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Formulation and optimization of Trimethoprim topical gel

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ABSTRACT: Background: A topical drug delivery system is one that is applied directly to an external body surface by inducting, spraying, or dusting on or instilling. **Aim:** The aim of this present research work was to get local action and reduce the side effects in contrast to the oral dosage form. Trimethoprim is an antibacterial drug and has been used in the treatment of bacterial infections such as boil or folliculitis caused by *Staphylococcus aureus*. **Method:** The concentration of the drug and Carbopol 940P were selected i.e., 1 and 2 % respectively. Various penetration enhancers such as Six different penetration enhancers were used from different categories i.e., natural (Neem Oil and Menthol), semi-synthetic (Ethanol and Propylene glycol), and synthetic (Oleic and Caprylic acid). **Result:** Three concentrations (2, 5, and 10 %) of each penetration enhancer were used to formulate F1 to F18 batches by using the dispersion method. The variation in their concentration was studied for their effect on the drug release profile and permeation enhancement. All the formulations were investigated for homogeneity, pH, drug content, spreadability, extrudability, rheological study, gel strength, *in vitro* diffusion study, *in vitro* microbial study, and stability studies. Maximum cumulative % release obtained from the formulations F3, F9, and F15 was 96.365, 80.949, and 91.106 % respectively. **Conclusion:** Formulation F3 having 10 % Neem Oil was found to be the best formulation with a maximum release of 96.365 and a good inhibition zone.

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INTRODUCTION:

A topical delivery system is one that is applied directly to an external body surface either by injecting it, spraying or dusting it on, or by instilling it [1]. Topical delivery can be defined as the application of a drug-containing formulation to the skin to get local action and directly treat cutaneous disorders (e.g. acne) or the cutaneous manifestations of a general disease (e.g. psoriasis), bacterial or fungal infection with the intent of containing the pharmacological or other effects of the drug to the surface of the skin or within the skin [2,3]. The skin of an average adult body covers a surface area of approximately 2 m^2 and receives about 1/3rd of the blood

circulating through the body. The thickness of the human skin ranges from 0.5 mm on the eyelids to 4 mm on the heels. An average human skin surface is known to contain, on average 40 to 70 hair follicles and 200-300 sweat ducts on every square centimeter of the skin [4,5].

The main objective of formulating the topical gel of Trimethoprim was to reduce gastrointestinal incompatibility and to get local action. Trimethoprim is a bacteriostatic antibiotic. Trimethoprim binds to dihydrofolate reductase and inhibits the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF). The is an essential precursor in the thymidine synthesis pathway and interference with this pathway inhibits bacterial DNA synthesis [6]. Trimethoprim (5-[(3,4,5-trimethoxyphenyl)methyl]pyrimidine-2,4-diamine) is an anti-infective, anti-malarial drug. Trimethoprim is used to treat boil furuncle, an infection of hair on the skin follicle (most of the skin is covered with tiny hairs that grow out of the hair follicle). It is usually caused by (bacterium) called *Staphylococcus aureus* [7].

It is a white or yellowish-white powder, sparingly soluble in chloroform, slightly soluble in ethanol (95 %), very slightly soluble in water, and practically insoluble in ether. It is given either alone or in combination with sulfamethoxazole. The drug has to be administered 2 to 3 times daily so as to maintain an adequate plasma level of the drug and the dose of the drug is also high i.e. 200 mg which creates Gastrointestinal problems. Grasto-intestinal irritation should be the major side effect in the case of the marketed oral dosage form. To overcome this problem it was formulated in topical dosage form.

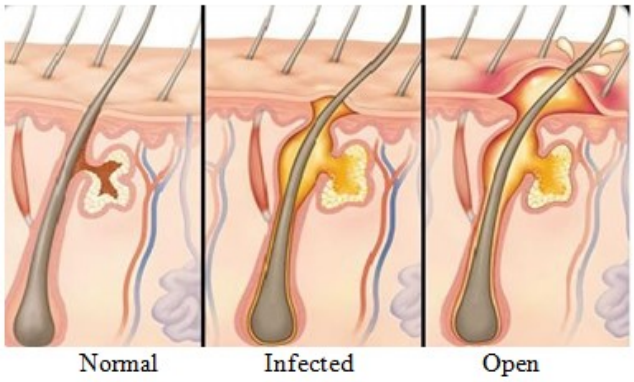

Fig 1. Showing infection of boil.

Penetration enhancers are used to remove the barrier resistance of the stratum corneum reversibly [8]. Among various penetration-enhancing methods used, the use of chemical penetration enhancers is one of the most suited. In the present study penetration enhancers obtained from natural, semisynthetic, synthetic sources were employed to increase the permeation of the drug [9].

Neem oil is a vegetable oil pressed from the fruits and seeds of neem (*Azadirachta indica*) [10]. Menthol is a subclass of Terpenes and terpenoids are usually the constituents of volatile oil. Their chemical structure consists of repeated isoprene (C_5H_8) units and shows good penetration enhancers. Oleic acid and caprylic acid are unsaturated fatty acids that are more effective in enhancing the percutaneous absorption of drugs than their saturated counterparts. Ethanol is the most commonly used alcohol as a transdermal penetration enhancer; Polyethylene glycol has also shown good penetration-enhancing properties [11].

It is evident that research on topical application of Trimethoprim is underway and currently, there are no topical marketed formulations available. To avoid the gastric and other side effects of oral dosage form, topical gel is formulated and evaluated to get local action.

MATERIALS AND METHODS:

Trimethoprim was obtained as a gift sample from Cure Tech, Baddi. Carbopol 934P, Carbopol 940P was gifted by SD Fine Chem Ltd. Neem oil, Menthol, Propylene glycol, Oleic acid, Caprylic acid was provided by Genuine Chemical Co. Mumbai, Hi-Media, Merck, SD Fine Chem Ltd., respectively. Solvents used are all of analytical grade. Double distilled water was used throughout the study.

Preparation of Gel:

The gel was prepared by dispersion method (Table 1). The polymer Carbopol 940 was dispersed in measured quantities of distilled water with the help of a magnetic stirrer and allowed swelling for 2 h. The drug was dissolved in DMSO (q.s.) and propylparaben was dissolved in ethanol (q.s.) and the above prepared solution was added in the previously dissolved solution of Carbopol 940 in distilled water. After complete addition penetration enhancer was added and mixed thoroughly. Dispersion obtained was neutralized with required quantity of triethanolamine to pH 7.4 to obtain gel [12,13].

Fourier Transform Infrared Analysis:

The main application of the FTIR spectrophotometer is the determination of the identity of a compound by means of spectral comparison with that of an authentic sample and verification of the presence of functional groups in an unknown molecule. The sample was

Table 1. Composition of Trimethoprim Topical Gel.

Ingredients % w/w	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Trimetho-prim	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
C 940 P	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Neem Oil	2	5	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Menthol	-	-	-	2	5	10	-	-	-	-	-	-	-	-	-	-	-	
PG	-	-	-	-	-	-	2	5	10	-	-	-	-	-	-	-	-	-
Ethanol	-	-	-	-	-	-	-	-	-	2	5	10	-	-	-	-	-	-
Oleic acid	-	-	-	-	-	-	-	-	-	-	-	-	2	5	10	-	-	-
Caprylic acid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	5	10
PP	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
DMSO	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
TEA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water (up to)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

q.s. – Quantity sufficient, PG – Propylene Glycol, C 940 P - Carbopol 940 P, PP – Propyl Paraben.

mounted in the FTIR compartment and scanned at wavelengths 4000 to 400 cm^{-1}. For analysis, IR spectra of the pure drug have been performed and no major differences were observed in the absorption peak pattern.

Selection criteria of polymer and drug:

Selection of concentration of polymer:

Gels were prepared using different polymers such as Carbopol 934P and Carbopol 940P. The gel prepared with Carbopol 940P shows better results when evaluated for Viscosity, Homogeneity, pH, Spreadability, Clear gel, and Extrudability. Carbopol 940 having a concentration of 1 % shows good results.

Selection of concentration of drug:

The concentration of the drug was selected by the Agar cup and plate method. To determine the minimum inhibitory concentration, a different concentration of Trimethoprim in DMSO (1, 2, 3, and 4 %) was selected for the study of antibacterial activity. Lyophilized spores of staphylococcus were grown in a Nutrient broth medium. Slants were prepared and finally, suspension of reproductive cells should be mixed in Nutrient agar Medium and poured in sterile petridishes, and allowed to solidify. Holes of 5 mm depth were done with a borer. A drug was added to it using a micropipette. The concentration of bacteria was kept constant. The zone of inhibitions was measured. The 2 % concentration was selected for antibacterial activity.

Evaluation of Gel Formulations:

***Physical appearance*:**

The gel was visually inspected for clarity, color, odor, and texture [14].

Homogeneity:

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

Grittiness:

All the formulations were evaluated microscopically for the presence of particles if any. No appreciable particulate matter was seen under the light microscope. Hence obviously the gel preparation fulfills the requirement of freedom from particulate matter and from grittiness as desired for any topical preparation [15].

Determination of pH:

The pH of the formulated gels was determined using a digital pH meter. The electrode was immersed in the gel and readings were recorded from a pH meter [16].

Viscosity measurement [17]:

The viscosity of the gel was determined using a Brookfield viscometer at 25±0.3 °C. The spindle no. 64 used for determining the viscosity of gel at 25 rpm.

Drug content uniformity [18]:

The drug content estimation was carried out by dissolving an accurately weighed quantity of hydrotropic starch gels equivalent to 10 mg of drug was added to 10 ml of volumetric flask and the volume was made up to 10 ml with methanol. 1 ml filtrate was transferred into another 10 ml of volumetric flask and the volume was made up to 10 ml with methanol. And again 1 ml of the above solution was diluted with 10 ml of methanol. The content was assayed at 260 nm against reagent blank by using Shimadzu UV/visible spectrophotometer. The drug content was carried out in triplicate.

Table 2. Physicochemical characters of Gels formulations.

Formulation	Homogeneity	Grittiness	Extrudability (Wt. required in g)
F1	+++	-	420
F2	+++	-	467
F3	+++	-	432
F4	+++	-	540
F5	+++	-	480
F6	++	-	534
F7	+++	-	538
F8	++	-	480
F9	+++	-	505
F10	+++	-	420
F11	++	-	474
F12	+++	-	432
F13	++	-	580
F14	+++	-	493
F15	+++	-	521
F16	++	-	576
F17	++	-	476
F18	++	-	518

+++ (Excellent), ++ (Good), - (No grittiness).

Table 3. Physiological evaluation data of Trimethoprim gel formulations.

Formulations	pH	Drug content (%)	Viscosity (Cps)	Spreadability (g.cm/s)
F1	7.1±0.18	95.82±0.038	20650±20.81	33.07±1.11
F2	7.2±0.10	96.72±0.028	25000±15.27	37.27±1.31
F3	7.4±0.15	99.15±0.034	31500±.30.00	31.42±0.82
F4	7.4±0.10	94.63±0.049	22510±25.16	33.07±1.11
F5	7.5±0.15	94.73±0.046	20900±30.55	30.00±1.53
F6	7.2±0.11	94.95±0.066	24100±20.81	31.42±0.00
F7	7.4±0.17	98.27±0.028	24320±25.16	28.75±0.72
F8	7.2±0.15	97.90±0.062	24540±25.16	27.64±0.63
F9	7.3±0.15	98.64±0.028	35480±20.00	26.66±0.56
F10	7.2±0.21	95.82±0.078	29550±20.81	24.07±1.11
F11	7.1±0.15	99.72±0.059	26000±15.27	33.27±1.31
F12	7.4±0.14	97.15±0.014	25300±.30.00	39.42±0.82
F13	7.3±0.12	99.85±0.049	29610±25.16	38.07±1.11
F14	7.4±0.15	99.53±0.046	20900±30.55	26.00±1.53
F15	7.1±0.16	97.35±0.018	32100±20.81	35.42±0.00
F16	7.5±0.19	94.87±0.023	16870±25.16	26.75±0.72
F17	7.4±0.13	98.90±0.016	18760±25.16	33.64±0.63
F18	7.1±0.12	99.64±0.024	17510±20.00	24.66±0.56

Extrudability study:

The extrudability of formulations from aluminum collapsible tubes was determined using a universal tube filling machine. Aluminum collapsible tubes filled with 10 g gels were held between two clamps. A tube was compressed and the extrudability of the formulation was determined in terms of weight in grams required to extrude a 0.5cm ribbon of gel in 10 s [11].

In vitro Antibacterial Study:

The final formulations F3, F9, and F15 were studied for antibacterial activity. An appropriate amount (100 mg) of Gel was dissolved in a sufficient quantity of DMSO

Table 4. Zero Order drug release data of Trimethoprim gels of formulation F1-F6.

Time (h)	Cumulative % Drug Released					
	F1	F2	F3	F4	F5	F6
0.5	1.574± 1.345	3.664± 1.245	5.852± 1.239	2.034± 1.320	2.954± 1.045	3.567± 1.090
1	4.333± 1.239	8.137±1.567	15.319±1.312	7.552± 1.290	10.895±1.456	11.620±1.236
2	7.747± 1.189	18.865±1.643	29.426±1.289	13.375±1.487	19.534±1.543	21.624±1.171
3	12.191±1.586	29.746±1.008	45.769±1.687	20.871±1.034	28.897±1.239	34.804±1.192
4	19.603 ±1.090	42.732±0.989	62.948±1.990	30.513±1.180	39.625±1.659	48.932±1.240
5	29.119±1.130	56.135±1.037	80.378±1.280	41.965±1.160	50.910±1.869	68.048±1.586
6	40.307±1.170	67.783±1.168	96.366±1.190	49.879±1.140	67.546±1.799	87.637±1.894

Table 5. Zero Order drug release data of Trimethoprim gels of formulation F7-F12.

Time (h)	Cumulative % Drug Released					
	F7	F8	F9	F10	F11	F12
0.5	4.640± 1.004	5.657± 1.723	7.997± 1.456	3.504± 1.107	3.444± 1.452	4.161± 1.965
1	9.405± 1.339	12.790±0.869	16.747±1.009	7.737± 1.290	7.976± 1.153	9.363± 1.843
2	15.828±1.386	21.902±0.799	26.584±1.874	12.903±1.374	14.086±1.896	16.382 ±1.635
3	23.463±0.992	32.895±1.163	38.064±1.359	19.683±1.593	22.935±1.247	27.910±0.996
4	32.477±1.723	44.641±1.498	50.242±1.829	28.687±1.742	32.585±1.249	39.820±1.335
5	43.261±1.120	57.375±0.863	63.868±1.150	38.397±1.829	46.062±1.182	53.249±1.617
6	57.891±1.854	70.973±1.854	80.949±1.278	49.673±1.814	59.730±1.913	67.443±1.562

Table 6. Zero Order drug release data of Trimethoprim gels of formulation F13-F18.

Time (h)	Cumulative % Drug Released					
	F13	F14	F15	F16	F17	F18
0.5	0.516± 0.224	1.574± 1.118	2.968± 1.713	2.520± 0.953	2.640± 1.120	6.435± 1.214
1	2.522± 1.613	6.116± 1.134	8.262± 2.074	5.325±1.278	5.850± 1.140	14.610±1.428
2	6.256± 0.915	12.971±1.695	15.479±1.196	9.765± 1.554	12.930±1.651	23.130±1.515
3	12.205±1.442	21.443±1.248	25.093±1.228	16.200±1.961	21.435±1.932	32.070±1.873
4	20.272±1.579	32.087±1.016	38.413±1.119	23.520±1.872	32.610±1.041	41.520±1.624
5	28.492±1.105	44.390±0.864	61.750±1.071	32.175±1.885	44.325±1.621	52.140±1.573
6	38.064±1.361	57.124±1.915	91.106±1.915	41.760±1.443	56.370±1.096	65.115±1.924

and was evaluated by the measurement of the mean diameter of the growth inhibitor zone in millimeters.

Spreadability:

The spreadability of formulations was determined by an apparatus suggested by Multimer 45, which was fabricated in the laboratory and used for slides fixed on a wooden block and upper slide with one end tied to a glass slide and the other end tied to the other end tied to a weight pan. An excess of gel (2 to 5 g) was placed in between two glass slides and then 1000 g weight was placed on slides for 5 min to compress the sample to a uniform thickness. Weight (80 g) was added to the pan. The time (seconds) required to separate the two slides, was taken as a measure of spreadability [11,18]. It was calculated using the formula,

S= M.L/T ….(1)

Where, S=spreadability, M=weight tied to upper slide, L= length of glass slide, T= time taken shorter time interval, to cover the distance of 6.5 cm, indicates better spreadability.

***In vitro Diffusion studies*:**

The *in vitro* diffusion studies of prepared gel were carried out using the Keshary-Chien diffusion cell. About 500 mg of gel containing 7.69 mg of Trimethoprim was spread uniformly on the cellophane membrane. In the Modified Franz diffusion cell, 6 ml of phosphate buffer was used as the receptor compartment. The donor compartment was kept in contact with the receptor compartment and the temperature was maintained at 37±0.5 °C. A sample of 1 ml was

withdrawn at different time intervals and replacement was done with 1 ml of fresh buffer. The drug concentration on the receptor fluid was determined spectrophotometrically against blank [19,20].

Analysis of the release data:

The data of *in vitro* Trimethoprim permeation from various topical gels through cellophane membranes were evaluated kinetically using four kinetic models that are zero order, first order, Higuchi, and Korsmeyer Peppas equation. Regression analysis was adopted to compute the constant and correlation of data (r^2) [21].

Stability studies and statistical analysis:

For stability studies, tablets from formulation batch F3 were placed in wide-mouth air-tight glass containers and stored at 40 ±2 ºC / 75 ± 5 % RH for 2 months. The tablets were observed after a time interval of 7 days up to 2 months for any physical defect and then analyzed by carrying out the determination of drug content and dissolution profile [22].

RESULTS AND DISCUSSION:

In the present study, topical gels of Trimethoprim were prepared in 18 formulations with varying concentrations of penetration enhancers such as Natural (Neemoil, Menthol), semisynthetic (Propylene Glycol, Ethanol), Synthetic (Oleic acid, Caprylic acid).

All the trimethoprim gel formulations in Table 1 show no clogging or lumps which indicates a good texture of the system. The complication of bubble generation was not observed while formulating the Carbopol formulations.

Increasing the concentration of penetration enhancers shows remarkable change in the enhancement of *in vitro* drug release. Natural penetration enhancers show a better release profile as compared to semisynthetic and synthetic.

Drug excipient compatibility studies did not show significant differences in FTIR spectra. All the prominent peaks of Trimethoprim were present in the drug excipient mixture which clearly indicates that there is no interaction between drug and polymer.

All the formulations were investigated for homogeneity, pH, drug content, spreadability, extrudability, rheological study, gel strength, *in vitro* diffusion study, *in vitro* microbial study, and stability studies. All gel formulations were elegant in appearance. A thin and smooth film was formed on application to the skin and easily washable with water. The drug content of Trimethoprim in topical gel was found to be 94.6±0.041 to 99.5 ±0.027 %.

The present work revealed that Neem Oil, Propylene glycol, and Oleic acid show the best release as compared to their respective class penetration enhancer. Maximum cumulative % release obtained from the formulation F3, F9, F15 was 96.365, 80.949, 91.106respectively. Formulation F3 having 10 % Neem oil was found to be the best formulation with a maximum release of 96.365 %. *In vitro, the* anti-bacterial study was done on the bacteria *Staphylococcus aureus* with F3, F9, and F15 formulations. Anti-bacterial activity was evaluated by the measurement of the diameter of the growth inhibition zone and the F3 formulation exhibited a good inhibition zone. Formulation F3 shows maximum zone of inhibition i.e., 52.27±0.34 mm. The zone of inhibition of *Staphylococcus aureus* is shown in Fig 7.

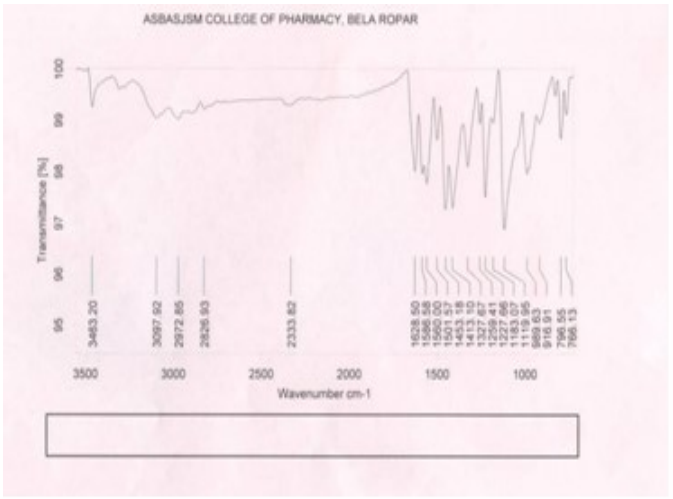

Fig 2. FTIR Spectra of Drug.

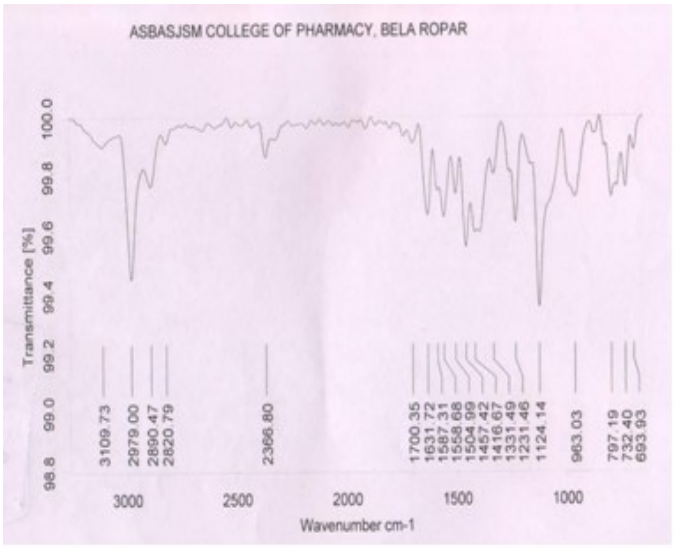

Fig 3. FTIR Spectra of Drug+Polymer.

Table 7. Kinetic analysis of the release data of trimethoprim from the prepared gel formulations.

Formulation	Coefficient of Correlation (R^2) value				
	Zero Order release	First Order release	Higuchi diffusion model	Korsmeyer Peppas Model (release exponent-n)	Best Fitted model
F1	0.954	0.922	0.803	0.427	Zero order
F2	0.995	0.959	0.887	0.753	Zero order
F3	0.999	0.824	0.908	1.0261	Zero order
F4	0.991	0.971	0.880	0.427	Zero order
F5	0.991	0.938	0.888	0.679	Zero order
F6	0.986	0.855	0.863	0.929	Zero order
F7	0.985	0.941	0.876	0.578	Zero order
F8	0.997	0.954	0.909	0.722	Zero order
F9	0.995	0.920	0.918	0.728	Zero order
F10	0.986	0.957	0.872	0.512	Zero order
F11	0.981	0.934	0.855	0.631	Zero order
F12	0.989	0.939	0.872	0.722	Zero order
F13	0.966	0.942	0.808	0.437	Zero order
F14	0.983	0.944	0.850	0.628	Zero order
F15	0.930	0.723	0.766	0.953	Zero order
F16	0.984	0.960	0.858	0.446	Zero order
F17	0.985	0.949	0.854	0.627	Zero order
F18	0.995	0.968	0.931	0.616	Zero order

Table 8. Stability profile of Formulation F8 at different temperature.

Time in days	Refrigerated (4°C/75%RH)		Real Time Storage (30^{0}C/75%RH)		Accelerated (40°C/75%RH)	
	D.C	P.A.	D.C	P.A.	D.C	P.A.
0	9.915	+	9.915	+	9.915	+
7	9.907	+	9.897	+	9.902	+
14	9.896	+	9.882	+	9.884	+
21	9.889	+	9.863	+	9.865	+
28	9.874	+	9.851	+	9.852	+
35	9.856	+	9.842	+	9.849	+
42	9.849	+	9.834	+	9.834	+
49	9.836	+	9.821	+	9.804	+
60	9.825	+	9.815	+	9.785	+

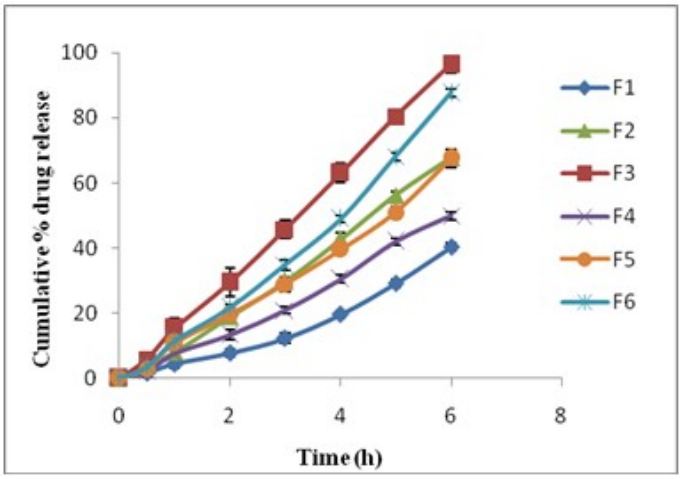

Fig 4. *In vitro* zero order drug diffusion profile of formulation F1-F6.

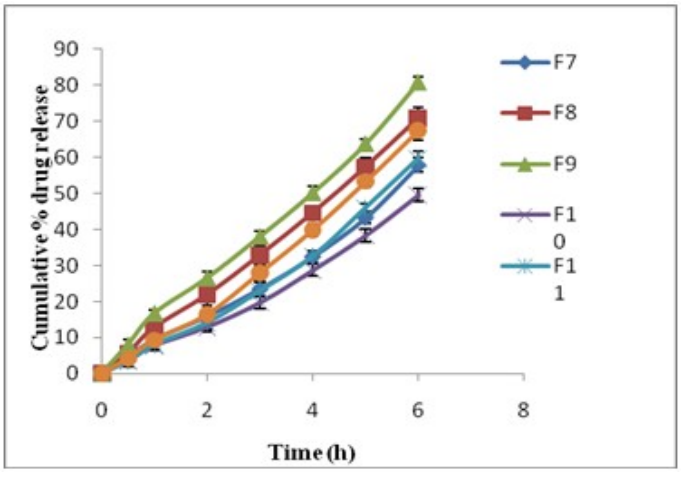

Fig 5. *In vitro* zero order drug diffusion profile of formulation F7-F12.

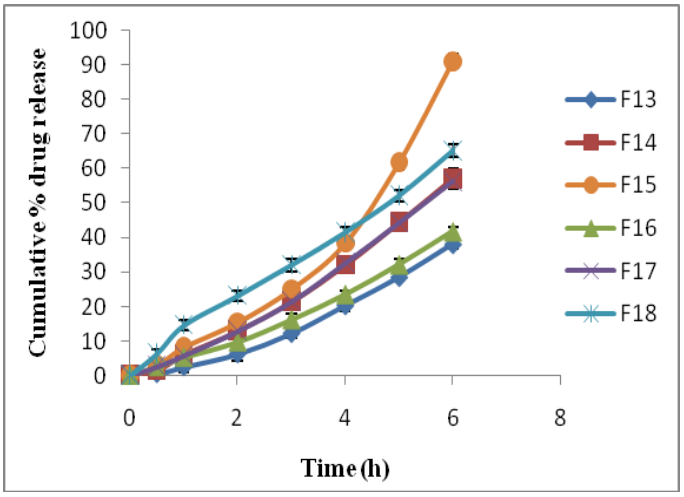

Fig 6. *In vitro* zero order drug diffusion profile of formulation F7-F12.

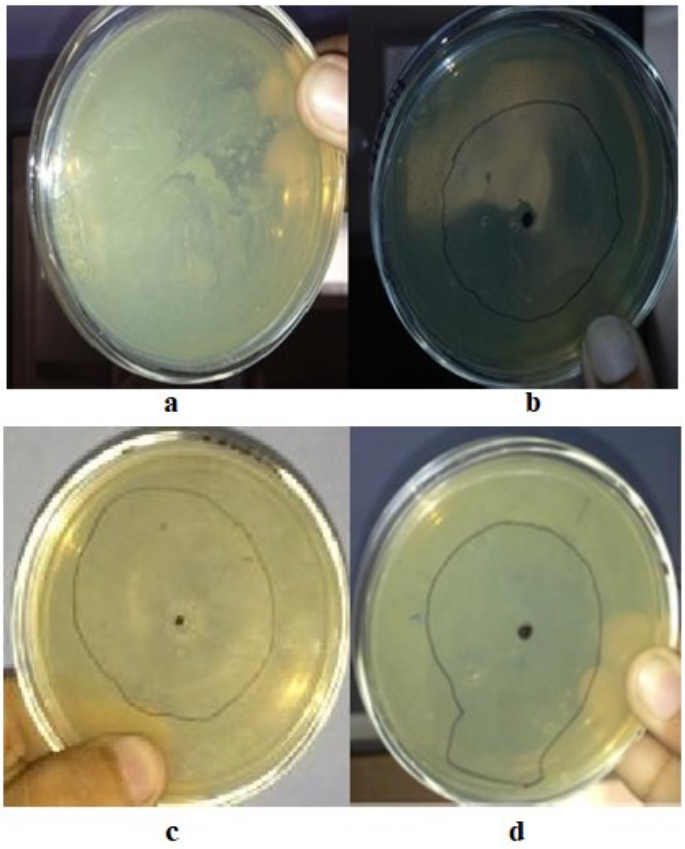

Fig 7. Shows (a): Control, in (b), (c) & (d) the growth inhibition zones of F3, F9, and F15 respectively against *Staphylococcus aureus*.

CONCLUSION:

The result obtained showed that a 1 % concentration of Carbopol 940P polymer is suitable for gel formulation. With an increase in concentration of penetration enhancers the diffusion coefficient increases. Natural penetration enhancers show better results as compared to synthetic and semisynthetic penetration enhancers. Neem oil 10 % shows a maximum *in vitro* drug release and *in vitro zone* of inhibition. All the formulations were stable for 2 months and showed no change in physical appearance and drug content. So it was concluded that the selected formulation is effective in the treatment of disease. Solid lipid nanoparticles can be investigated as a novel topical dosage form for future research. The problem of partition coefficient can be reduced by nanoparticles because the particle size of the model drug in nanoparticles is reduced and it can easily penetrate the skin.

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