Release Kinetics Data of Granisetron Hydrochloride Transdermal Patch with RSPO (F4 to F6)**

| S.No | Root Time | % CUM Drug Release |      |      |
|------|-----------|--------------------|------|------|
|      |           | F4                 | F5   | F6   |
| 1    | 0.707107  | 86.4               | 87.1 | 86.1 |
| 2    | 1         | 80.4               | 80.7 | 81.7 |
| 3    | 1.414214  | 79                 | 77.5 | 77.5 |
| 4    | 2         | 61.7               | 59.6 | 61.3 |
| 5    | 2.44949   | 4                  | 3.5  | 3.8  |
| 6    | 2.828427  | 1.75               | 2.5  | 1.00 |



**Fig.No.13 Higuchi Release Kinetics Data of Granisetron Hydrochloride Transdermal Patch with RSPO (F4 to F6)**

**Table 12: Kinetic data of Granisetron Hydrochloride Transdermal patches**

| Formulation Code |                | ZERO ORDER | FIRST ORDER |
|------------------|----------------|------------|-------------|
| F-5              | r <sup>2</sup> | 0.980      | 0.814       |
|                  | Slope          | 8.093      | 0.159       |
|                  | Intercept      | -4.706     | 0.585       |

## 6. CONCLUSION

The present research work was carried out to develop matrix type transdermal therapeutic systems of Granisetron hydrochloride. The characterization of physicochemical properties of the prepared transdermal drug delivery system of Granisetronhydrochloride using two polymers such as Eudragit RLPO and RSPO in different ratio had shown that the formulations are physic-chemically stable including the absence of drug-polymer interaction, which was ascertained by FTIR study. The Granisetron hydrochloride's release rate from the polymeric matrix patches can be varied by selecting appropriate ratio of hydrophilic (HPMC and hydrophobic (EC), Eudragit RLPO and RSPO) polymers. Usually the release rate and rate of permeation can be retarded to get sustained release characteristic of the formulation by incorporating higher proportion of hydrophobic (EC) polymer. Matrix patches showed an initial burst effect to provide the loading dose of the drug, followed by sustained release, indicating a promising potential of the Granisetron hydrochloride matrix patches as an alternative to the conventional dosage form. Further work is recommended in support of its efficacy claims by long term pharmacokinetic and pharmacodynamic studies on human beings.

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## SP-9

**EFFICACY OF HOLISTIC UNANI TREATMENT IN PSORIASIS: A CASE SERIES**

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**ABSTRACT**

Psoriasis is a chronic autoimmune inflammatory disease disfiguring skin, affecting millions of people worldwide. In psoriasis both genetic and environmental influences have a critical role. Psoriasis represents a significant public health challenge, affecting approximately 125 million people globally. The World Health Organization (WHO) has recently declared and recognized psoriasis as a serious, chronic, disfiguring, disabling, noncommunicable disease. Unani Medicine has claim on safe and effective management of a host of chronic dermatoses including psoriasis but needs evaluation and validation on scientific evidences. Psoriasis is described as TaqashshureJild in Unani Medica literature. According to Majoosi, it is caused by GhaleezAkhlāt expelled externally at skin causing prolonged itching, dryness and shedding of skin. According to Tabri, it is usually caused by humour Sauda, abnormal dam or abnormal Safra and may involve whole body. Conventional treatment lacks safe and curative role in treatment of this disease. A case series study conducted to evaluate Unani medicine claim of safe & effective treatment for this disease. 11 Patients attending the outpatient department of Regional Research Institute of Unani Medicine, Patna were given Majun Ushba 6 gm, Khamira Sandal 6 gm, Sharbat Unnab 20 ml twice daily orally and Marham Safeda Kafoori locally applied on area of lesion for 12 weeks, advised to follow up at every 2 weeks. Efficacy and response to treatment was assessed after 12 weeks by PASI and PDI scales. Highly significant difference observed at  $p < 0.001$  assessed by students paired t test for comparing pre treatment (at baseline) and post treatment (at 12 weeks) scores of PASI and PDI scales. Unani management may be considered as safe and more effective approach for psoriasis if used in its holistic principles.

**KEYWORDS:** *Psoriasis; Unani Medicine; TaqashshureJild; PASI; PDI, Majun Ushba.*

**1. INTRODUCTION**

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. (Rooks) Psoriasis represents a significant public health challenge, affecting approximately 125 million people globally.<sup>1</sup> Like many people with immune-mediated inflammatory diseases, patients with psoriasis experience a high degree of morbidity and, unlike their autoimmune counterparts who are marked by 'invisible inflammation', patients with psoriasis have a highly visible condition and sometimes endure social stigma due to these characteristics.<sup>2</sup> The World Health Organization (WHO) has recently declared and recognized psoriasis as a serious, chronic, disfiguring, disabling, noncommunicable disease. (C.E.M. et al) Various modes of treatments are available for the management of psoriasis like topical and systemic administration of steroids, phototherapy and combination of both. Similar to other auto-immune diseases, conventional treatment of psoriasis has

limitations and drawbacks. Adverse effects like hepatotoxicity, nephrotoxicity, bone marrow suppression, hyperlipidaemia, adrenal insufficiency, Cushing's syndrome, other consequences of immunosuppressive therapies and frequent relapses lead us to seek its better alternative treatment.<sup>3-5</sup>



**Fig 1. Patients with Psoriasis**

Unani Medicine has claim on safe and effective management of a host of chronic dermatoses including psoriasis but needs evaluation and validation on scientific evidences. (Central Council for Research in Unani Medicine (CCRUM). Traditional Knowledge Digital Library. New Delhi: CSIR-Ministry of AYUSH, Government of India; 2017.) Psoriasis is described as TaqashshureJild in Unani Medica literature. According to Majoosi, it is caused by GhaleezAkhlal expelled externally at skin causing prolonged itching, dryness and shedding of skin. (Majoosi AIA. Kaamilus Sana'ah. New Delhi: CCRUM; 2010.) According to Tabri, it is usually caused by humourSauda, abnormal dam or abnormal Safra and may involve whole body. It's always associated with itching. (Tabri AHAIM. Al MualajatulBuqratiya. New Delhi: CCRUM; 1994.) Arzani stated that in this disease scales from are shed like that of fish. (Arzani A. Tibbe Akbar. New Delhi: IdaraKitabushShifa.)

The principles of treatment include Tanqiya (Evacuation of morbid matter), Tasfiyae Dam (cleaning toxins of blood), Tartebe Mizaj (Moisturising skin) and Taskeen (Soothing). Several Unani pharmacopoeial preparations are available as 'ready-to-use combinations' which have been prepared using standard operating principles. (Unani pharmacopoeia PART - II VOLUME - I) Among these we have selected these oral and local formulations as per Unani guidelines of treatment; (Bayazekabeer)

- Majun Ushba 6 gm twice daily orally
- Khamira Sandal 6 gm twice daily orally
- SharbatUnnab 20 ml twice daily orally
- MarhamSafedaKafoori locally.

Though few studies available on use of above medicines individually in psoriasis, this combination was found most effective in clinical experience on holistic ground.<sup>6-8</sup>



## 2. MATERIALS AND METHODS

11 Patients attending the outpatient department of Regional Research Institute of Unani Medicine, Patna were clinically diagnosed as psoriasis. Grattage test and positive Auspitz sign were found positive in all. Disease Severity and quality of life was assessed by Psoriasis Area Severity Index (PASI) and Psoriasis Disability Index (PDI) scales respectively.<sup>9</sup> A detailed history and physical examination were done for all patients. Then patients were given Majun Ushba 6 gm, Khamira Sandal 6 gm, SharbatUnnab 20 ml twice daily orally and MarhamSafedaKafoori locally applied on area of lesion for 12 weeks. Each patient was advised to follow up at every 2 weeks interval to assess the progress of disease and effect of treatment. Efficacy and response to treatment was assessed after 12 weeks by PASI and PDI scales.<sup>10-11</sup>

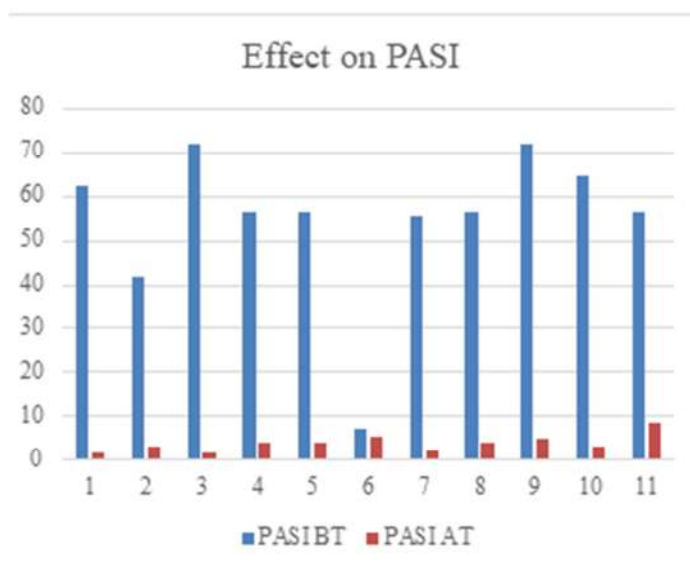
## 3. RESULTS<sup>12-15</sup>

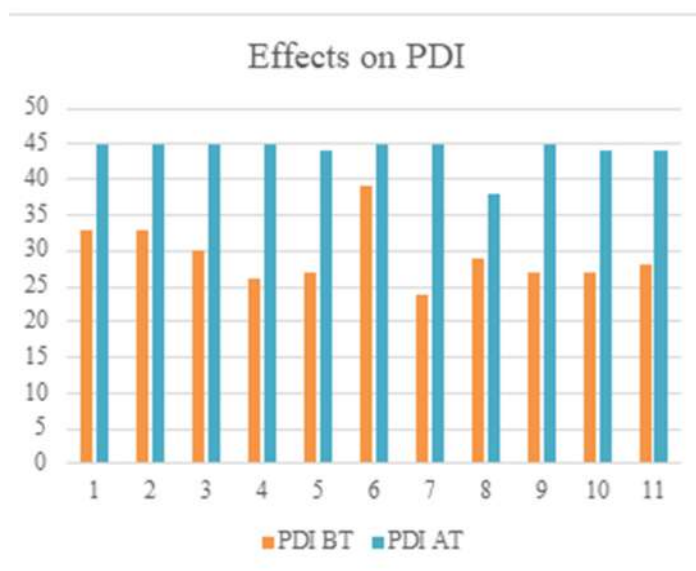
Female and 8 male patients were studies between ages 13 to 65 (Mean age 40.9). Demographic & clinical profile of the patient is given in Table No. 1.

| <b>Table 1.Demographic &amp; clinical profile</b> |             |
|---|-------------|
| Age (yr) (Mean±SD)                                | 40.9±19.08  |
| <i>Gender</i>                                     |             |
| Male N(%)   | 8 (72.7)    |
| Female N(%)                                       | 3 (27.3)    |
| <i>Duration of disease (years)</i>                |             |
| Median (range)                                    | 10 (17)     |
| <i>Disease severity</i>                           |             |
| PASI Median (range)                               | 56.4 (64.8) |

After 12 weeks of intervention patients' response to treatment was analysed statistically. Students paired t test is used for comparing pre treatment (at baseline) and post treatment (at 12 weeks) scores of PASI and PDI scales. Highly significant difference observed at  $p < 0.001$  summarized in Table No. 2. No adverse drug reaction observed in any patient under study.

| <b>Table 2. Effects of intervention on PASI and PDI</b> |               |              |
|---|---------------|--------------|
|   | At Baseline   | At 12 weeks  |
| PASI (Mean±SD)  | 54.68 ± 17.86 | 3.9 ± 1.90   |
| PDI (Mean±SD)   | 29.36 ± 4.22  | 44.09 ± 2.07 |





#### 4. DISCUSSION & CONCLUSION

Psoriasis being multifactorial disease of autoimmune nature has become difficult to cure radically. Conventional molecular approach may address one or pathology at a time but not at all. Adverse drug reactions and drug resistance are further hindrance in long term treatment of this chronic disease. In holistic Unani Medicine the pathological concept of psoriasis is derangement of humours and their quality at macroscopic level. This whole system approach targets all the clinical features of the disease simultaneously. One study suggested that a combination of Unani formulations orally and topically may be an effective and safe treatment alternative in patients with psoriasis who have contraindications to other therapies. ( Khanna et al) In research of Unani Medicine, use of single formulation is not appropriately found effective for all patients. Rather in clinical practice more than 2 formulations are usually advised to treat the patients effectively. Restrictions of research methodology do not allow us to administer multiple regimens due to difficulty in assessment of effectiveness of one formulation, but we can assess the degree of effectiveness of this system of medicine in that particular disease. Hence a series of cases were observed and analyzed as initial evidence of Unani treatment holistically. After intervention the severity of psoriasis decreased significantly. In one case lesser change observed because the patient has mild clinical features before treatment and responded positively. The quality of life as measured by PDI also improved significantly in all patients after treatment. Even after careful observation no adverse effect was found in any case. Thus, the Unani management may be considered as safe and effective approach for psoriasis. It is notable that consideration of various aspects of disease beyond conventional research restriction (for targeting one or two drug only) is more important for the benefit of patient. Further large-scale study is needed to evaluate more about this treatment in terms of efficacy and safety.

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SP-10

## OPTIMIZATION OF NIFEDIPINE 20 MG MOUTH DISSOLVE TABLET BY USING VARIOUS DISINTEGRANT

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### ABSTRACT

The most common preferred route is oral route of administration. Today oro-dispersible tablet from novel drug delivery system gain importance from patient. Which is administered to the patient to control the attack of angina or hypertension, but for immediate control, Oro-dispersible tablet is oral solid dosage form in which the tablet gets dispersed in oral cavity in absence of water. Various manufacturers formulate this formulation by various methods. The most important thing in this formulation is masking of taste of drugs. Generally oro-dispersible tablets are prepared by direct compression method. Dry granulation, wet granulation, Spray drying is the various methods for preparation of oro-dispersible tablet. Oro-dispersible tablet generally contains filler, glidant, anti-adherent super disintegrant, sweetener and resins. Evaluation parameter includes hardness, friability, wetting time, moisture uptake, disintegration test, and dissolution test. Wetting time, Disintegration time, and Dissolution test is directly proportional to the hydrophobic ingredient added for lubrication, anti-adherent, Glidant action. These hydrophobic ingredients are Magnesium Stearate. To oppose the action of magnesium stearate, hydrophilic additives are incorporated viz Sodium lauryl sulphate. The concept of Mouth Dissolve Drug Delivery System emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate or dissolve to release a drug as soon as they come in contact with saliva in oral cavity, thus obviating the need for water during administration, an attribute that makes them highly attractive for paediatric and geriatric patients. Difficulty in swallowing conventional tablets and capsules is common among all age groups especially on elderly and dysphasic patients. Elderly patients may find the administration of the conventional oral dosage forms difficult as they regularly require medicines to maintain healthy life. Children may also have difficulty in ingesting because of their under developed muscular nervous system. The problem of swallowing tablets is also evident in travelling patients who may not have ready access to water. Aforementioned problems can be resolved by means of Mouth Dissolving Tablets. Some tablets are designed to dissolve in saliva within few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed as fast disintegrating tablets, as they may take about to disintegrate completely.

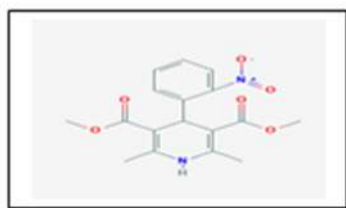
**KEYWORDS:** - Oro dispersible Table Nifedipine 20 mg, cross Carmillose Sodium, Sodium starch glycolate, Cross povidone.

## 1. INTRODUCTION

Qualities are built in the pharmaceutical formulation by design the formulation. The total quality in the product is known as Total Quality Management. To gain this goal of optimized quality product, the knowledge obtained from pharmaceutical development studies and manufacturing provides the scientific background.<sup>1</sup> Although it is based on different pharmaceutical studies, but it has its aim that it minimizes the end product testing and Increases the chances of regulatory acceptance by different pharmaceutical governing bodies. The aim and objective of the present study is to develop and evaluate oro dispersible tablet of Nifedipine and enhance the onset of action of Nifedipine and also to study the influence of excipients on the physical characteristics of the tablets by applying two level three factor factorial designs taking Nifedipine as model drug which is used in the treatment of the Hypertension, Angina Pectoris, cardiac arrhythmia.<sup>2</sup> The study of this formulation to select the best possible excipient combination of semi synthetic & natural and artificial additives to development of formulation. Super disintegrants viz Cross carmilllose sodium, sodium starch glycolate, cross povidone are added to formulate the dispersible tablets among all the diluents and finally the effect of the various super disintegrants on the Disintegration time and dissolution properties of the tablet were also determined.<sup>3-5</sup>

## 2. MATERIAL AND METHOD

|               |                        |
|---------------|------------------------|
| Formula       | : $C_{17}H_{18}N_2O_6$ |
| Molar mass    | : 345.335 g/mol        |
| Melting point | : 172 to 174 °C        |



Nifedipine was patented in 1967 and approved for use in the United States of America in 1981. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system for various cardiac diseases. It is available as a generic medication in various dosage form and various formulation range from 5 mg to 20 mg. Nifedipine is odorless, yellow crystalline tasteless Powder. Nifedipine is water insoluble. Chemically Nifedipine is a Dihydropyridine Calcium Channel Blocker. The mechanism of action of Nifedipine on heart is as a Calcium Channel Antagonist. The chemical classification of Nifedipine is Dihydropyridine.<sup>6</sup> Nifedipine is a first generation calcium channel blocker used to treat hypertension and angina pectoris and other cardiovascular diseases. Nifedipine therapy is associated with a low rate of serum enzyme elevations and has been linked to several instances of clinically apparent acute liver injury.. Nifedipine is a potent vasodilator agent with calcium antagonistic action. It is a useful anti-angina agent that also lowers blood pressure and hypertension.<sup>7-8</sup>

## 2. MATERIAL AND THEIR USE WITH OBTAINED SOURCES<sup>9</sup>

**Table 1: Materials their sources and Uses**

| S. No. | Material                        | Use of ingredients | Sources  |
|--------|---------------------------------|--------------------|--|
| 1      | Nifedipine                      | Active Ingredients | J.B. chemicals. Anklashwar   |
| 2      | Lactose                         | Diluents           | Pacific India.<br><br>A Pharmaceutical exporter,<br>Village-Dhana, Bagbania<br>Nalagarh, Solan, (H.P.) |
| 3      | Microcrystalline cellulose      | Diluents           |  |
| 4      | Sodium starch Glycolate         | Disintegrants      |  |
| 5      | Cross Carmillose sodium         | Disintegrants      |  |
| 6      | Cross povidone                  | Disintegrants      |  |
| 7      | Aspartame                       | Sweetener          |  |
| 8      | Methyl Paraben & Propyl paraben | Preservative       |  |

|    |                            |                    |  |
|----|----------------------------|--------------------|--|
| 9  | Mannitol                   | Diluents/Sweetener |  |
| 10 | Starch Direct compressible | Antiadhrants       |  |
| 11 | Magnesium stearate         | Glidant            |  |
| 12 | Talc                       | Lubricants         |  |

### 3. PREPARATION OF NIFEDIPINE 10 MG ORO DISPERSIBLE TABLET BY DIRECT COMPRESSION METHOD<sup>10</sup>

**Table 2: Preparation of Nifedipine 10 Mg Oro Dispersible Tablet by Direct Compression Method**

| s. N o | Ingredients             | C1 (mg)    | C2 (mg)    | C3 (mg)    | C4 (mg)    | C5 (mg)    | C6 (mg)    | C7 (mg)    | C8 (mg)    | C9 (mg)    |
|--------|-------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| 1      | Nifedipine              | 20         | 20         | 20         | 20         | 20         | 20         | 20         | 20         | 20         |
| 2      | Cross Carmillose Sod.   | 24 (6%)    | 16 (4%)    | 8 (2%)     | ---        | ---        | ---        | ---        | ---        | ---        |
| 3      | Sodium starch Glycolate | ---        | ---        | ---        | 24 (6%)    | 16 (4%)    | 4 (2%)     | ---        | ---        | ---        |
| 4      | Cross povidone          | ---        | ---        | ---        | ---        | ---        | ---        | 24 (6%)    | 16 (4%)    | 4 (2%)     |
| 5      | Lactose                 | 90         | 98         | 106        | 90         | 98         | 106        | 90         | 98         | 106        |
| 6      | Aspartame               | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         |
| 7      | Methyl Paraben          | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          |
| 8      | Propyl Paraben          | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 1          |
| 9      | Mannitol                | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         | 50         |
| 10     | Starch DC grade         | 105        | 105        | 105        | 105        | 105        | 105        | 105        | 105        | 105        |
| 11     | Micro crystalline ce.   | 40         | 40         | 40         | 40         | 40         | 40         | 40         | 40         | 40         |
| 12     | Magnesium stearate      | 8          | 8          | 8          | 8          | 8          | 8          | 8          | 8          | 8          |
| 13     | Talc                    | 8          | 8          | 8          | 8          | 8          | 8          | 8          | 8          | 8          |
|        | <b>Total</b>            | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> | <b>400</b> |

All the ingredients of formulation i.e. Active ingredients and additives were passed through 60 # sieve separately, Magnesium stearate and talc through 40 #, The ingredient were mixed by geometrical mixing and Tablet were compressed on 9.5 mm sizes of flat round punch to get tablet by using Rimeck Single rotary compression machine.<sup>11-12</sup>

### 4. RESULT AND DISCUSSION: POST COMPRESSION PARAMETER AND STUDIES<sup>8,9,13-15</sup>

**Table 3. Post Compression Parameter and Studies**

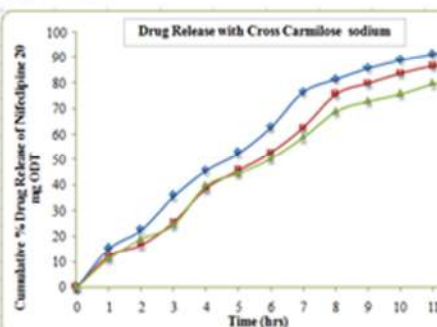
| Formulation code | Assay of Drug (%) | Disintegration Time (Sec) | Dissolution (%) | Hardness (Kg/cm2) | Friability (%) | Thickness (mm) |
|------------------|-------------------|---------------------------|-----------------|-------------------|----------------|----------------|
| C1 (CCS 6 %)     | 99.11             | 6-9                       | 93.35           | 3.70              | 0.69           | 4.02           |
| C2 (CCS 4 %)     | 98.31             | 8-12                      | 87.18           | 3.40              | 0.58           | 4.06           |
| C3 (CCS 2 %)     | 98.20             | 13-19                     | 81.59           | 3.30              | 0.81           | 3.94           |
| C4 (SSG 6 %)     | 98.38             | 12-17                     | 88.69           | 3.40              | 0.41           | 4.02           |
| C5 (SSG 4 %)     | 98.65             | 16-24                     | 82.45           | 3.30              | 0.78           | 3.98           |
| C6 (SSG 2%)      | 98.48             | 19-28                     | 76.92           | 3.30              | 0.65           | 3.96           |
| C7 (CP 6 %)      | 98.28             | 17-23                     | 85.69           | 3.50              | 0.72           | 3.98           |
| C8 (CP 4 %)      | 98.32             | 22-27                     | 79.63           | 3.20              | 0.68           | 4.02           |
| C9 (CP 2 %)      | 98.39             | 23-29                     | 72.52           | 3.80              | 0.51           | 4.04           |



Drug dissolution Data of Nifedipine 20 mg Tablet with Cross carmillose sodium

| Time (hrs) | Cumulative % Drug Release |              |              |
|------------|---------------------------|--------------|--------------|
|            | C1 (CCS 6 %)              | C2 (CCS 4 %) | C3 (CCS 2 %) |
| 0          | 0                         | 0            | 0            |
| 1          | 15.29                     | 12.38        | 11.1         |
| 2          | 22.69                     | 16.69        | 18.6         |
| 3          | 35.69                     | 25.59        | 24.4         |
| 4          | 45.69                     | 38.69        | 39.8         |
| 5          | 52.57                     | 45.92        | 44.4         |
| 6          | 62.57                     | 52.69        | 50.2         |
| 7          | 76.18                     | 62.57        | 58.4         |
| 8          | 81.35                     | 75.67        | 68.8         |
| 9          | 85.69                     | 79.81        | 72.4         |
| 10         | 88.98                     | 83.64        | 75.4         |
| 11         | 91.27                     | 86.69        | 79.4         |
| 12         | 93.35                     | 87.18        | 81.4         |

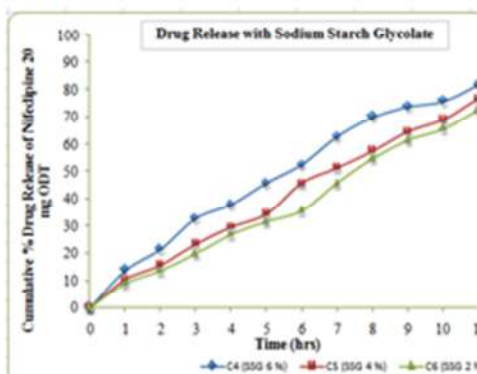
Drug Dissolution Graph of Nifedipine 20 mg tablet with Cross Carmillose sod. 6%, 4% 2%



Drug dissolution Data of Nifedipine 20 mg Tablet with Sodium starch Glycolate

| Time (hrs) | Cumulative % Drug Release |              |              |
|------------|---------------------------|--------------|--------------|
|            | C4 (SSG 6 %)              | C5 (SSG 4 %) | C6 (SSG 2 %) |
| 0          | 0                         | 0            | 0            |
| 1          | 13.69                     | 10.23        | 8.8          |
| 2          | 21.51                     | 15.69        | 13.4         |
| 3          | 32.69                     | 23.51        | 19.4         |
| 4          | 37.89                     | 29.68        | 26.4         |
| 5          | 45.65                     | 34.52        | 31.4         |
| 6          | 52.36                     | 45.69        | 35.4         |
| 7          | 62.47                     | 51.39        | 45.4         |
| 8          | 69.82                     | 57.67        | 54.4         |
| 9          | 73.69                     | 64.52        | 61.4         |
| 10         | 75.69                     | 68.98        | 65.4         |
| 11         | 81.69                     | 76.59        | 72.4         |
| 12         | 88.69                     | 82.45        | 76.4         |

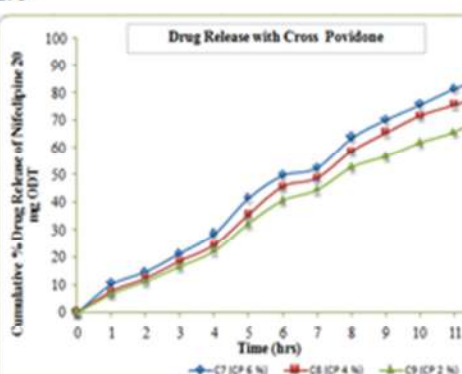
Drug Dissolution Graph of Nifedipine 20 mg tablet with Sod. Starch Glycolate . 6%, 4% 2%



Drug dissolution Data of Nifedipine 20 mg Tablet with Cross Povidone

| Time (hrs) | Cumulative % Drug Release |             |             |
|------------|---------------------------|-------------|-------------|
|            | C7 (CP 6 %)               | C8 (CP 4 %) | C9 (CP 2 %) |
| 0          | 0                         | 0           | 0           |
| 1          | 10.21                     | 7.52        | 6.5         |
| 2          | 14.62                     | 12.54       | 11.2        |
| 3          | 21.25                     | 18.51       | 16.6        |
| 4          | 28.64                     | 24.37       | 22.3        |
| 5          | 41.52                     | 35.62       | 32.2        |
| 6          | 49.62                     | 45.67       | 40.7        |
| 7          | 52.36                     | 48.69       | 44.6        |
| 8          | 63.57                     | 58.64       | 52.7        |
| 9          | 69.92                     | 65.51       | 56.6        |
| 10         | 75.61                     | 71.62       | 61.7        |
| 11         | 81.27                     | 75.62       | 65.5        |
| 12         | 85.69                     | 79.63       | 72.4        |

Drug Dissolution Graph of Nifedipine 20 mg tablet with Cross Povidone . 6%, 4% 2%



## 5. CONCLUSION

After completion of this experiment the results obtained and conclude that Optimization of oro dispersible tablet of Nifedipine 20 mg formulation by using various super disintegrants i.e. Cross Carmillose sodium, cross Povidone, Sodium starch glycolate gives results are mentioned below:

1. Nifedipine Active drug stable with different excipients.
2. The hardness of compressed tablet by direct compression method found in the rage of 3.2 to 3.8 kg/cm<sup>2</sup>.
3. The Thickness of the prepared tablets of all 5 formulations was found between 3.94 mm. to 4.06 mm.

4. The Friability of the compressed tablet found within the range i.e. less than 1%. Maximum Friability for C5 contains 4 % is 0.86 %
5. The in vitro disintegration studies are found to be in 6 to 29 seconds. Formulation C1 contains 6 % CCS show in vitro disintegration time i.e. 6-9 seconds.
6. On the basis of disintegration time formulation C1 with 6% CCS facilitate the faster disintegration in the mouth. The *in-vitro* % drug releases from fast dissolving tablets of Nifedipine 20 mg prepared by direct compression method were found to be in the range of 99.11 %. Hence, finally it was concluded that the prepared oro dispersible tablets of Nifedipine 20 mg may prove to be potential candidate for effective fast disintegrating tablet dosage form.

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