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Research Article

Pharmaceutics for effective drug dosage

Stable Solid Dispersion Incorporated Sustained Release Oral Gel of 23 mg Donepezil Hcl

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Abstract: The objective of the present study is to formulate and evaluate stable solid dispersion incorporated sustained release oral gel of donepezil Hcl. Solid dispersions were prepared using HPMC K100M and stearic acid using physical mixture, co-grinding and fusion methods and incorporated into the previously prepared gel bases using sodium CMC and sodium alginate and suitable formulation was optimised. All the formulations were subjected to physicochemical evaluation parameters. Solid dispersions of donepezil were prepared with HPMC K100 and stearic acid by using different methods like physical mixtures, co grinding and fusion method in the ratios of 1:1, 1:2 and 1:3. From the *invitro* dissolution studies, it was found that SD made by co grinding and fusion method showed sustained release and were selected and incorporated into the gel formulations made of SCMC 4% and sodium alginate 4%. The release studies of solid dispersion incorporated gel SD-HPMC K100M showed (SDG1) 87.55% and (SDG2) 88.9% at 8th hour and SD-stearic acid showed (SDG3) 83.26% and (SDG4) 82.57% at 8th hour. It was concluded that stearic acid solid dispersions incorporated in sodium CMC gels (SDG3) were optimised using short term stability studies with no leakage of drug in comparison to solid dispersions of HPMC K100M in sodium CMC gel I. Physico-chemical evaluation parameters were carried out for optimised formulations and found to be within limits. The optimized SD incorporated gel formulation of donepezil can be an alternative to SR tablet in improving the compliance of the geriatric patients.

Keyword: Solid dispersion, sustained release, gel, solid dispersion incorporated gel

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1. INTRODUCTION

The solid dispersion containing oral gels is very widely studied for improving the geriatric patient compliance. [1] Nowadays most of the pharmaceutical scientists were involved in developing an ideal drug delivery system. Any novel drug delivery system should provide the advantage of delivering directly in to the site. Oral controlled or sustained release formulations should provide reproducibility and predictability. In order to improve the patient compliance, oral formulations should be given less frequently. The oral gels are also can be formulated as sustained release dosage form to provide once daily dosage to enhance the patient compliance.[2] This may also provide fewer side effects, improved efficacy and steady state delivery. Sustaining a hydrophilic drug is always a challenge. Hence solid dispersions (SD) incorporated formulations are formulated to sustain the release. Solid dispersions are solid products consisting of hydrophobic drug and hydrophilic carrier incorporated using various methods such as physical mixture, co-grinding, fusion and melting method. The carrier can be either crystalline or amorphous solids. When the SD is exposed to liquid media, the carrier dissolves and the drug gets discharged as fine mixture but here water insoluble carrier is selected for sustained release of drug from the polymer matrix. [3] The drug selected for the present work is donepezil Hcl. It is used in the treatment of Alzheimer's disease (AD).The biopharmaceutical classification of donepezil Hcl is class I (high solubility and high permeability). Donepezil has been found to be one of the most effective symptomatic treatments for AD available in the market with additional potential as a disease-modifying therapy. Donepezil is used in the treatment of AD. An increase in adverse effects was seen at lower dosages. Hence 23 mg dose is used for the treatment of moderate to severe AD to reduce the side effects.[4] The present study is aimed at developing sustained release solid dispersion incorporated oral gel of donepezil Hcl using various polymers by simple method.

2. MATERIALS AND METHODS

2.1 Materials

Donepezil Hcl was received as a gift sample from Cipla Ltd Mumbai. Sodium carboxy methyl cellulose (SCMC), Carbopol 934p, Hydroxy propyl methyl cellulose (HPMC), stearic acid was purchased from Yarrow chem Ltd. sodium alginate and gelatin were purchased from S D fine chemicals. All other ingredients are of analytical grade.

2.2 Preparation of solid dispersion

Methods used for preparation of solid dispersion (SD) are

2.2.1 Co grinding

Donepezil was triturated with a minimum quantity of ethanol in a glass mortar until it dissolved. The carrier (HPMC and stearic acid) was then added, and the suspension was triturated rapidly at room temperature until the solvent evaporated and passed through sieve no 60. [5]

2.2.2 Physical mixture

Physical mixtures of donepezil and HPMC/stearic acid in powder form were mixed in mortar and passed through sieve no. 60. The physical mixtures were prepared in the following ratios: donepezil: HPMC in the ratios of 1:1, 1:2, 1:3. [5,6]

2.2.3 Fusion method

Solid dispersion of Donepezil & carriers (HPMC/stearic acid) in ratios of 1:1, 1:2 and 1:3 were obtained by melting the carrier in a porcelain dish at 70 – 75°C and to this Donepezil was added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was pulverized, passed through 60 mesh sieve and stored in a desiccator until used for further studies.[6,7]

2.2.4 Preparation of solid dispersion incorporated oral gel

Gels are prepared by soaking the polymers overnight in water. These mixtures (Table 1)were triturated and required amount of solid dispersion equivalent to 230 mg of drug was added to these prepared gel bases and mixed vigorously till uniform gel was formed. Then required quantities of methyl and propyl paraben were added to the polymer dispersion before the drug solution was added. Sodium saccharine (Sweetening agent) was added to the polymer dispersion and stirred continuously until it formed a homogeneous product. The volume was made up with distilled water and stirred vigorously. [7-9]

Table 1. Formulation table for solid dispersion incorporated oral gel

Ingredients (mg)	SDG1	SDG2	SDG3	SDG4
SD of 23mg equivalent Donepezil Hcl	690	690	690	690
Sodium CMC	400	-	400	-
Sodium alginate		400	-	400
Glycerin (ml)	1.5	1.5	1.5	1.5
Methyl paraben 0.1%	10	10	10	10
Propylparaben 0.1%	10	10	10	10
Sodiumsaccharin	30	30	30	30
Purified water	Up to 10gm			

Note: SDG1: solid dispersion made of HPMC K100M using cogrinding (1:2) incorporated in sodium CMC gel
SDG2: solid dispersion made of HPMC K100M using cogrinding (1:2) incorporated in sodium alginate gel
SDG3: solid dispersion made of stearic acid using fusion method (1:2) incorporated in sodium CMC gel
SDG4: solid dispersion made of stearic acid using fusion method (1:2) incorporated in sodium alginate gel

2.3 Evaluation of solid dispersions

2.3.1 Drug content and percent yield of SD

Physical mixtures and SDs equivalent to 10 mg of Donepezil HCL prepared were weighed accurately and dissolved in a 100 ml of 6.8 pH phosphate buffer. The stock solutions were filtered through a membrane filter (0.45 mm). The solutions were then diluted suitably with buffer. The drug content was analysed at 230 nm using a UV spectrophotometer. Each sample was analysed in triplicate.[5]

2.3.2 Dissolution study

The dissolution studies were performed using a US Pharmacopeia type II dissolution test apparatus. The samples equivalent to 23 mg Donepezil HCL were placed in a dissolution vessel containing 900 ml of 6.8 pH phosphate buffer maintained at 37 ± 0.5°C and stirred at 50 rpm. 5ml samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper no. 41, the concentration of donepezil was determined spectrophotometrically at 230 nm.[5,6]

2.3.2 IR- Spectroscopic studies

FT-IR spectroscopy was employed to ascertain the compatibility between donepezil and the selected polymers using SHIMADZU FT-IR. Drug and the carriers selected were initially checked using FT-IR. The optimized formulations compatibility i.e., stearic acid was mixed with drug / polymer in 1:2 ratio and the spectra were taken. FT-IR spectrum of donepezil was compared with FT-IR spectra of donepezil-solid dispersion mixture.[10]

2.3.3 Stability studies

Stability studies were conducted on donepezil Hcl SDs to assess their stability with respect to their physical appearance, drug content, FTIR spectroscopy and drug-release characteristics after storing them at room temperature for 1 month. [5]

2.4 Evaluation of solid dispersion incorporated gel

2.4.1 Physicochemical evaluation of solid dispersion incorporated oral gels

Gels were evaluated for their appearance, pH, drug content, viscosity, extrudability and homogeneity.

2.4.2 Physical Appearance

The physical appearance of the formulation was checked visually and the color of the formulation was checked out against white background.

2.4.3 Determination of pH

The pH of Donepezil HCl gel formulations was determined using digital pH meter, which was calibrated using buffers of pH 4 and 7 before the measurements. The measurement of pH of each formulation was done in triplicate and average values were calculated.[12]

2.4.4 Drug content

Formulation equivalent to 10 mg of drug was diluted with distilled water and after suitable dilutions the absorbance was measured at 230 nm using UV visible spectrophotometer. The drug concentration was calculated by using the formula. [11,12]

$$\% \text{ drug content} = \frac{\text{Concentration of drug in the sample solution}}{\text{Equivalent concentration of drug taken}} \times 100$$

2.4.5 Extrudability

It was determined by using a tube filled with the gel, having a tip of 5mm opening and by measuring the amount of gel that extruded through the tip when pressure was applied on the tube [11]

2.4.6 Homogeneity

All the developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates. [13]

2.4.7 Viscosity measurement

Brookfield digital viscometer (model DV-II+ pro) was used to measure the viscosity (in cps) of the prepared gel formulations. The spindle number 63 was rotated at 15 rpm.

2.4.8 In-vitro release study – solid dispersion incorporated oral gel

Measurement of the in-vitro release of Donepezil HCL from the solid dispersion incorporated polymer gel was carried out using the USP type II paddle apparatus at 37°C. 900ml of simulated intestinal fluid (pH 6.8) was used as the release medium and the paddle rotation speed was set to 50 rpm. From the prepared gels 1gram of gel which contains 23mg of drug was added to the release medium. A 5ml portion of the fluid was removed at suitable time intervals and the volume was kept constant by adding the same amount of release medium at the same temperature. The samples were analyzed at λ_{max} of 230 nm using spectrophotometer.[12]

3. STATISTICAL ANALYSIS

The standard deviation calculations were analysed using Microsoft excel. The release kinetics of the formulation were analysed using Microsoft excel.

4. RESULTS AND DISCUSSION

4.1 Drug content and percentage yield

The yield from melting method was low due to stickiness of the material produced. The percentage yield was found to be from 88.28% to 90.19%. However reproducibility was obtained with this method. The percentage yield of SD's from co grinding ranged from 92.39% and 95.38% and

physical mixtures ranged from 96.38% to 9819%. The amount of drug ranged from 98.03% to 99.18% in physical mixtures and 94.22% to 97.18% for co grinding and 94.17% to 97.13% for fusion method.

4.2 *Dissolution study*

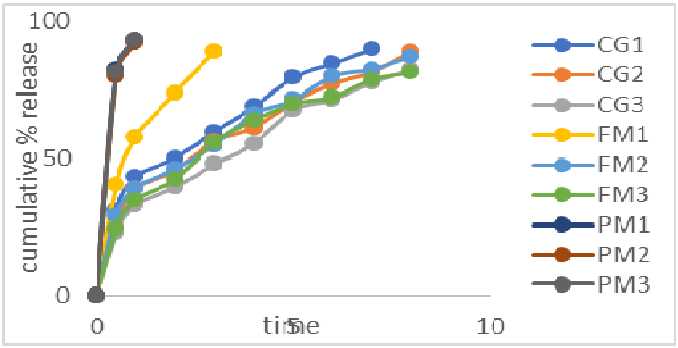

Fig 1. Dissolution study of solid dispersion

The dissolution profiles of donepezil Hcl SD's of physical mixture, co grinding and fusion method in pH 6.8 phosphate buffer are shown in Figure1. Donepezil Hcl was completely dissolved within a few minutes, reflecting its high aqueous solubility. The dissolution from the physical mixture showed approximately the same behaviour of pure donepezil Hcl, with only a very slight initial slowing down of the drug dissolution rate due to the presence of the hydrophilic HPMC, which reduces the drug wettability. In co grinding and fusion method the release decreased as the polymer drug ratio increased.

4.3 *IR- Spectroscopic studies*

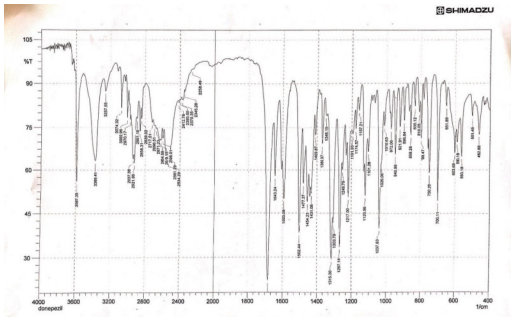

Fig 2a. FTIR spectra of Pure drug (Donepezil Hcl)

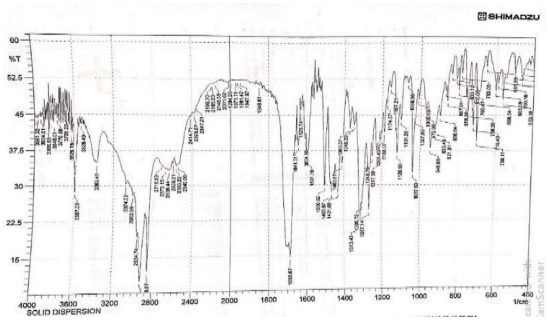

Fig 2b Solid dispersion of drug with-stearic acid

Table 2. FTIR interpretation of pure donepezil hydrochloride

S.no.	Region in cm^{-1}	Bond	Functional group
1	3369	N-H	Aliphatic primary amine
2	2921	$>CH_2$	Methylene CH stretch
3	1715	C=O	Ketone

IR spectroscopy was carried out to check the compatibility between drug and carrier. IR spectrum of mixtures of drug and the carrier, (Donepezil Hcl and stearic acid) was recorded and compared with individual reference spectra for any spectral interference. The functional group of the drug , aliphatic primary amine at 3369 cm^{-1}, methylene group and ketone group was retained in the spectra of the mixture. From the figure 2a and 2b and Table 2, it was concluded that there is no presence of any interference between drug and the carrier used. Hence no incompatibility found with the drug and the carrier.

4.4 *Stability studies*

No visible changes in the appearance of the SD were observed at the end of the storage period and the results were tabulated in table 3.

Table 3. Results of evaluation parameters of SD incorporated gel formulations

FC	pH	Viscosity (cps)	Drug content	Extrudability
SDG1	6.8±0.19	3685.2	97.32±0.11	++
SDG2	6.9±0.19	3276.12	96.07±0.28	+
SDG3	6.9±0.02	3655	98.34±0.09	+++
SDG4	6.4±0.08	3125	97.21±0.17	++

Note: +++ excellent, ++ satisfactory, +good n=3

4.5 *Physical appearance*

Formulation SDG1 was white opaque with moderate viscosity and the gel state was stiff. Formulation SDG2 was a slight cream color with moderate viscosity and clear gel. Formulation SDG3 was white clear with good viscosity and the gel state was opaque and transparent. Formulation SDG4 was a slight cream color with moderate viscosity and stiffness.

4.6 *Homogeneity*

Homogeneity of optimised solid dispersion incorporated oral gel was observed to be good and satisfactory.

4.7 *pH*

pH of the prepared SD incorporated gels is reported in Table: 3. All the values lie between 6.4 to 6.8 which is ideal for intestinal delivery.

4.8 *Viscosity*

The measurement of viscosity was done using Brookfield viscometer and the values are reported in the above Table.2

4.9 *In-vitro release study – solid dispersion incorporated oral gel*

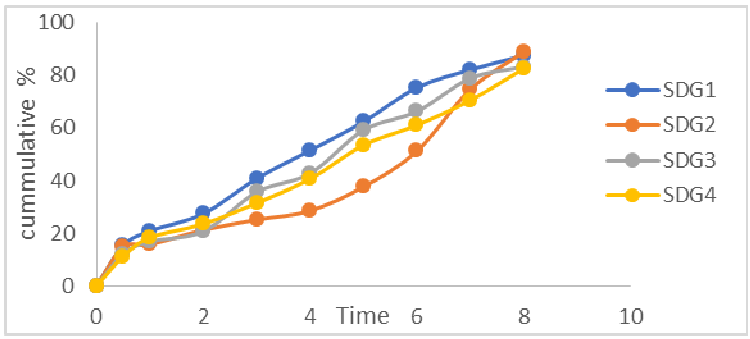

Fig 3. In-vitro release studies of solid dispersion incorporated sustained release oral gel

The in-vitro drug release data is shown in the above figure 3. The formulations made using SD-HPMC K100M SDG1 showed 87.55% and SDG2 showed 88.9% at 8th hour. The formulations made using SD-stearic acid SDG3 and SDG4 showed 83.26% and 82.57% at 8th hour respectively. From the above results it was observed that SDG3 showed better sustained action when compared to other formulations. This was the same results obtained with metformin sustained release solid dispersion prepared with various carriers published by Patil et.al. [5]

4.10 *Stability studies for the solid dispersion incorporated oral gel*

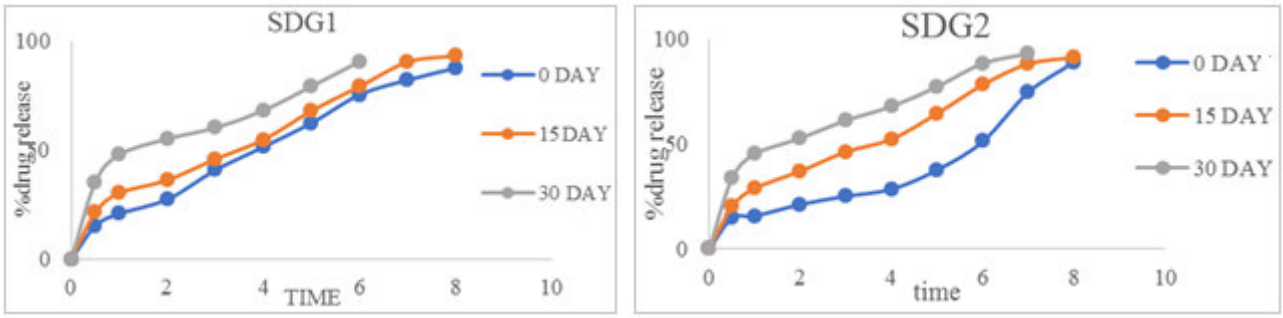

Fig 4. Cumulative % release of SD- HPMCK100M incorporated oral gel

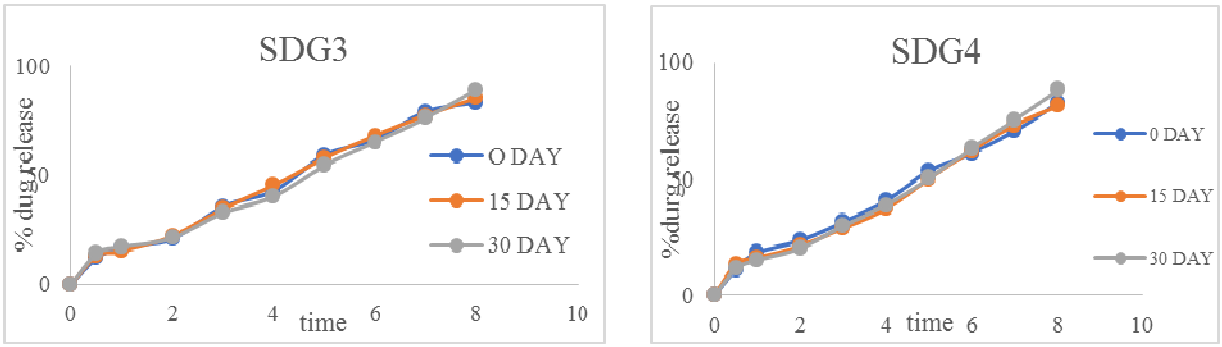

Fig 5. Cumulative % release of SD- stearic acid incorporated oral gel

From the above stability studies, figure 4 and 5, it was observed that the gels formed using SD-HPMC K100M showed faster release on the 30th day, because the HPMC in the solid dispersion got swollen on longer storage in the gel base as it is a hydrophillic polymer. Due to this, faster release of drug from the solid dispersion and dose dumping was seen.[12] As in the case of gels formed with SD-stearic acid there were no dose dumping seen even after one month because stearic acid is a hydrophobic carrier and it does not absorb water from the gel. The gels made of HPMC SD started leaking because of the hydrophilic nature of HPMC. Moreover these hydrophilic gels upon entering in to stomach, may lose the gel structure and drug may get released faster and dose dumping can occur. Hence in order to protect the drug from gastric environment, stearic acid which is a hydrophobic carrier was used for the preparation of SD and this was incorporated in gel. When this gel enters stomach, though the migrating motor complex (MMC) contractions are more, stearic acid can reach the intestine and sustain the release of the drug. From the results it was concluded that formulation SDG3 showed stability towards leakage and does not show major difference in drug release from the gel when comparing the result of the first day with the last day of one month study, proving that stearic solid dispersion incorporated gels can sustain the drug for longer time. [14-16]

5. CONCLUSION

In the present work solid dispersions were prepared using stearic acid and HPMC K 100. These were incorporated into gelling agents such as SCMC, Carbopol, sodium alginate and gelatin to formulate oral gels. Solid dispersion incorporated gels were prepared to sustain the release of this water-soluble drug. The stability studies of the stearic acid solid dispersion incorporated gel showed sustained release and stability up to one month compared to HPMC K100 SDs which showed leakage of large amounts of drug within the second week. Hence it can be concluded that stearic acid SDs incorporated oral gels can be suitable for water soluble drugs with required stability throughout the shelf life. This oral gel formulation also improves patient compliance and is suitable for geriatric population. Further long term research is required to study the stability of both the formulations.

6. AUTHORS CONTRIBUTION STATEMENT

Mr. Anudeep reddy carried out the research study and the idea was conceived and guided by Dr.P.K.Lakshmi.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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