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Research Article

Optimized Formulation of Trimethoprim-Infused Topical Gel for Targeted Therapeutic Applications

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ARTICLEINFO

ABSTRACT

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

Keywords: Antibacterial; Topical drug delivery; Staphylococcus aureus; Penetration Enhancer; Topical Gel

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1.Introduction

A topical delivery system is one that is applied directly to an external body surface either by innucting it, by 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 effect 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 approximately 2 m2 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 the average 40-70 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 the gastro-intestinal incompatibility and to get the local action. Trimethoprim is a bacteriostatic antibiotic. Trimethoprim binds to dihydrofolate reductase and inhibits the reduction of dihydro folic acid (DHF) to tetrahydro folic acid (THF). THF is an essential precursor in the thymidine synthesis pathway and interference with this pathway inhibits bacterial DNA synthesis [6]. Trimethoprim (5-[(3,4,5-trimethoxy phenyl) methyl] pyrimidine-2,4-diamine) is anti-infective, anti-malarial drug. Trimethoprim is used to treat boil furuncle an infection of a hair on the skin follicle (most of the skin is covered with tiny hairs that grow out of hair follicle). It is usually caused by (bacterium) called staphylococcus aureus [7,8,9].

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

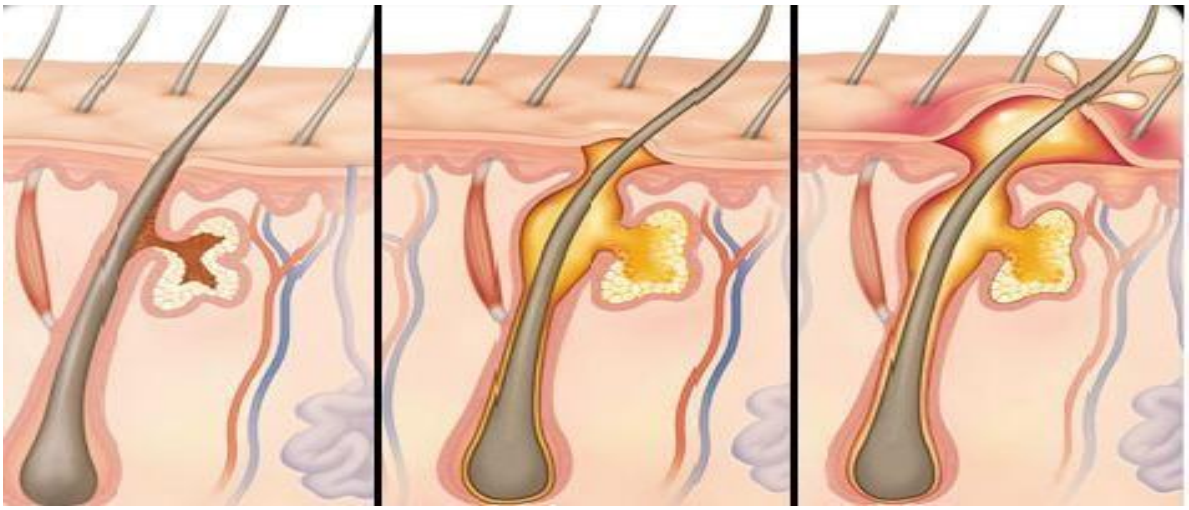

Figure 1: Showing infection of boil.

Penetration enhancing methods used, use of chemical penetration enhancer is one of the most suited. In present study penetration enhancers obtained from natural, semi synthetic, synthetic sources were employed to increase permeation of drug [11].

Neem oil is a vegetable oil pressed from the fruits and seeds of neem (***Azadirachtaindica***) [12]. Menthol is subclass of Terpenes and terpenoids are usually the constituents of volatile oil. Their chemical structure consists of repeated isoprene (C5H8) units and shows good penetration enhancers. Oleic acid and caprylic acid are unsaturated fatty acids are more effective in enhancing 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 [13-14]. 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 evaluate to get local action.

2. 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.The gel was prepared by dispersion method. The polymer Carbopol 940 was dispersed in measured quantity of distilled water with the help of magnetic stirrer and allow to swell for 2 hr. 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 [15-16].

Fourier transform infrared analysis

The main application of FTIR spectrophotometry is the determination of 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 mounted in FTIR compartment and taken scan at wave length 4000 cm¯1 to 400 cm¯1. For analysis, IR spectra of the pure drug have been performed & no major differences were observed in the absorption peak pattern.

3.Selection criteria of polymer and drug

Selection of concentration of polymer

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

Selection of concentration of drug

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

4.Evaluation of formulation

Physical appearance [17,18]

Gel was visually inspected for clarity, colour, odour, texture.

Homogeneity [17,18]

All 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.

Grittiness [*17,18]*

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

Determination of pH [*18,20]*

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

Viscosity measurement [19]

The viscosity of the gel was determined using a Brookfield viscometer at 25±0.3°C. spindle

no. 64 used for determining viscosity of gel at 25 rpm.

Drug Content Uniformity [21,22]

The drug content estimation was carried out by dissolving accurately weighed quantity of hydrotropic starch gels equivalentto 10 mg of drug was added to 10 ml of volumetric flask and the volume were made up to 10 ml with methanol. 1 ml filtrate was transferred into another 10 ml of volumetric flask and volume was made up to 10 ml with methanol. And again 1 ml of 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.

$$\textit{Drug content} = \frac{\textit{Absorbance} \times \textit{Dilution factor}}{1000} \times \frac{1}{\textit{Slope}}$$

Extrudability study [*11,23,24]*

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

In vitro Antibacterial Study

The final formulation F3, F9, F15 were studied for antibacterial activity. Appropriate amount (100 mg) of Gel was dissolved in sufficient quantity of DMSO and was evaluated by the measurement of the mean diameter of growth inhibitor zone in millimeter. Formulation F3 shows maximum zone of inhibition i.e 52.27±0.34 mm. Zone of inhibition of staphylococcus aureus were shown in figure 7.

Spreadability [*11,23,24]*

Spreadability of formulations was determined by an apparatus suggested by Multimer45, which was fabricated itself in laboratory and used for slide fixed on wooded block and upper slide with one end tide to glass slide and other end tied with other end tied to weight pan. An excess of gel (2–5 gm) was placed in between two glass slides and then 1000 gm weight was placed on slides for 5 min to compress the sample to a uniform thickness. Weight (80 gm) was added to pan. The time (seconds) required to separate the two slides, was taken as a measure of spreadability.

In vitro Diffusion studies [21,22,23,24]

The *in vitro* diffusion studies of prepared gel were carried out using Keshary-Chien diffusion cell 500mg of gel containing 7.69 mg of Trimethoprim was spread uniformly on the cellophane membrane. In Modified Franz diffusion cell 6 ml of phosphate buffer was used as receptor compartment. The donor compartment was kept in contact with the receptor compartment and the temperature was maintained at 37±0.5°C. Sample of 1ml was withdrawn at different time interval and replacement was done with 1mlof fresh buffer. The drug concentration on the receptor fluid was determined spectrophotometrically against blank.

Analysis of the release data [25]. The data of *in vitro* Trimethoprim permeation from various topical gels through cellophane membrane were evaluatedkinetically using four kinetic models. Regression analysis was adopted to compute the constant and correlation of data (r2).

Zero order kinetics

$Q = kot$ (1)

Where Q is the % of drug released at time t, ko is the zero-order release constant and t is thetime in hours.

First order kinetics

$\ln (100-Q) = \ln 100 - k1t$ (2)

Where k1 is the first order release constant.Higuchi kinetics

$Q = kHt1/2$ (3)

Where Q is the amount of drug released at time t per unit area & kH is the Higuchi releaserate constant.

$kH = 2Co (D/\pi)1/2$ (4)

Where Co is the initial drug concentration & D is the diffusion coefficient. Korsmeyer peppas equation

$Mt/M\infty = ktn$ (5)

Where $Mt/M\infty$ is the fraction of released drug at time t & n is the release exponent. n value is indicative for the drug release mechanism, If $n \leq 0.5$ it is a fickian diffusion mechanism, $0.5 < n < 1$ it is a non-fickian mechanism (anomalous diffusion) and if $n = 1$, so release mechanism from the formulation follows a zero order mechanism (case-2 relaxation). In case of $n > 1$, it indicates a super case-2 transport. Anomalous diffusion or non-fickian diffusion refers to combination of both diffusion and erosion-controlled release rate while case-2 relaxation and super case-2 transport refer to erosion of the polymeric chain.

Stability studies and statistical analysis

For stability studies, tablets from Formulation Batch F3 were placed in wide mouth air tight glass container 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.

5. Result and discussion

In the present study topical gels of Trimethoprim were prepared in 18 formulation with varying concentration of penetration enhancers such as Natural (Neem oil, Menthol), semisynthetic (Propylene glycol, Ethanol), Synthetic (Oleic acid, Caprylic acid). All the trimethoprim gel formulations in table 1 shows no clogging or lumps which indicate good texture of system.

Table 1: Composition of Trimethoprim Topical Gel

Ingredients % w/w	F1	F2	F3	F4	F5	F6	F7	F8	F9
Trimethoprim	2%	2%	2%	2%	2%	2%	2%	2%	2%
Carbopol 940 P	1 %	1%	1%	1%	1%	1%	1%	1%	1%
Neem Oil	2%	5%	10%	-	-	-	-	-	-

Menthol	-	-	-	2%	5%	10%	-	-	-
Propylene Glycol	-	-	-	-	-	-	2%	5%	10%
Propyl Paraben	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
TEA	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

Ingredients % w/w	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
Trimethoprim	2%	2%	2%	2%	2%	2%	2%	2%	2%
Carbopol 940 P	1 %	1%	1%	1%	1%	1%	1%	1%	1%
Ethanol	2%	5%	10%	-	-	-	-	-	-
Oleic acid	-	-	-	2%	5%	10%	-	-	-
Caprylic acid	-	-	-	-	-	-	2%	5%	10%
Propyl Paraben	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
TEA	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

The complication of bubble generation was not observed while formulating the Carbopol formulations. Physicochemical characters of gels formulations are shown in Table 2. Increasing the concentration of penetration enhancers shows remarkable change in the enhancement of *in vitro* drug release. Natural penetration enhancers shows better release profile as compared to semisynthetic and synthetic.

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

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 indicate that there is no interaction occur between drug and polymer. Physiological evaluation data of trimethoprim gel formulations are shown in Table 3.

Table 3: Physiological Evaluation Data of Trimethoprim Gel Formulations.

Formulations	pH	Drug content (%)	Viscosity (Cps)	Spreadability (g.cm/sec)
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

All the formulation were investigated for homogeneity, pH, drug content, spreadibility, 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 were found to be 94.6 ± 0.041 to 99.5 ± 0.027.

The present work revealed that Neem Oil, Propylene glycol and Oleic acid shows best release as compared to their respectiveclass

penetration enhancer. Maximum cumulative % release obtained from the formulation F3, F9, F15 was 96.365, 80.949, 91.106 respectively. Formulation F3 having 10% Neem Oil was found to be the best formulation with maximum release of 96.365.

In Vitro anti-bacterial study was done on bacteria Staphylococcus aureus with F3, F9, F15 formulation. Anti-bacterial activity was evaluated by the measurement of the diameter of growth inhibition zone and F3 formulation exhibited a good inhibition zone. *In vitro* release studies of formulated gels using Keshary-Chien

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	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
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	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
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	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
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

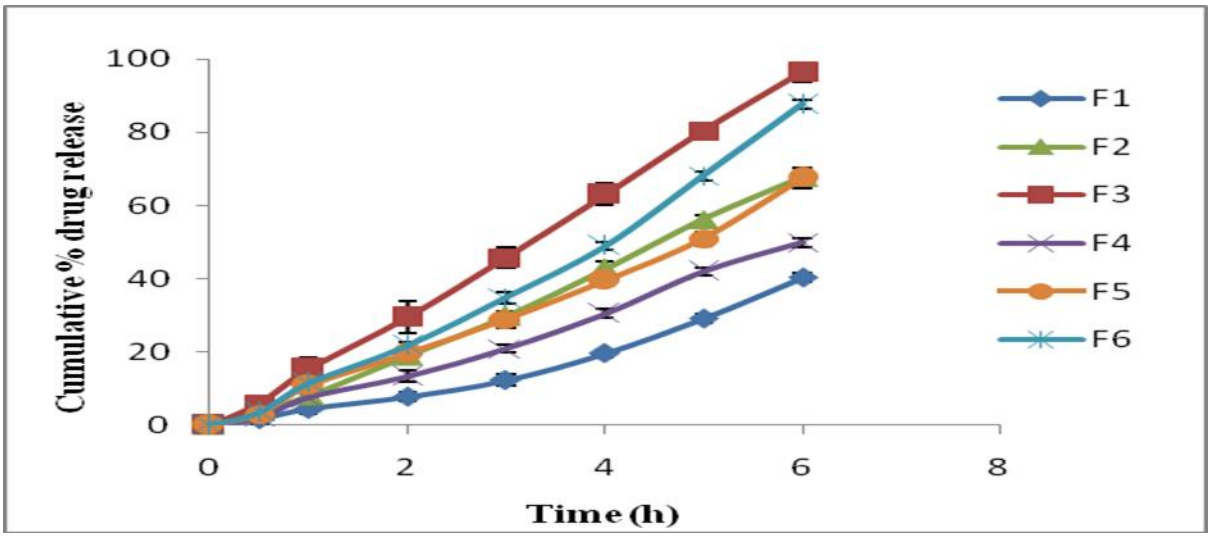

Figure 4: *In vitro* zero order drug diffusion profile of formulation F1-F

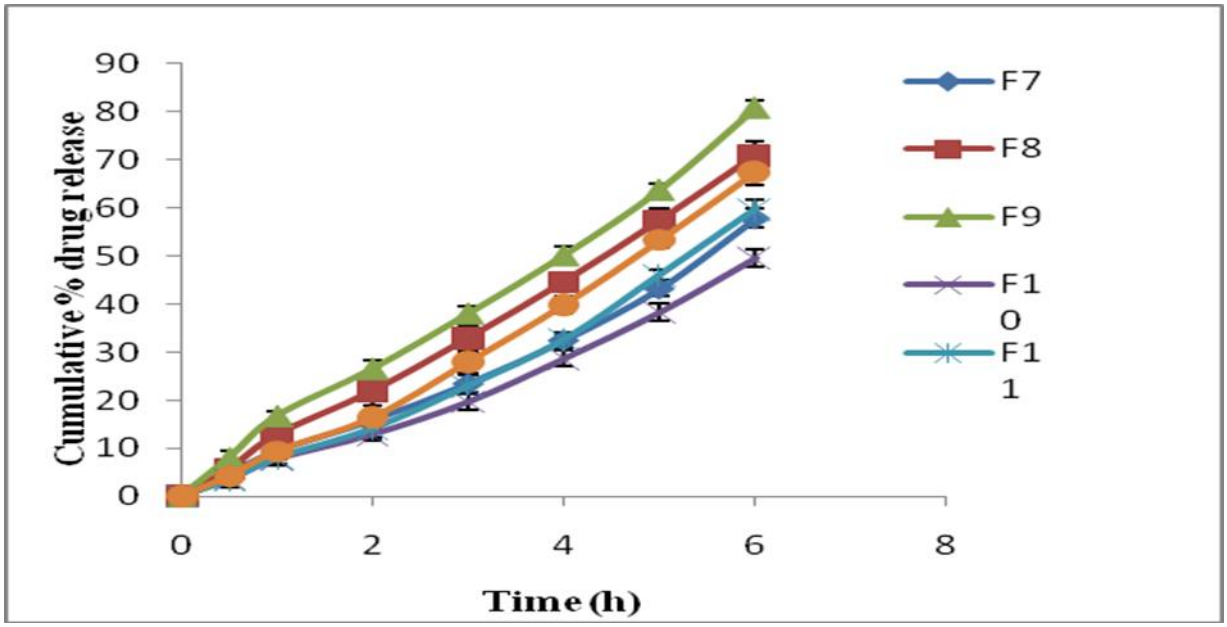

Figure 5: *In vitro* zero order drug diffusion profile of formulation F7-F12

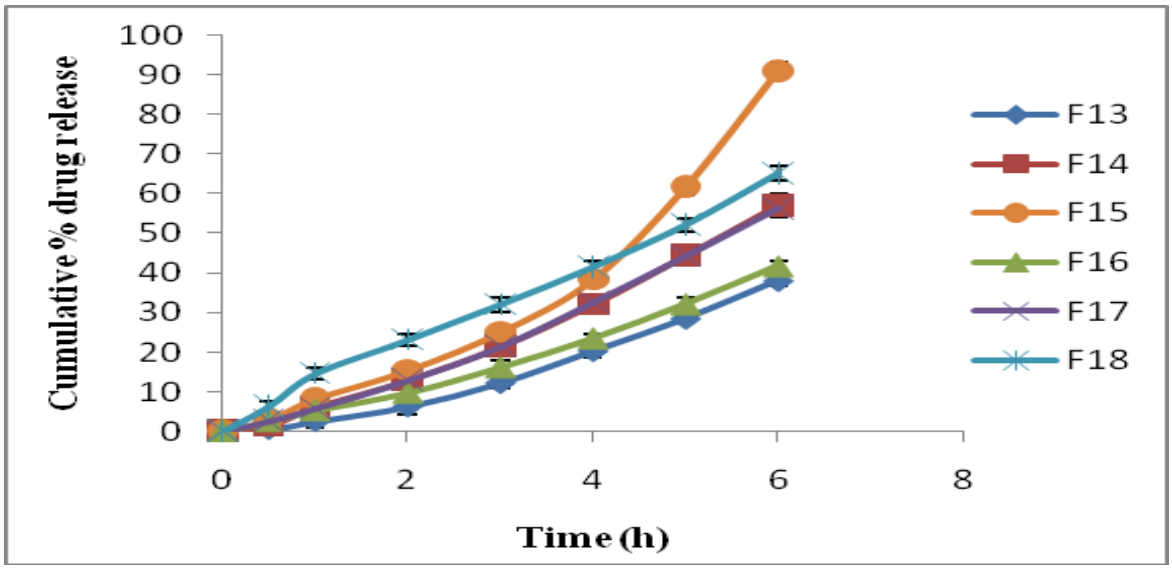

Figure 5: *In vitro* zero order drug diffusion profile of formulation F7-F12

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

6.Conclusion

The result obtained showed that 1% concentration of Carbopol 940P polymer is suitable for gel formulation. With 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 maximum *in vitro* drug release and *in vitro* zone of inhibition. All the formulation 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 an novel topical dosage form for future research. As the problem of partition coefficient can be reduced by nanoparticles because the particle size of model drug in nanoparticles is reduced and it can be easily penetrated into the skin.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authorship contribution statement

Akash Ingale: Supervision, Validation, Methodology, Investigation, Writing – original draft, **Parag Patil:** Conceptualization, Administration, Funding, Data Curation.

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