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FORMULATION DEVELOPMENT AND EVALUATION OF INDOMETHACIN EMULGEL

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ABSTRACT
The present study is an attempt to develop and evaluate emulgel of Indomethacin in order to improve patient compliance by sustaining its action and by reducing its gastrointestinal and other systemic side effects. Emulgel formulations were prepared using Carbopol 934 and Carbopol 974 as gelling agents. The prepared emulgels were evaluated for their physical appearance, pH, viscosity, Spreadability, extrudability, drug content, in vitro drug release, ex vivo drug release and stability studies. All the prepared formulations showed acceptable physicochemical properties. In vitro drug release study indicated that the release of Indomethacin varied according to the concentration of the polymer. The drug release decreases with increase in the concentration of the gelling agent. Formulation F1 showed maximum drug release 84.31 ± 0.43 % in 24 hours and was selected as optimized formulation. Ex vivo release study was carried out with formulation F1 and it showed 70.34 ± 0.34 % release of the drug in 24 hours. The release rate of the formulation F1 was found to follow diffusion controlled mechanism. The formulation F1 was found to be stable with respect to physical appearance, pH, and drug content at all temperature and conditions for one month. Hence, the study concludes that emulsion based system is more effective system for controlled delivery of Indomethacin.

Key words: *Topical Drug Delivery, Emulgel, Indomethacin, Gelling agents.*

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INTRODUCTION

Indomethacin is potent Non-steroidal Anti-inflammatory Drug and is widely used in Rheumatoid arthritis, Ankylosing spondylitis, Osteoarthritis, Acute painful shoulder (bursitis and/or tendinitis), and Acute gouty arthritis, however, toxicity limits its use.[1] It has wide spectrum of gastrointestinal side effects ranging from mild dyspepsia to gastric bleeding and other systemic side effects.[1] Further, the non compliance of the therapy because of the frequent dosing is one of the major problems. Thus in the context, it is vital to reduce the side effects of Indomethacin by any possible means. Hence topical delivery of Indomethacin is considered as an ideal method to minimize side effects of Indomethacin and to improve the patient compliance. Recently, use of emulgels as topical drug delivery systems has gained interest. An emulgel is a gellified emulsion prepared by mixing an emulsion either water-in-oil (W/O) type or O/W (oil-in-water) type with a gelling agent.[2] As it is a combination of emulsion with gel, it provides dual control release and improved contact time of drug. The main advantage of the emulgel that lipophilic drugs can be easily formulated into gels.[2] Due to solubility problems, most of lipophilic drugs cannot be formulated directly as hydrogel. For this reason; emulgel provide better stability and release of the lipophilic drug in comparison with simple hydrogel base. Other advantages for emulgel include; better stability, high loading efficiency, more production economical with low cost.

The aim of the present investigation is to formulate Emulgel of Indomethacin using Carbopol 934 and Carbopol 974 as gelling agents. The work was aimed to develop the emulgel which controls the release of Indomethacin upto 24 hours.

MATERIALS

Indomethacin was obtained as a gift sample from Indian Drugs and Pharmaceutical Ltd., Rishikesh, Uttarakhand. Carbopol 934 and Carbopol 974 were obtained from Molychem, Mumbai. All other chemicals were used of analytical grade and without any further chemical modification.

METHODS

Preparation of Emulgel :

Different formulations were prepared using varying amount of gelling agent. The method only differed in process of making gel in different formulation. The preparation of emulsion was same in all the formulations. The gel bases were prepared by dispersing Carbopol 934 and Carbopol 974 in distilled water separately with constant stirring at a moderate speed using mechanical shaker. Formulations F1, F2 and F3 were prepared by Carbopol 934 and F4, F5 and F6 by Carbopol 974 as gelling agent. The pH of all the formulations was adjusted to 5.5 to 6.5 using Triethanolamine (TEA).

The oil phase of the emulsion was prepared by dissolving Span 80 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 80 in purified water. Methyl paraben was dissolved in propylene glycol and mixed with aqueous phase. Acetone was also mixed in aqueous phase. Indomethacin, being hydrophobic was dissolved in oil phase. Oleic acid was also mixed in oil phase. Both the oily and aqueous phases were separately heated to 70° to 80°C, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature.

The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the Emulgel.[3,4] The composition of different formulations has been shown in Table 1.

Evaluation of Emulgel :

1. Physical Examination

The prepared emulgel formulations were inspected visually for their colour, homogeneity, consistency and phase separation.[5]

2. Measurement of pH

The pH of emulgel formulations was determined by using digital pH meter. 1 g of gel was dissolved in 100 ml of distilled water and it was placed for 2 hours. The measurement of pH of each formulation was done in triplicate and average values were calculated. [6]

3. Rheological Study

The viscosity of the formulations was determined using a Brookfield Viscometer with spindle 07. The formulation whose viscosity was to be determined was added to the beaker and was allowed to settle down for 30 min at the assay temperature (25±1ºC) before the measurement was taken. Spindle was lowered perpendicular in to the centre of emulgel taking care that spindle does not touch bottom of the jar and rotated at a speed of 50 rpm for 10 min. The viscosity reading was noted.[7]

4. Spreading Coefficient

Spreading coefficient was determined by apparatus suggested by Mutimer *et al* (1956). It consists of a wooden block, which is attached to a pulley at one end. Spreading coefficient was measured on the basis of 'Slip' and 'Drag' characteristics of emulgel. A ground glass slide was fixed on the wooden block. An excess of emulgel (about 2 g) under study was placed on this ground slide. The emulgel preparation was then sandwiched between this slide and second glass slide having same dimension as that of the fixed ground slide. The second glass slide is provided with the hook. Weight of 1 g was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the two slides. Measured quantity of weight was placed in the pan attached to the pulley with the help of hook. The time (in sec) required by the top slide to separate from ground slide was noted.[8,9] A shorter interval indicates better Spreading coefficient.

It is calculated by using the formula:

S = M. L /T

Where M = weight tied to upper slide

L = length of glass slides

T = time taken to separate the slides

5. Extrudability Test (Tube Test)

Extrudability test is based upon the determination of weight required to extrude 0.5 cm ribbon of emulgel in 10 sec from lacquered collapsible aluminum tube. The test was performed in triplicate and the average values were calculated. The extrudability was then calculated by using the following formula.[10]

Extrudability = Weight applied to extrude emulgel from tube (in gm) / Area (in cm^2)

6. Drug Content Determination

Weigh accurately 1 g of emulgel and it was dissolved in 100 ml of Ethanol. The volumetric flask was kept for 2 hour and shaken well in a shaker to mix it properly. The solution was passed through the filter paper and filtered. The absorbance was measured spectrophotometrically at 320 nm after appropriate dilution against corresponding emulgel concentration as blank.[2, 11]

7. *In Vitro* Drug Release Study

The *In Vitro* drug release study of the emulgel formulations were carried out in modified Diffusion cell using egg membrane. The membrane was clamped carefully to one end of the hollow glass tube of dialysis cell (2.3 cm diameter; 4-16 cm^2 area). Then 2.5g of Indomethacin Emulgel equivalent to 25 mg was applied uniformly on the membrane. 50 ml of PBS pH 7.4 used as dissolution media was added to receptor compartment. The donor compartment was kept in contact with receptor compartment. This whole assembly was kept on a magnetic stirrer and the solution on the receptor side was stirred continuously using a magnetic bead and temperature of the cell was maintained at 37±0.5°C. Samples (5 ml) were taken at suitable interval of time over a period 24 hours and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically at 320 nm and the cummulative % drug release was calculated.[12,13] The Graph was plotted between cummualtive % drug release versus time is shown in figure 1.

8. *Ex Vivo* Drug Release Study

The *ex vivo* drug release study of selected formulation F1 was carried out in a modified Diffusion cell, using rat skin. A section of skin was cut and clamped carefully to one end of the hollow glass tube of dialysis cell (2.3 cm diameter; 4-16 cm^2 area) keeping the dorsal side upward. Then 2.5g of Indomethacin Emulgel equivalent to 25 mg was applied uniformly on the skin. PBS pH 7.4 was used as dissolution media. The donor compartment was kept in contact with receptor compartment. This whole assembly was kept on a magnetic stirrer and the solution on the receptor side was stirred continuously using a magnetic bead and temperature of the cell was maintained at 37±0.5°C. Samples (5 ml) were taken at suitable interval of time over a period 24 hours and replaced with equal amounts of fresh dissolution media. Samples were analyzed spectrophotometrically at 320 nm and the cumulative % drug release was calculated.[13, 14] The Graph was plotted between % Cummualtive % drug release versus time is shown in figure 2.

9. Release kinetics of selected formulation

The results obtained from *ex vivo* release study of formulation F1 were plotted in different kinetic models. The mathematical models are used to evaluate the kinetics and mechanism of drug release from formulations. The model that best fits the release data is selected based on the correlation coefficient (R^2) value in various models. The model that gives high R^2 value is considered as the best fit of the release data. Mathematical models are

- Zero order kinetics (Cumulative % drug release v/s time).
- First order kinetics (Log % cumulative drug retained v/s time).
- Higuchi model (% cumulative drug release v/s square root of time).
- Peppas model (log % cumulative drug release v/s. log time). [15,16]

10. Stability study of selected formulation

The prepared emulgel formulation F1 was packed in aluminium collapsible tubes (5 gm) and subjected to stability studies at 5°C, 25°C/ 60% RH, 30°C/65% RH, and 40°C/75% RH conditions for a period of 1 month. Samples were withdrawn at 7 day time intervals and evaluated for physical appearance, pH, and drug content.[17]

RESULTS

Physical Examination

In terms of physical appearance, emulgel formulations were pale yellowish viscous creamy preparations with smooth homogenous texture and glossy appearance. No phase separation was observed. Observations are shown in table 2.

Measurement of pH

The pH of all emulgel formulations was found to be between 5.8 ± 0.050 to 6.25 ± 0.074 as shown in table 3, which lies in the normal pH range of the skin (5.5-7.4) and would not produce any skin irritation.

Rheological Study

The viscosity study was carried out on all the formulations (F1-F6) using Brookfield viscometer. It was found that the viscosity of the formulations increases with the increase in the concentration of the gelling agent as shown in table 3.

Spreadibility Test

Spreadibility test was carried out for all the formulations (F1-F6). Spreadibility plays and important role in patient compliance and help in unifom application of emulgel to the skin. A good emulgel takes less time to spread and will have high spreadibilty. The spreadibilty of formulated emulgel formulations was decreased as the concentration of gelling agent increased. The spreadibilty coefficient was found to be highest for formulations containing Carbopol 934 as the gelling agent i.e. F1, F2 and F3 respectively as shown in table 3.

Extrudability Test

Extrusion of emulgel from the tube is an important during application and the patient compliance. Emulgel with high consistency may not extrude from the tube easily, whereas low viscous emulgels may flow quikly. Extrudability of formulations was found to be good. The results are shown in table 3.

Drug Content Determination

The drug content of the formulated emulgels was estimated spectrophotometrically at 320 nm. The % drug content of all prepared emulgel formulations were found to be in the range of 94.47 ± 1.43 % to 98.53 ± 0.89 % as shown in table 3. All the formulations showed uniformity in drug content and were with in the limits which indicated that the drug was uniformly dispersed throughout the formulation.

***In Vitro* Drug Release Study**

In vitro drug release study was carried out for all formulations F1-F6. The release of Indomethacin from the emulgels was varied according to concentration of polymer. The release of the drug from its emulsified gel formulation can be ranked in the following descending order: F1 > F4 > F5 > F2 □ F3 □ F6, where the amounts of the drug released after 24 hour were 84.31 ± 0.43 % , 78.62 ± 0.42 % , 73.85 ± 0.29 %, 70.12 ± 0.25 %, 67.32 ± 0.09 %, and 65.31 ± 0.29 % respectively as shown in table 4 and figure 1. The progressive increase in the amount of drug diffusion through membrane from formulation attributed to gradual decrease in the concentration of polymer. It has been concluded that, if we increase the concentration of polymer, the diffusion of drug through the membrane also decreases.

***Ex Vivo* Drug Release Study**

This study was carried out with best optimized formulation F1. The study showed that release of the drug from formulation F1 was 70.34 ± 0.34 % in 24 hours as shown in figure 2.

Release kinetics

The results obtained from *ex vivo* release study of optimized formulation F1 were plotted in different kinetic models. Regression coefficient (R2) values of different kinetic models are shown in Table 5. Since the R^2 value was high for Higuchi model kinetics, it can be concluded that the Formulation F1 best follows Higuchi model release kinetics. Higuchi equation explains the diffusion release mechanism, so formulation F1 follow the diffusion mechanism of drug release. Additional evidence for the diffusion controlled mechanism was obtained by Korsmeyer Peppas model. The diffusion exponent ‘n’ value was found to be 0.7468 which is in the range of 0.5-1 indicating Non-Fickian diffusion mechanism.

Stability Study

The formulation F1 was found to be stable upon storage for one month, no significant changes were observed in its physical appearance, pH, and drug content.

DISCUSSION

From the above results we can conclude that Indomethacin Emulgel formulations prepared with Carbopol 934 and Carbopol 974 showed acceptable physicochemical properties (physical appearance, pH, viscosity, spreadibility, extrudability, and drug content). Formulation F1 was selected as best optimized formulation, since it showed higest drug release 84.31 ± 0.43 % in 24 hours. *Ex vivo* drug release of formulation F1 was found to be 70.34 ± 0.34 % in 24 hours. Formulation F1 was found to be stable upon storage for one month, no significant changes were observed in its physical appearance, pH, and drug content. Hence, the emulsion based system is more effective system for controlled delivery of Indomethacin and thus found useful to improve the patient compliance.

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TABLES & FIGURES

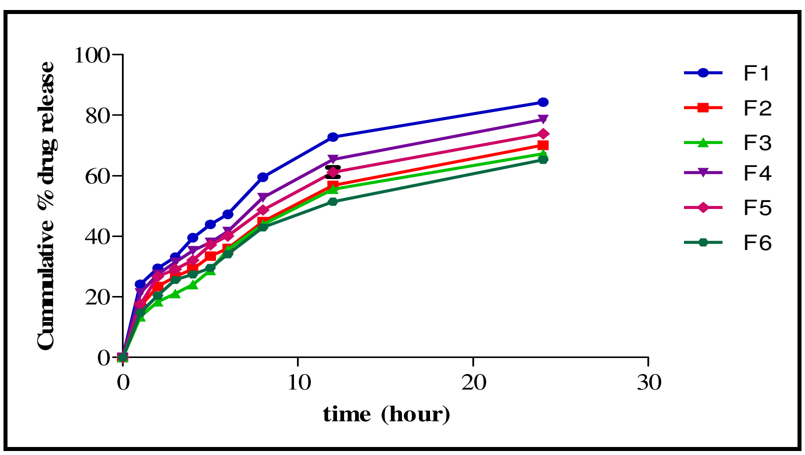

Figure 1 : *In Vitro* Drug Release Profile of Formulations F1-F6

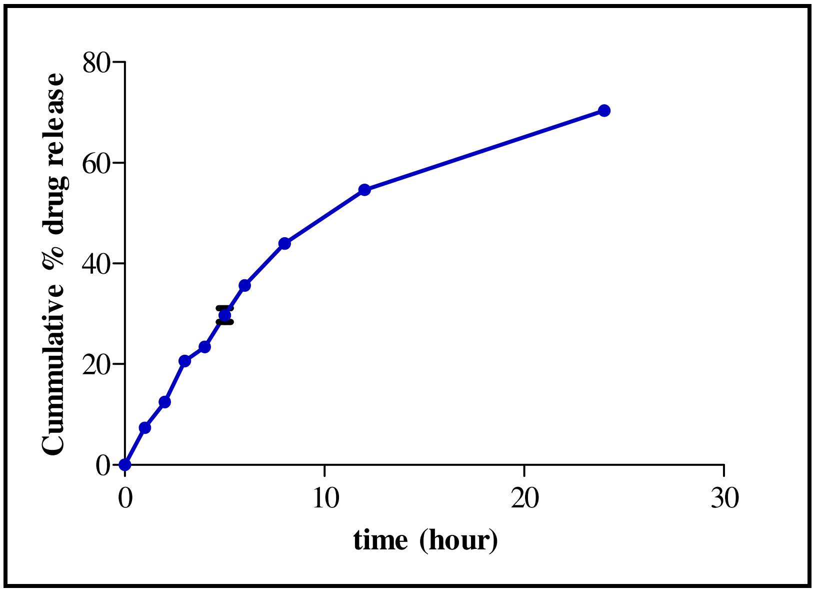

Figure 2 : *Ex Vivo* Drug Release Profile of Formulation F1

Table 1 : Compositions of Indomethacin Emulgel formulations (w/w %)

Ingredients	F1	F2	F3	F4	F5	F6
Indomethacin	1	1	1	1	1	1
Carbopol 934	1	1.2	1.4	-	-	-
Carbopol 974	-	-	-	1	1.2	1.4
Oleic acid	2	2	2	2	2	2
Light liquid paraffin	4	4	4	4	4	4
Acetone	2	2	2	2	2	2
Propylene glycol	5	5	5	5	5	5
Tween 80	0.5	0.5	0.5	0.5	0.5	0.5
Span 80	1	1	1	1	1	1
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Triethanolamine	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2 : Physical Parameters of Formulations F1-F6

S. No.	Formulation code	Colour	Phase separation	Homogeneity	Consistency
1.	F1	Pale yellow	None	++	++
2.	F2	Pale yellow	None	++	++
3.	F3	Pale yellow	None	++	++
4.	F4	Pale yellow	None	++	++
5.	F5	Pale yellow	None	++	++
6.	F6	Pale yellow	None	++	++

++ indicates Good

Table 3 : Physicochemical Properties of Formulations F1-F6

S. No.	Formulation code	Viscosity (Centipoise)	pH	Spreadibility (g.cm/sec)	Extrudability (g/cm^2)	% Drug content
			(Mean±SD ; n=3)			
1.	F1	8320	5.8 ± 0.050	29.36 ± 0.49	12.20 ± 0.014	98.53 ± 0.89
2.	F2	11500	6.1 ± 0.045	24.73 ± 0.5	13.70 ± 0.027	94.47 ± 1.43
3.	F3	14720	5.9 ± 0.052	18.43 ± 1.02	15.14 ± 0.012	97.32 ± 1.12
4.	F4	12350	6.2 ± 0.048	26.73 ± 0.71	12.42 ± 0.070	97.89 ±1.07
5.	F5	15280	6.25 ± 0.074	23.56 ± 0.58	14.06 ± 0.050	95.33 ± 0.89
6.	F6	17520	5.7 ± 0.030	16.6 ± 0.52	15.49 ± 0.270	95.21 ± 1.06

Table 4 : *In vitro* Drug Release Profile of Formulations F1-F3

Time (hour)	Cummulative % Drug Release (Mean±SD ; n=3)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	24.19 ± 0.03	16.97 ± 0.07	13.45 ± 0.03	21.27 ± 0.18	17.56 ± 0.09	14.83 ± 0.05
2	29.42 ± 0.12	23.47 ± 0.02	18.34 ± 0.08	27.48 ± 0.11	26.71 ± 0.86	20.45 ± 0.12
3	33.12 ± 0.08	26.71 ± 0.36	21.12 ± 0.05	31.47 ± 0.09	29.13 ± 0.03	25.64 ± 0.32
4	39.52 ± 0.20	29.32 ± 0.47	24.09 ± 0.17	35.28 ± 0.01	32.09 ± 1.15	27.48 ± 0.08
5	43.92 ± 0.12	33.49 ± 0.15	28.78 ± 0.13	38.05 ± 0.21	37.21 ± 0.33	29.62 ± 1.23
6	47.28 ± 0.23	36.05 ± 0.11	35.6 ± 0.26	41.64 ± 0.17	40.16 ± 0.91	34.09 ± 0.27
8	59.58 ± 0.34	44.91 ± 0.18	43.93 ± 0.21	52.76 ± 0.1	48.67 ± 0.62	42.96 ± 0.43
12	72.81 ± 0.28	56.78 ± 0.11	55.62 ± 0.23	65.39 ± 0.18	61.63 ± 1.50	51.47 ± 0.17
24	84.31 ± 0.43	70.12 ± 0.25	67.32 ± 0.09	78.62 ± 0.42	73.85 ± 0.29	65.31 ± 0.29

Table 5 : Regression co-efficient (R^2) values of kinetic models and diffusion exponent (n) of Peppas for *Ex vivo* release data of formulaion F1

Formulation code	Zero Order	First Order	Higuchi Model	Peppas Model		Best Fit Model
	R^2	R^2	R^2	R^2	N	
F1	0.8765	0.9663	0.9713	0.9622	0.7468	Higuchi

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