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RESEARCH ARTICLE

Formulation, Evaluation and Release Kinetics of Low Viscosity Metronidazole Gel with Varying Amount o f Carbopol

Debatri Roy[1], Sudipta Das[1]*, Madhurima Panda[1], Sabnam Sultana[1], Mrittika Mandal[1], Ishita Sil[1], Baban Majumder[1]

1 Department of Pharmaceutics, Netaji Subhas Chandra Bose Institute of Pharmacy, Nadia, 741222, West Bengal, India

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* **Corresponding author**.

sudiptapharmacy6@gmail.com

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Abstract

Objective: The study is centered on formulation and evaluation of low viscosity metronidazole gel with varying amount of Carbopol. **Methods:** Formulations (F1, F2 and F3) of Metronidazole in gel form were done in varying amounts of Carbopol. Prepared gels were inspected for surface pH, viscosity, spreadability, antimicrobial susceptibility, drug content percentage, in vitro process of drug release, release kinetics and stability testing. **Findings:** Formulation pH was placed in between 5 and 6. Measured viscosity of F3 was 34.16 Pa.sec for high-rise amount of Carbopol and for F2 & F1 it was 33.43 Pa.sec and 30.44 Pa.sec respectively. Highest spreadability was achieved for F1 which was 9.72 gm.cm/sec and for F2 and F3 it was 7.3 gm.cm/sec & 6.62 gm.cm/sec. Release study for drug (*In vitro*) report for F1, F2, and F3 was 91.945 %, 89.612 % and 88.598 % respectively for 120 minutes study. Drug release kinetics was scrutinized by First Order model, Zero Order model, Higuchi model, Hixon-Crowell model and Korsmeyers-Peppas model. **Novelty:** This study formulates low viscosity gel of metronidazole using polymer Carbopol. The viscosity of gel formulation can alter drug release pattern and spreadability in better way. Study was focused on improvement of spreadability which is linked with easy absorption in to the application area. Low viscosity aqueous gel can spread easily.

Keywords: Periodontal Disease; Metronidazole; Carbopol; In Vitro Type Drug Release; Kinetics For Drug Release

1 Introduction

This project is based on the formulation, characterization & evaluation of metronidazole gel for the local treatment of periodontitis.

"Periodontal Disease" is correlated with periodontium. Microfloral changes, different pathological variation are clinical symptoms and the inflammation in the gums marks to identify this disease. In this disease periodontal pocket forms which weakens the teeth sulcus. Normally the gap between gingiva and teeth is 1 -2 or 3 mm. In case of periodontitis the gap goes to 5mm or more.

Metronidazole is an important active substance that has been widely used for treatment of some protozoal and anaerobic bacterial infections. Bioadhesive dosage forms like gel of metronidazole is used for the disorders at mucosal surface. The side effects that caused by systemically administered drugs, MTZ gel helps to minimize it. It also reduces the abundant dosage of the systemic drugs. This gel formulations requires polymers as adhesive components. The effects on viscidity may be explained by increased viscosity and also by increasing semi solid nature of products containing Carbopol. This metronidazole gel has been prepared as antibacterial formulation also. The preparations were checked by its physical properties i.e., pH, viscosity, spreadability, stability & the performance in *in-vitro* drug release study. Metronidazole is the prototype of nitroimidazoles. In 1959, it was introduced for Trichomoniasis. In later it was noticed as a highly active amoebicide. For cases that persist after oral treatment and where resistant trichomonads are suspected, Metronidazole as active substance has been widely used. For anaerobic protozoa, Giardia Lamblia it has broad spectrum cidal activity. The gel specifically has bactericidal action against anaerobic microorganisms. That are well-known to be the chief pathogens related to periodontitis [(1)].

Biofilm-associated inflammatory disease Periodontitis is specified by the demolition of periodontal tissue. Three identical factors are responsible in periodontitis that are permitting host, existence of pathogens belongs to periodontal disease, and lower amount of beneficial bacterial species for periodontal health [(2)]. Metronidazole has notable effectiveness in treating anaerobic brain abscesses. Countless clinicians still think metronidazole to be the 'gold standard' antibiotic against with other antibiotics. Metronidazole has activity against protozoans like Entamoeba histolytica, Giardia lamblia and trichomonas vaginalis for which the drug was first approved as an effective treatment. For cases that persist after oral treatment and where resistant trichomonads are suspected a union of oral and topical therapy may be effective. In the crevice fluid of gingiva and in the saliva Metronidazole penetratration is well. In the crevice fluid the metronidazole concentration and protein concentration i.e. drug concentrations which are unbound in plasma are nearly equal. So, in case of periodontal type disease pharmacokinetic study of this drug can be applicable.

Metronidazole is useful for the amoebiasis, giardiasis and trichomoniasis disease. It exerts antibacterial [(3)], antiprotozoal activities both. Metronidazole is scrupulous harmful to anaerobic and microaerophilic kind microorganisms. After take up the cell through diffusion certain redox protein operatives reduces nitro group to a reactive (highly) nitro radical and exerts cytotoxicity in anaerobic bacteria. Cytotoxicity can be decreased through inhibition of its reductive activation. Moreover, O2 competes with Metronidazole nitro radical for the free electrons that goes to be generated during metabolism (energy) of anaerobic bacteria [(4)]. After the concentration falls below the minimum inhibitory concentration (MIC) the post antibiotic effect of metronidazole extends beyond 3 hrs. With Disulfiram, alcohol and warfarin Metronidazole interacts easily. If we use disulfiram with metronidazole, it can produce acute conditions of confusion. Combining these medications may produce some psychotic reactions such as delusions and hallucinations in some patients. With metronidazole the consequences of anticoagulation of warfarin may be potentiated. Metronidazole grows the risk for over anticoagulation where acenocoumarol used by patients. This fusion must be avoided [(5)].

The formulations are used in the inhibition of formation of dental plaque, treats and prevents gingivitis. Also used after the periodontal surgery or treatment that promotes gingival healing. In the execution of recurrent aphthous ulceration it is applied. The formulation is also useful in the execution of recurrent oral candida infections. Its application has been associated with toxicity; however it is hardly characterized [(6)]. It is also being explored as a prophylactic agent in numerous surgical procedures. Metronidazole, as a 5-nitroimidazole compound is effective on anaerobic bacteria & protozoan disease. Mostly, metronidazole is tolerable drug but rarely creates serious adverse effects on the nervous systems. For these adverse effects treatment must be stopped. Pancreatitis is infrequent but potentially dangerous and unfortunate effect of metronidazole**.** The adverse effect of metronidazole gel is local and comes after the application. Bitter taste and temporary local tenderness, Headache can also come. In the dorsum layer of the tongue a superficial discoloration may occur. Discoloration of teeth may also occur. This adverse effect is disappeared after discontinuing the treatment.

In this study metronidazole gel was prepared with single polymer carbopol. Novelty in that study is to prepare less viscous gel because drug release can be improved or increased if gel is not thick.

For this Metronidazole gel preparation Carbopol was used as gelling agent. For buccal, transdermal, ocular, rectal & nasal delivery systems of drugs, carbopol is majorly used. Previous research works had combined Agarose with carbopol to prepare smart gel [(7)]. But this study contains simple polymer carbopol. Carbopol is also used in floating tablets [(8)]. After long time stirring the system becomes Thixotropic in gel preparation. Concentration of carbopol is concerned with a good quality gel preparation & the rates of drug release are extremely sensitive to the rheological behavior of the gel formulations that are topically used. Some research work contains multiple polymers and oil phase like liquid paraffin [(9)]. But oily phase does not absorb easily, so this study was done excluding any oily phase. Therefore, this flow behaviour of this excipient acts as function of neutralization. Polymer concentration is concerned with the evaluation of Carbopol. Till a certain of pH range, it works as jellifying agent & their potential uses are characterized as dermatological bases. The other excipient for this preparation was Lactic acid. To

dissolve Carbopol completely lactic acid was used. Lactic acid has its antibacterial property. It reduces the microbial growth in gingival plaque.

2 Methodology

2.1 Materials

Table 1. Amounts of materials for gel composition

Ingredients	F1	F2	F3
Metronidazole	250mg	250mg	250mg
Carbopol	250mg	500mg	750mg
Lactic acid	2ml	2ml	2ml
Distilled water	q.s.	q.s.	q.s.

2.2 Method of preparation for metronidazole gel

Carbopol of different amounts was taken for all three formulations. A magnetic stirrer was used to dissolve Carbopol with distilled water at 50 RPM for 20 minutes. Temperature of the distilled water was kept within 20-25°C. Metronidazole was incorporated into the formulation of required and same concentration. Lactic Acid (2%) was used later for a complete dissolution & to make a gel formation slowly.

3 Results and Discussion

3.1 PH test

pH of prepared three formulations were tested with litmus paper. The litmus paper color was examined for each sample and matched for pH determination. Result of pH testing was within range for all formulations. pH of Metronidazole gel for F1, F2 and F3 was 5, 5 and 6 respectively.

3.2 Viscosity

Viscosity of formulations was calculated manually by using a metal ball falling method. Measurement of ball diameter was done by vernier calipers. Density of formulations was measured by mass and volume.

All three formulations of 30 ml were incorporated in the measuring cylinder. Height of gels was taken. Metal ball was allowed to fall from air surface and time to reach at bottom of cylinder was measured by stopwatch. From these values of distance and timing, velocity of balls was calculated. Resulting Viscosity of F1, F2 and F3 was respectively 30.44, 33.43 and 34.16 Pa.sec.

Viscosity measurement result was such like that F3 achieved the highest viscosity and F1 shown the lowest viscosity because of Carbopol quantity.

$$\eta = \frac{mg - \frac{4}{3}r^3 g\rho}{6rv}$$

Where, η = Viscosity of gel, m= mass of metal ball, g = gravitational force, r= radius of ball, ρ= density of gel and v= velocity of ball.

3.3 Spreadability testing

Glass slides were used for this test. The length of the glass slide was measured. Between two glass slides excess sample of the formulations were placed. 20 gm weight was given on the upper glass slide for 5 minutes to compress the sample. For separation timing of two slides (in seconds) was taken for measurement of Spreadability[10]. Rheological measurements are correlated with Spreadability. Spreadability of F1 was greater than other formulation which was 9.72 gm.cm/sec. spreadability of F2 and F3 was 7.31 and 6.62 gm.cm/sec respectively.

Spreadability, S = M. L/T

Where, M= weight attach to upper slide, L= Glass slide Length, T=Time required to separate the slides.

3.4 Percentage Drug Content

From all three formulations (F1, F2, F3), 1 ml of sample was taken hold of different test tubes which was liquefied in 9 ml of water for making up the volume 10 ml. For dissolution magnetic stirrer was used. In the UV Spectrophotometer absorbance was checked for formulations. According to result of drug content F1 had shown the highest drug content 98.895 %. F2 and F3 had shown 98.884 % and 97.956 % of drug content but less than F1.

Percentage Drug Content = (Actual drug content/Total amount of drug taken) × 100

3.5 *In-vitro* Drug Release Study

Release study of Drug was achieved by diffusion process. A semi-permeable membrane (Supplied by Abron Exports) was taken of suitable size and soaked with distilled water before 15 minutes of use. 0.5 ml of the gel formulation was taken individually in test tubes. The end section of test tubes semi-permeable membrane was tied with thread. The sample tubes were immersed in beakers of distilled water (100 ml). To a distance of 1cm under the surface of medium (distilled water), the neck of the sample tubes was immersed and for agitation magnetic kind stirrer was used, temperature of medium was kept at 25°C throughout the study. Aliquotes of 5 ml from the beakers were withdrawn periodically at 15 minutes interval for 2 hrs and each time equal volume was restored with distilled water. After withdrawal of 5 ml sample, it was thinned out with distilled water (5 ml). Release of drug was estimated by checking the absorbance of samples using UV spectrophotometer at 320 nm. Table 2 represents drug release results for F, F2 and F3 according to time. After 120 minutes it was founded that F1 was showing better result for percentage of release from drug. Highest percentage of release from drug was 91.945 % for F1. Where, F3 had shown the lowest release of drug about 88.598 % within 120 minutes of study.

Table 2. *In-vitro* Drug release study of gels

Time (minutes)	% Drug release		
	F1	F2	F3
15	34.982	31.92	26.36
30	42.263	39.297	36.198
45	50.465	47.434	45.428
60	79.622	77.696	75.485
75	85.668	81.964	78.881
90	89.489	87.693	86.768
105	91.945	89.612	88.598
120	88.657	86.978	85.206

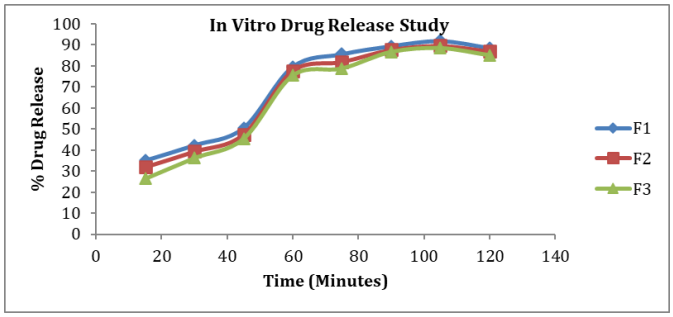

Fig 1. Timevs % Drug Release study of Metronidazole gel

3.6 Drug Release kinetics determination

Release kinetics for gel formulations was resolved by plotting against different kinetics models [11].

Equation, $F = K_o t$ is for kinetics, zero order; where F, t and K_o is drug fraction, release (in time) and release constant (zero order) respectively.

Equation, ln (1-F) = - K_1t for First order kinetics; where F, t and K_1 represents drug fraction, released (in time) and the release constant (first order).

Equation $F=K_H t^{1/2}$ is for Higuchi model; where F, t and K_H is drug fraction, released (in time) and the Higuchi dissolution constant respectively.

Equation, $Q^{1/3}=kt+Q_0^{1/3}$ is for Hixson-Crowell model; where drug release (in time), the starting value for Q and rate constant is Q, t, Q_0 sequentially.

Equation, $F=K_p t^n$ is for Korsmeyer-Peppas model, where F, t, Kp and n represents the drug fraction, release (in time) and the Korsmeyer-Peppas (rate constant), and exponent for release serially [12]

Kinetic models study had shown that F1 and F2 mostly follow zero order reaction which means rate of reaction was not depending upon concentrations (gels). Regression co-efficient for F1 and F2 (Zero order model) was 0.9914 and 0.9901 respectively Table 3

Table 3. Result of curve fitting of metronidazole releasing from gel

Kinetic models	Regression co-efficient		
	F1	F2	F3
Zero Order model	0.9965	0.9922	0.9621
First Order model	0.9904	0.9855	0.9071
Higuchi model	0.9822	0.9612	0.9852
Hixon-Crowell model	0.9936	0.9862	0.9245
Korsmeyer-Peppas model	0.9631	0.8105	0.6562

Fig 2. Zero Order Model

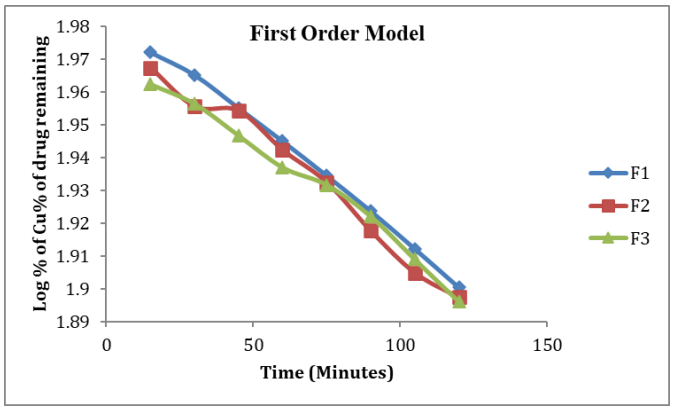

Fig 3. First Order Model

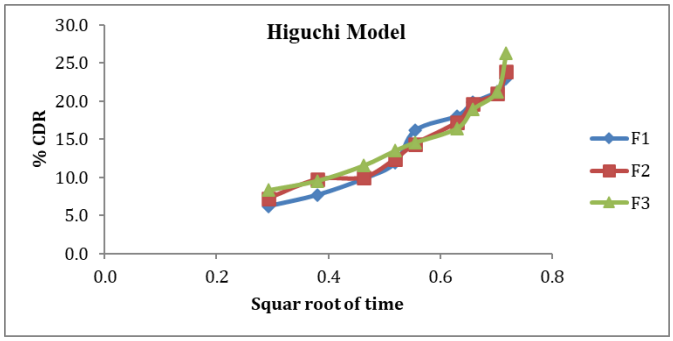

Fig 4. Higuchi Model

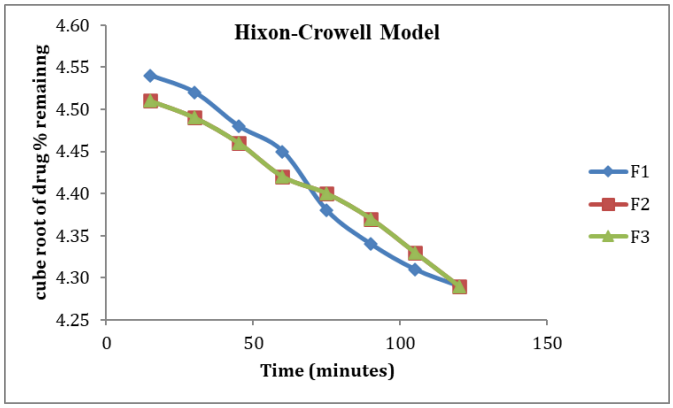

Fig 5. Hixon-Crowell model

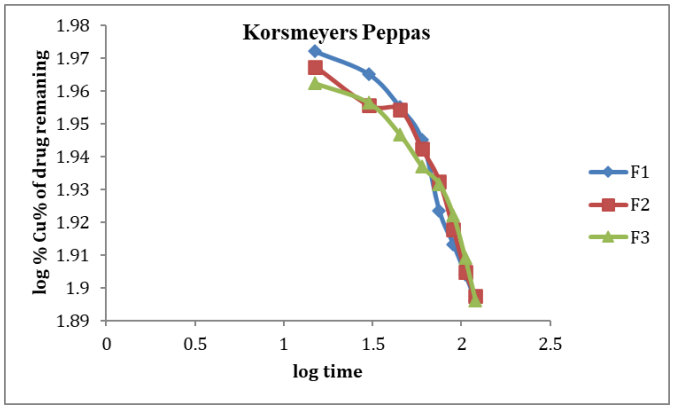

Fig 6. Korsmeyers Peppas model

3.7 Antimicrobial Susceptibility Test

For culture media, beef extract, peptone and agar were used and dissolved in solvent (distilled water) and thereafter autoclaved for 30 minutes at 121°c. After autoclaving nutrient agar media was poured in three separate Petri dishes. After solidification of agar gel the test was performed by inoculating with metronidazole formulations at outside of the agar plate. Afterward it was incubated (24 hours). After 24 hours of incubation the bacterial growth was observed Figure 1. Zone (inhibition) for each formulation was measured. Bacterial Susceptibility to each of the metronidazole formulation was compared. Zone (inhibition) for F1 was larger than F2 & F3.

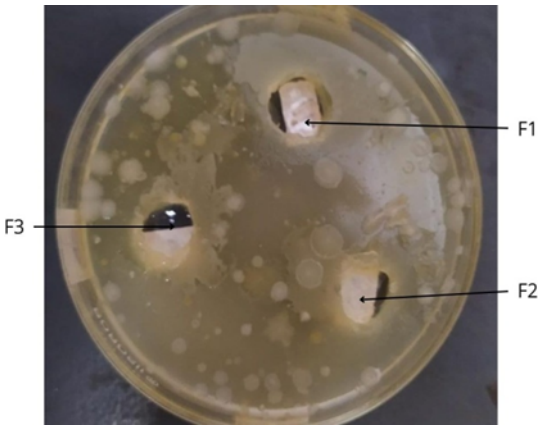

Fig 7. Zone of inhibition of metronidazole formulation

3.8 Stability Test

After 1 month storage, stability test was done for all gel formulations by checking color, odour, pH testing, percentage of drug content and *in-vitro* release study of drug. Even after 1 month storage it was founded that no changes in appearance (color) and odour was noticed there. All of these formulations were whitish transparent with a pleasant odour. pH of formulations was unchanged and within 5 to 6. After storage, drug content for F1, F2, and F3 was 95.842%, 93.224% and 91.531% sequentially. After stability testing, *in vitro* drug release study was done (Table 4).

Table 4. *In-vitro* drug release study (after 1 month)

Time(mints)	% Drug release		
	F1	F2	F3
15	34.253	30.512	25.566
30	39.229	38.102	35.078
45	48.542	46.659	44.136
60	78.245	76.525	74.289
75	82.669	80.865	77.355
90	87.782	86.686	85.625
105	90.327	88.594	87.462
120	88.243	85.249	84.585

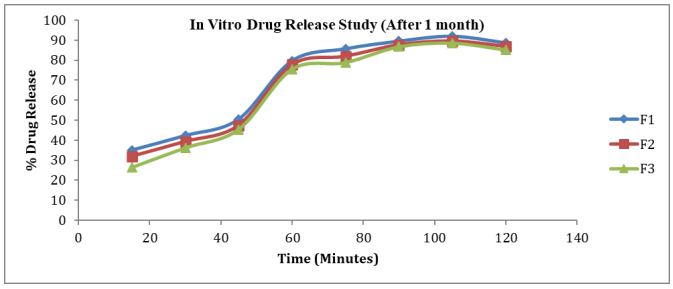

Fig 8. Timevs % Drug release study (after 1month preparation of gels)

Periodontitis disease generates periodontal junction inflammation and this said to be one main causes of oral morbidity all over the world [13]. Three formulations of Periodontal metronidazole gels were prepared & evaluated by pH test, viscosity, spreadability, antimicrobial test, drug content, *in-vitro* release study of drug, release kinetics and stability testing. So as to check drug release, decrease in the side effects, & bioavailability (increasing) of the drug at the site of action was aim of this study.

Novelty of this study is formulating low viscosity gel of metronidazole by using single polymer, Carbopol. Researches already done for metronidazole gel formulations but most of them were emulsion gels or bigels [14]. Research works were done with multiple polymers which make formulation more viscous and reduce spreadability. Because it was observed during studies that viscosity of gels can alter drug release pattern, oleo gel showed lower drug release pattern then hydrogels [15] so this study concentrating on that portion. Metronidazole proved as low cost and effective drug for its activeness for anaerobic kind bacteria, most effective pharmacokinetic and along with pharmacodynamic drug properties, and less adverse effects. In this study three different amount of carpobol had been added in formulations. During Spreadability testing it was founded that F1 has the highest Spreadability (9.72 gm.cm/sec). In viscosity analysis it was distinguished that F3 has highest viscosity (34.16 Pa.Sec) but F1 has lowest viscosity (30.44 Pa.Sec). From this current analysis it must be confessed that less viscous gels have better Spreadability. pH result of wholly formulations was within natural skin pH range suitable for topical gels which was 5 to 6. Percentage drug content test results had again shown the highest value for F1 (98.895 %). After evaluating gels by drug release study, it was spotted that F1 gave the highest percentage of *in-vitro* drug release which was 91.945 %, for F2 and F3 it was 89.612 % and 88.598 %. Release kinetics was determined by Zero order, First order, Higuchi model, Hixon-Crowell and Korsmeyer-Peppas [16,17]. Finally it was observed that F1 and F2 mostly follow zero order reaction with regression co-efficient values 0.9965 and 0.9922 sequentially. In antimicrobial susceptibility test nutrient agar culture media was used and after 24 hours study inhibition zone was measured. F1 had shown the highest Inhibition characteristics. For stability testing samples were stored since 1 month [18]. Stability testing reports was done for color, odour, pH testing, percentage of drug content and *in-vitro* drug release study. Stability testing used for evaluation of the effects of environment related factors on the consistency of the formulated product.There was absolutely no color and odour change observed during storage. After month, *in-vitro* drug release study had shown that release of F1, F2 & F3 was 90.327 %, 88.594% & 87.462 % respectively. The drug content of F1 was greater than other formulations (95.842 %), where F2 and F3 had 93.224 % and 91.531 % of drug content. From this current study conclusion founded that F1 had shown better results in different evaluation tests for the reason of its low viscosity. Also, F1 follows zero order reaction that denotes the release rate does not depends against the concentration accord to formulation.

4 Conclusion

This study presents the preparation of metronidazole gel formulation with single polymer Carbopol. The purpose of present investigation to prepare low viscosity gel for getting better drug release when applied topically was achieved. Spreadability of formulation improves absorption of drugs into application site; better spreadability was attained during study. Aqueous gels have better absorption capacity so attending study was focused on that. Antibiotic activity was estimated by zone of bacterial inhibition. Drug release study report had shown highest and most promising for F1 which was 91.945 %. In occasion of percentage drug content also F1 gave the highest value of 98.895 %. As collated to all three formulations F1 has low viscosity (30.44 Pa.Sec). So, it is concluded that low viscosity formulation has better drug release pattern. Spreadability of F1 was also elevated than other formulations. pH of entirely formulations were within the correct scale (5 to 6) of topical application. Zone of inhibition result had shown more positive report for F1. Drug release kinetics results of F1 and F2 best fitted in zero order reaction with R^2 values 0.9914 and 0.9901 respectively, so drug release was concentration independent. After 1 month stability testing at ambient temperature, it was determined that all batches particularly F1 was stable enough. Further studies can be done to prepare low viscosity gel formulations with any other polymer.

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