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Research Article

Pharmaceutics for Effective Drug Dosage

Effect of Excipients on Pharmaceutical Parameters on Topical Gel Loaded With Povidone Iodine, Honey and Aloe Vera

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Abstract: The aim of the study is to formulate and evaluate topical gels prepared with povidone iodine, honey and aloe vera using carbopol and poloxamer. Ninetopical gels were formulated using carbopol and poloxamerat various concentrations and evaluated for, rheological properties, *in vitro* drug release profile, release mechanism and *in vitro* antimicrobial activity, pH, spreadability, viscosity, flow index and flow behaviour for all the formulations and were found within acceptable range. The F8 has 99% of cumulative drug release percentage. The *invitro* mechanism release showed that F8 fits with first order kinetics (r^2 = 0.9967) followed by Higuchi model (r^2 = 0.9657) diffusion process based on Fick's Law. F8 formulation showed minimum inhibitory one of 34.46 mm and 27.57 mm for antibacterial and antifungal activity respectively, which exhibited more prominently than other formulations. Based on the findings, it was concluded that F8 has an effective antimicrobial activity and maximum drug release.

Keywords: Povidone Iodine, Honey, Aloe vera, Carbopol 940, Poloxamer, Drug Kinetics

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1. INTRODUCTION

Povidone iodine has broad spectrum of antiseptic activity when applied on the skins to treat and prevent infections in the wound caused by burns, minor cuts and scratches. Iodine was approved by FDA. FDA has recommended for placing it in the first aid kit and short term treatment up to 1 week, as in over-the-counter.[1,2] Honey and aloe vera, both were used from the immemorial days in India to treat various ailments. One among such uses is to treat the mild infections. Almeida KA, et al in 2018 from Brazil and Gupta et al in 2011from India also reported that the combination of honey and aloe vera has synergistic effects of antiseptic activity.[3,4] In addition to this, Gupta et al, reported that bandages impregnated with honey, fasten wound healing process, at minimal duration. As reported, this combination showed a good result in hypertrophic and wound due to burns when compared with silver sulfadiazine ointments.[4] Gels are semisolid dosage form intended to apply over the skin and/ or in the mucous membranes present in the buccal cavity. Gelconsists of two penetrating barriers where the colloidal particle is uniformly dispersed in the entire dispersion medium. The formation 3D matrix in the solvent is called as gel.[5-7]By using gelling agent(s) such as natural, synthetic or semi-synthetic polymer, gel is prepared. In the gel system polymer(s) are backbone to form the matrix. Based on the types of bonding gels are divided as (i) reversible and (ii) irreversible.[8] Stability of gel is based on the viscosity of the gel. A gel formulation needs an optimal concentration of polymer to maintain the viscosity of the gel.[9]In general, topical gel offers more merits than the demerits when compared with conventional dosage forms. Iodine, honey and aloe vera are known for their antiseptic activity. The topical drug delivery system has the following advantages (i) overcome first pass metabolism effect, (ii) avoidance of gastro-intestinal irritations and (iii) metabolic degradations occurs following the oral administration. One of the major disadvantages of topical gels is permeation of drugs through the skin. The permeationis affected by various factors like (i) skin conditions (ii) physicochemical characteristics of drug (iii) base and polymers used.[10] The aim of this study is to make an attempt to formulate topical gel loaded with povidone iodine, honey and aloe vera as well as the effects of excipients and *in vitro* antimicrobial activity for the formulated topical gels using carbopol 940 and poloxamer407 polymers.

2. MATERIALS AND METHODS

2.1 *Method of preparation of carbopol gel*

In the preparation of gel, Carbopol 940 was dispersed in 50: 50 propylene glycol: water system was stirred continuously at 500 rpm for 150 minutes (step I). In small quantity of water methyl paraben sodium, propyl paraben sodium, honey and aloe vera were dissolved (step II). In a separate beaker iodine and potassium iodide were dissolved with a few ml of alcohol (step III). Later, step II and step III were mixed well with a stirrer for 15 minutes. The resultant mixture was mixed to the step I and stirred for one hour. Then triethanolamine was added into it to make the preparation viscous and adjusted near to neutral pH.[11]The composition of honey loaded povidone iodine and aloe vera topical gel formulations are shown in Table 1.

2.2 *Method of preparation of poloxamer gel*

Poloxamer was slowly dissolved in cold water (undergoes transition) with constant stirring (Step I). In a separate beaker, iodine and potassium iodide were dissolved in few ml of alcohol (Step II). In another beaker with a small quantity of water, honey, aloe vera, methyl and propyl paraben sodium were dissolved (Step III). At the end, Step I and Step II were mixed and added to the polymer with continuous stirring for 1 hour. Then triethanolamine was added into it to make the preparation viscous and adjusted near to neutral pH. The prepared gel was packed in a wide mouthed glass jar. After covering the mouth with an aluminium foil, it was covered with screw capped plastic lid and kept cool.[11, 12]The composition of honey loaded povidone iodine and aloe vera topical gel formulations is shown in Table 1.

Table 1: ***Formulation of povidone iodine loaded honey and aloe vera topical gel (% w/w)***

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Povidone Iodine	1	1	1	1	1	1	1	1	1
Potassium iodide	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Honey	1	1	1	-	-	-	1	1	1
Aloe Vera	-	-	-	1	1	1	1	1	1
Carbopol 940	0.5	1	1.5	-	-	-	0.5	1	1.5
Poloxamer 407	-	-	-	10	15	20	10	15	20
Ethanol	5	5	5	5	5	5	5	5	5
Propylene Glycol	-	10	-	-	20	-	-	30	-
Triethanolamine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Methyl Paraben sodium	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Propyl Paraben sodium	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Purified water to	100	100	100	100	100	100	100	100	100

2.3 *Physicochemical evaluation of formulated topical gels*

2.3.1 Differential scanning calorimetry (DSC)

The DSC study was carried for identifying the incompatibility between povidone iodine, honey and aloe vera, polymers and their physical mixtures of povidone iodine, honey and aloe vera: polymer at 1:1 ratio. The samples were placed in the aluminium pan and heated at the rate of 20° C per min up to 300° C temperature by using a differential scanning calorimeter (TA-501; Shimadzu Corporation, Japan).[11] The data are not provided.

2.3.2 Visual examination

All the formulated gels were checked for its homogeneity, colour, phase separation and formation of lumps, if any by visually. Later it was allowed to set in the beaker.[13]

2.3.3 Spreadability test

Around 1 g of gel from each formula was placed between two slides and pressurized (size of each slide was about 7.5 cm^2). The slides were kept aside for 5 minutes and found to be no extra spreading in the slides. Diameter of spread was determined in cm and was taken to compare readings of spread of formulated gels. Each formula was tested for three times to get average readings.[14]

2.3.4 Determination of pH

For all the formulated gels, pH was determined by mixing 1g of each gel in 10ml of purified water later measured in a digital pH meter (pH Mettler-Toledo GmbH, Switzerland). Each formula was tested for three times to get average readings.[15]

2.3.4 Determination of Viscosity

The viscosity of the formulated gel (honey loaded with povidone iodine and aloe vera)was determined by using Brookfield Rotational Digital Viscometer DV II, model LVDV-E (in cPs). From each formula 1g of gel was placed in the griffin standard beaker and the T-bar spindle (S-96) was rotated at 10 rpm and the temperature was maintained at 25±1 °C.[15]

2.3.5 Determination of Drug Content[15]

Drug content was determine as reported by Jamal Mohamed et al in 2018. The content of iodine in the formulated gelswere analysed by using the official Pharmacopeia (USP) method.

2.3.6 Rheological Studies

The viscosity for different formulations were determined at room temperature by using rotational digital viscometer DV II, model LVDV-E (in η). 1g of formulated gels wereseparately placed in the griffin standard beaker with the T-bar spindle (S-96). (Jamal Mohamed A, et al, 2018) The apparent viscosity was determined at shear rate of 50 sec^{-1}. The flow index was determined by linear regression inthe logarithmic form of the following equation:[16]

$$\tau = \eta \times \gamma$$

Where"τ" is the shear tress,"γ" is the shearrate and"η"is the viscosity.

When the flow is ≥1, and ≤1, then it indicates that the gel flows Newtonian, shear thickening or thinning respectively. Evaluation was conducted in triplicate. Each formula was tested for three times to get average readings.

2.3.7 In vitro Method[10]

Release of iodine from different topical gel formulations were studied by using modified Keshary – Chien diffusion apparatus. A cellophane membranewas immersed in a phosphate buffer of pH 7.4 for 90 minutes prior to use. The impregnated membrane was pastedat one end of the compartment in the permeation apparatus. 1g of gel was introduced into the first compartment and named as "donor compartment" and was placed 1 cm inside a 100ml beaker having fresh phosphate buffer pH 7.4 named as "receptor compartment". It was stirred by using magnetic stirrer at a temperature of 32° C ± 1° C. Aliquot of 5 ml of dissolution media from the receptor compartment was removed at specific intervals of 15, 30, 45, 60, 75 and 90 minutes and assayed for iodine content. Every time, aliquots were removed with a phosphate buffer. Amount of iodine released at different intervals of time was calculated and plotted a graph between concentrationversus time. Calculation of drug release (%) is as follows:

$$\text{Drug Release (\%)} = [\text{Conc. of drug/ Label Claim}] \times 100$$

The drug content present in the formulations was determined by using the Indian pharmacopoeia method.[17,18]

2.3.8 Drug release mechanism and kinetic studies[19]

The results obtained from the *in vitro* drug release profile study were analyzed by correlation regression as follows:

Zero – order was computed by using Q= Qot

Where Q is the quantity of drug released at time t and A0is the rate of zero – order release.

First – order was computed by using in
(100 – Q) = ln 100 – Q1t

Where Q is the release of drug in percentage at time t, and C1 is the rate constant for first – order.

Higuchi's was computed by using
$Q = dr\ t_{1/2}$

Where Q is the release of drug in percentage at time t, and dr is the diffusion rate constant.

2.3.9 Antimicrobial activity

The following bacteria were used to study the anti-microbial activity: (i) *Staphylococcus aureus,* (ii) *Streptococcus pyogenes,* (iii) *Escherichia coli*and(iv) *Pseudomonas aeruginosa.* The following fungal strains were used to study theanti-microbial activity: (i)*Aspergillus niger,* (ii) *Aspergillus clavatus,* and (iii)*Candida albicans*were selected because of their clinical significance.[20,21] The stock cultures of bacteria and fungus was incubated for 24 hours at 37 ° ± 0.5 °C in nutrient media containing agar and potato dextrose agar respectively. The bacterial strains were inoculated in Mueller-Hinton agar disks at 37 ° ± 0.5 °C and nutrient agar slants at 4 ° ± 0.5 °C *In vitro* antimicrobial activity was determined for the selected gels (F2, F5 and F8). Antimicrobial activity of selected gels formulations were tested against 4 pathogenic bacteria (2 Gram-positive and 2 Gram negative) and 3 pathogenic fungi were determined by the agar disk diffusion method.[22,23]

Antimicrobial activity was performed by using agar well method. The three selected formulated gels were dissolved in sterilized water for injection. The minimum inhibitory zone around the disk was determined after 24 hours of incubation at 37° ± 0.5°C for bacteria and 72 hours for fungi at 28 ° ± 0.5 °C.

3. STATISTICAL ANALYSIS

The data represented were in mean ± SD. The statistical analysis was performed using Sigmastat (Demo Version). Permeation data was analysed using SAMPA software. P–value of <0.01 was considered as statistically significant.

4. RESULTS AND DISCUSSIONS

Topical gels provide various advantages than the oral dosage forms. Iodine should be used for external use only, which offers a good antiseptic effect over a wide range of microorganisms. Therefore, it is decided to formulate and evaluate, an effective topical gel with natural ingredients like honey and aloe vera,[24,3] which are already proven for their antiseptic activity.

4.1 *Physical Examination*

The formulated honey loaded povidone iodine and aloe vera topical gels were transparent in carbopol 940 and viscous in poloxamer with a soft and homogeneous appearance. The formulated gels were able to spread from 3 to 4 cm with 1g of gel. All the formulated topical gels were having pH between 5.2 and 6.5 values, at this range of pH will be comfortable and not cause irritation to the skin.[25]All the formulations were released the drug between 97.5% and 99.5%. The data are provided in Table 2. F2, F5 and F8 were selected for further studies, based on their optimal pH, spreadability, phase separation and the drug content.

Table 2:*Shows the Physical Properties of povidone iodine loaded honey and aloe vera topical gels*

Formulation Code	Appearance	pH	Phase Separation	Spreadability (cm)	Drug content (%)
F 1	Brown transparent	5.7	No	3.5	97.5
F 2		6.0	No	4	99.0
F 3		5.5	No	3	98.5
F 4	Pale brown transparent	5.2	No	4	99.0
F 5		6.0	No	3.5	98.5
F 6		5.5	No	2.5	97.0
F 7	Brown opaque, viscous	5.8	No	2.5	98.0
F 8		6.3	No	4	99.5
F 9		6.1	No	2.5	98.5

4.2 *Effect of concentration of polymer on drug release*

In vitro drug release profiles of topical gels having various concentrations of carbopol (0.5%, 1% and 1.5%) are provided in Fig 1 (F2, F5 and F8). The initial concentrations of topical gels in all the formulations were taken as 1%. The drug release increased as the concentration of polymer increased at the end of 90 minutes (P< 0.01) in all the three formulations. In the present study it showed that there is a direct relationship between coefficient relations i.e. flow index and viscosity. The data are provided in Table 3. Apart from the above fact, the viscosity increases as the concentration of polymer increases. In other hand, viscosity is indirectly proportional to the release of drugs from formulations and also penetration across the diffusion barriers. The reduction in the release might be due to higher microviscosity of the gel by adding more amount of polymer. Hence, results in reduced drug release and the pattern of flow from the gels may be due to higher polymer concentration and/ or viscosity.[26,27] The finding of the present study is similar to the Japan Patel et al., as the increase in polymer concentration decreases the drug release[10] and pattern of flow, which follows the theory of molecular diffusion[28].

Table 3:*Shows the rheological properties of povidone iodine loaded honey and aloe vera topical gels*

F. Code	Coefficient of determination (r2)	Flow Index (n)	Viscosity (centipoise) (η)	Flow Behaviour
F1	0.9080	0.2273	1629	shear thinning
F2	0.9179	0.2249	1007	shear thinning
F3	0.9905	0.2240	1836	shear thinning
F4	0.9112	0.1992	981	shear thinning
F5	0.9269	0.2196	1379	shear thinning
F6	0.9891	0.2296	2073	shear thinning
F7	0.9293	0.2325	2388	shear thinning
F 8	0.9844	0.2479	3952	shear thinning
F 9	0.9943	0.2547	4473	shear thinning

4.3 *Effect of drug release mechanism and kinetic studies*

The release profile was calculatedby using the different kinetic models like zero order kinetic percentage of cumulative drug release against time while for first order kinetics percentage of cumulative drug remaining in log against time and to calculate the Higuchi model cumulative percentage of drug release against square root of time.[11,29-31] The r^2valuesare provided in Table 4. The F8 formula has shown best fitting to the first order mechanism of release following the Higuchi model.[32,33] The results of the present study propose that F8 is more suitable for topical administration with maximum percentage of the spreadability and having good permeability through synthesised membrane after 90 minutes.

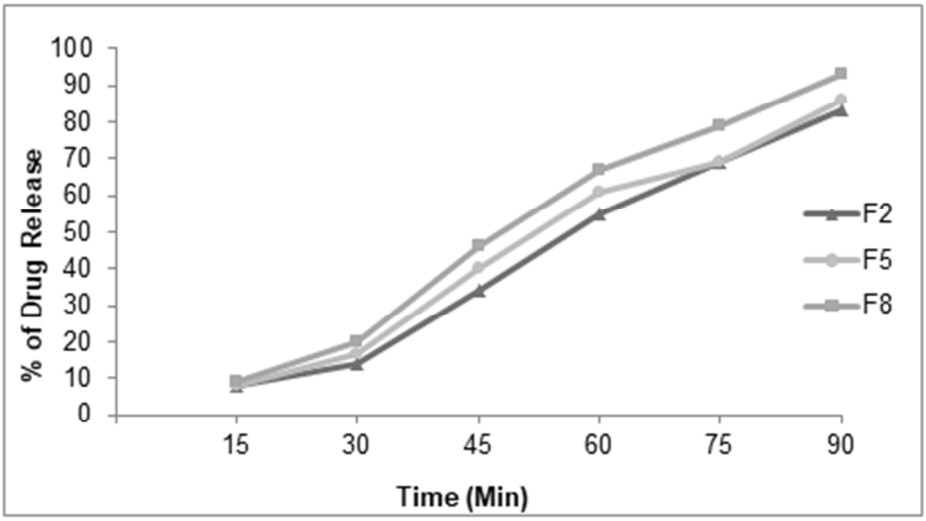

Fig 1: *In vitro drug release profile from various gel formulae*

Table 4:*Drug release mechanism and kinetics of all the formulations (F2, F5 And F8)*

F. code	Zero order (r2)	First order (r2)	Korsmeyer-Peppas (r2)	Hixson – Crowell (r2)	Higuchi (r2)
F2	0.8553	0.9259	0.9801	0.7706	0.9874
F5	0.9054	0.9371	0.9761	0.7785	0.9706
F8	0.9415	0.9657	0.9555	0.7993	0.9967

4.4 *Effect of antimicrobial activity*

Antimicrobial activity of selected formulations (F2, F5 and F8) was evaluated by measuring the inhibition zone of bacterial and fungus growth. The result of the antimicrobial activity is provided in Table 5. The antimicrobial activity of F8 has shown prominent antimicrobial activity when compared with F2 and F5 formulations against all the microorganisms. The zone of inhibition was measured between 17 mm and 26 mm for bacteria and 21 mm to 36 mm for fungus. The results show that the formulation F8, contains povidone iodine, honey and aloe vera, which is found to be highly effective against all the bacteria and fungus tested.

Table 5:*Antimicrobial activity of selected formulations (F2, F5 and F8)*

F. Code	Zone of inhibition (mm)						
	Antibacterial activity				Antifungal activity		
	E. coli	*P. aeruginosa*	*S. pyogenes*	*S. aureus*	*A. niger*	*A. clavatus*	*C. albicans*
F2	17.54±1.31	18.41±1.29	19.81±1.67	20.75±1.93	21.88±1.78	27.00±3.36	33.31±3.45
F5	18.32±1.25	19.76±1.40	20.47±1.68	21.92±2.03	22.06±1.64	29.20±2.83	34.49±3.68
F8*	20.03±1.94	22.93±1.51	24.44±2.05	26.39±2.55	23.66±2.19	30.58±3.88	36.55±3.76

Values are mean ± SD (n = 6); * P<0.01 when compared with F2 and F5

As the quantity of propylene glycol increased, the viscosity of the gels also increased. In the present study, drug permeation and release profile (Table 4) also increased. This indicates there is a correlation among bulk viscosity and drug permeation and release profile shows that the bulk viscosity[34, 10] is not influencing the release of povidone iodine. F2, F5 and F8 formulations showed higher drug permeation and release profile due to the presence of propylene glycol (10 to 30%), among them formulations with 20% of propylene glycol have shown maximum drug permeation and release profile. The formulations containing poloxamer 407 showed maximum drug release when compared with the other formulations either carbopol 940 or carbopol 940 and poloxamer 407. The findings from the present work showed that poloxamer 407 has good gelling property when compared with carbopol and good choice of gelling agent to prepare topical gels.

5. CONCLUSION

Based on the findings, it is to conclude that the povidone iodine loaded with honey and aloe vera was successfully formulated using various polymers and concentrations of topical gel. In the formulation F8 (Carbopol 940 and

Poloxamer), the drug release was increased with optimal polymers concentration. Out 9 formulations, F8 showed good physical properties like colour, homogeneity, optimal spreadability, viscosity, flow index, drug release, and antimicrobial activity when compared with other formulations.

6. AUTHOR CONTRIBUTION STATEMENT

Jamal Mohamed A designed and performed the experimental section whereas Perinbam K author assisted and supervised during the project. Vahitha V wrote the manuscript with support from Devanesan S and Janaki Raman KK.

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8. CONFLICT OF INTEREST

Conflict of interest declared none.

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