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FORMULATION, DEVELOPMENT AND CHARACTERIZATION OF IBUPROFEN MICROEMULGEL FOR ARTHRITIS

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ABSTRACT

Objective: Microemulgel is composed of aqueous phase, lipophilic phase, along with surfactant and co-surfactant, a suitable gelling agent is also incorporated. The drug Ibuprofen is non-steroidal anti-inflammatory drug. Its oral administration associated with many GIT, hepatic and renal problems. The main objective of the study was to formulate a stable topical microemulgel of ibuprofen in order to achieve the highest bioavailability with least side effects. **Method:** Pseudo ternary phase diagram was constructed in order to get the suitable concentrations of lipophilic phase, surfactant and co-surfactant. Phase titration method was used to prepare microemulsion, with surfactant and co-surfactant in a ratio of 2:1 respectively, along with gelling agent to form microemulgel. Formulations were evaluated to check appearance, pH, flowability, particle size, drug content, spreadability, drug release and skin irritation. **Results:** The globule size of microemulsion was 400 nm and zeta potential was -14 mV showing acceptable stability. Formulated emulgel showed good physical characteristics, suitable pH of 6.4 for skin. The drug content was 98.474%. The stability study showed that the ibuprofen was stable in phosphate buffer pH of 6.8. The carbopol 940 as a gelling agent showed high release rate values. The release rate of the optimized formulation, F1 was 94% and it followed Korsmeyer Peppas model (n=0.467). **Conclusion:** The prepared formulation was cost-effective because of promising highest bioavailability. The results suggest the potential use of developed microemulgel is mainly for topical delivery of ibuprofen, ensuring the safe use.

Keywords: Microemulsion, Analgesic activity, Zeta potential, Topical Formulation, Ibuprofen.

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INTRODUCTION

Microemulsions are a superior drug delivery system because of high penetrations capability, its small size, enhanced dissolution rate, easy preparation, stability, clarity, incorporation of various drugs, improved bioavailability, can be formulated for various routes (ophthalmic, nasal, oral, parenteral and topical). Microemulsions differ from macroemulsions mainly by their size and particles shape dispersed in continuous phase. Microemulsions range from 10-100 nanometers and convention emulsions range from 1-20 micrometers **[1]**.

Microemulsion benefits with enhance bioavailability, low surface tension, small droplet size and cost effectivity. Microemulsion provides sustained and controlled release and novel delivery system for topical, percutaneous, transdermal and parenteral route **[2].** Microemulsion gives more diffusion, large surface area, solubilization and absorption rate so attributed as potential drug delivery system skin. Because of super solvent nature of microemulsions, act as both hydrophilic and hydrophobic vehicle for drugs and increase the solubility and bioavailability**.** By rapid penetration and reduced barriers for stratum corneum due to its properties, microemulsion is the best topical drug delivery system **[3].**

Ibuprofen has a well-established safety profile. Being a Non selective cox inhibitor, it is effective analgesic with significant anti-inflammatory action. In geriatrics population, when used to treat arthritis, these is a risk of renal, gastric or hepatic side effects **[4].** Ibuprofen is an OTC available

NSAID's and used as a prescription drug for arthritis pain and inflammation treatment. Use in children, ibuprofen is considered to be safe especially comparatively to paracetamol and useful for fever and acute pain **[5].** Compared with paracetamol, in certain conditions, ibuprofen is more effective. Ibuprofen dose potency ranges from 200 to 800 mg. It is usually taken thrice a day orally with dose of 400 to 800mg. It has good oral bio-availability but it can be improved by administering it via other routs **[6].** Ibuprofen therapy may induce nephropathy but it is rarely observed at usual over the counter doses. Oral administration of ibuprofen in older people with arthritis has a drawback that it has renal and hepatic side effects **[7].** Types of topical formulations of ibuprofen available in market are gels, foam dressing and spray but no formulation is available as microemulgel **[8].**

The purpose of the study was to formulate microemulgel of ibuprofen, stabilize it according to its environmental conditions and get the good bioavailability **[9]**. This will help in preventing side effects of ibuprofen followed by oral route administration. The study also determined best suitable surfactants and co-surfactant and their ratios in which these were used, developing blends of oi or lipophilic phase and surfactant/co-surfactant, quantity of aqueous phase used. It was also intended to load the drug into this emulgel **[10]**.

MATERIALS AND METHODS

Materials

The ingredients used HPMC K15, Carbopol 934 and Carbopol 940, Tween 20, Tween 80, Clove oil, were purchase from Sigma Aldrich Pakistan. Ibuprofen was a gift from Sigma Aldrich Pakistan. Monobasic phosphate, sodium hydroxide, Triethanolamine (TEA) and PEG were purchased from MERCK Pakistan. Freshly prepared distilled water was used.

Method

To formulate emulgel, first step was to prepare microemulsion. The oil phase was prepared and the drug was incorporated in it. Then it was mixed with aqueous phase containing surfactant and co-surfactant (in 2:1, respectively) via phase titration method. The pH was raised in between 6 and 6.5 using TEA. To create a homogeneous, creamy emulgel, the gel - forming agent was gradually introduced to the microemulsion in a 1:1 ratio while being constantly and uniformly stirred. Oils, surfactants, and co surfactants are screened for microemulsion. Various oils, such as almond oil, clove oil, liquid paraffin, and oleic acid, along with different surfactants, Tween 20, Tween 80, and cosurfactants like propylene glycol, were evaluated to find the best combination of oil, surfactant, and cosurfactant phases in which the ibuprofen was soluble for producing microemulsion. In 3 ml of each of these oils, surfactants, and cosurfactants, excess amount of ibuprofen was added. These mixtures were then stirred for 24 hours and vortexed for 10 minutes before being left at room temperature for an additional 24 hours. The samples were then taken and tested at 282 nm in an ultraviolet (UV) spectrophotometer. Ibuprofen displayed highest solubility in clove oil when compared to other oils, therefore it was chosen. When combined with clove oil, Tween 20 and propylene glycol demonstrated the best emulsifying properties and improved ibuprofen solubility among all surfactants and co surfactants. The water titration method was used to plot the pseudo-ternary phase diagram. Cosurfactants and surfactants were combined in various weight ratios (1:1, 1:2, 1:3, 2:1 and 3:1). Different w/w ratios of oil and the surfactant and cosurfactant combination were well mixed (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1). Drop by drop, distilled water was introduced to the various mixtures of oil/Surfactant and co surfactant mix resulting the cloudy preparation. Pseudo ternary phase diagram was constructed by using trial version of a software called Chemix School, and microemulsions were prepared based on ternary phase diagram. By the help of this pseudo ternary phase diagram, the stable microemulsion formulations were prepared for further studies.

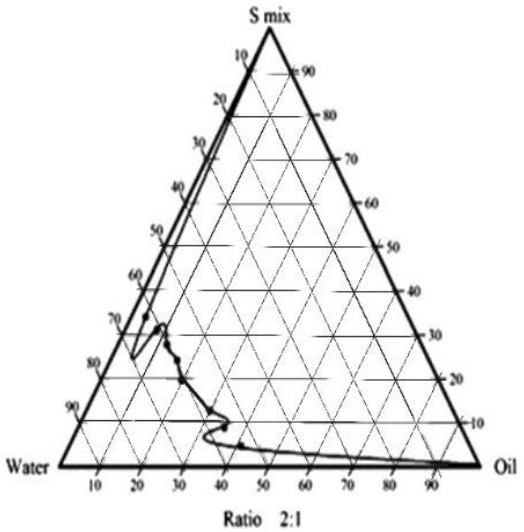

Figure 1: Pseudo ternary phase diagram of microemulsion.

Formulation Components

Four different formulations were prepared, their ingredients and concentrations used are given in **Table 1**.

Table 1: Ingredients for (100 g) formulations F1, F2, F3, F4.

Ingredients	**F_1**	**F_2**	**F_3**	**F_4**
Ibuprofen (g)	2	2	2	2
Tween 20 (ml)	27	-	-	27
Tween 80 (ml)	-	25	25	-
Clove Oil (ml)	10	10	10	10
PEG (ml)	13	13	13	13
HPMC (g)	-	5	-	-
Carbopol 934 (g)	2	-	-	-
Carbopol 940 (g)	-	-	-	1.5
Triethanolamine (ml)	q.s	-	-	q.s
Distilled water(ml)	q.s	q.s	q.s	q.s

Pre-formulation Studies

Flowability

The angle of repose was calculated via inverted funnel method. A heap was formed and its diameter was measured. By using the given formula angle was calculated.

Angle of repose(θ) = $tan^{-1}\frac{2h}{d}$

h= Height d= diameter

Carr's index value was calculated with the help of measuring cylinder. The weighed quantity of powder was put into it and tapped 100 times/min to get tapped volume for 20 mins. Tapped density was calculated and then Carr's index and Hausner's was calculated by using formula.

Melting point

Melting point apparatus (Fischer John's apparatus) was used to calculated the melting point.

Crystallinity

The crystallinity was observed by using microscopic method in which drug was dissolved in a solvent and then observed under microscope.

Post-formulation Studies

Clarity

The clarity of the microemulgel was checked by placing it in a transparent beaker and viewing it in front of light.

pH

The pH of microemulsion was calculated with the help of calibrated pH meter.

Globule size and zeta potential

The Globule size and zeta potential of microemulsion was measured. Zetasizer Nano – ZS (Malvern instruments, Worcestershire, UK).

Drug Content

To perform drug content test, 1 ml of ME was added in a test tube with 9 ml of phosphate buffer solution (PBS) of 6.8 pH. The mixture was shaken vigorously for 30 mins and then left for 24 hrs. After 24 hrs, the mixture was again vigorously shaken. Then we centrifuged the mixture at 4000 rpm for 15 mins. 1 ml of supernatant was taken and 9 ml of buffer was added. Then we run this mixture on UV spectrophotometer and the results was obtained.

Phase Separation

The phase separation test was performed by applying stress on the microemulsion system by the help of centrifugation. The microemulsion was subjected to 3000 rpm in centrifuge for 15 mins.

Standard Calibration Curve

The drug was dissolved in a PBS of 6.8 pH to make 1mg per ml solution to make stock solution. Then working solution of 20 microgram/ml was made from stock solutions. After this, the dilutions of 2mcg/ml, 4,6,8,10 mcg per ml was prepared. Then all the dilutions were run on UV spectrophotometer and wavelength was set at 282nm.

FTIR and DSC Analysis

A test for drug compatibility was carried using FTIR spectroscopy. The spectrum of pure drugs, carbopol 940, and a 1:3 ratio of the physical mixing of drugs and carbopol 940 determined using Fourier-transform infrared spectroscopy (FTIR) are shown. Alkenes' C-H (stretching) peaks at 2988.29, 2949.21, and 2867.97, the carbonyl group's C=O peak, and other important peaks **Fig. 3** shows the permeation profile of ibuprofen through rat epidermis, stretching at 1707.22, aromatic C=C at 1504.04, and alkyl halide groups such as C=F at 1454.85, 1266.87, 1225.51, and 1179.08, which are preserved in the physical mixture. Thus, it demonstrated that the medication and the polymer employed in the formulations are compatible.

Thermal Analysis Systems Model Q 10 (TA Instruments) was employed to obtain DSC curves for both heating and cooling.

Permeability

The permeability of ME was checked by using Franz diffusion cell apparatus. Soaked filter paper in water was used as permeable membrane. 1ml of microemulsion placed in the donor compartment of the apparatus and the paraffin was wrapped around the apparatus to prevent evaporation. The whole assembly was placed on magnetic stirrer with the temperature of 37 °C at

60 rpm. 10 samples were drawn and run-on UV-spectrophotometer.

Kinetic Drug Release

The drug release rate was observed using the MS Excel and DD solver extension.

RESULTS

Pre-formulation Studies

Table 2: Flow properties of solids.

Tests	Results
Angle of repose	49°
Carr's index	34%
Hausner ratio	1.4
Flow property	Poor flow
Melting point	157.5°
Crystallinity	Blade shaped crystals

Post formulation Studies

Table 3: Post formulation study.

Tests	Results
Clarity	Clear
pH	6.4
Globule size	400 nm
Drug content	98.47%
Zeta potential	-14 mV
Skin irritation	Non irritable

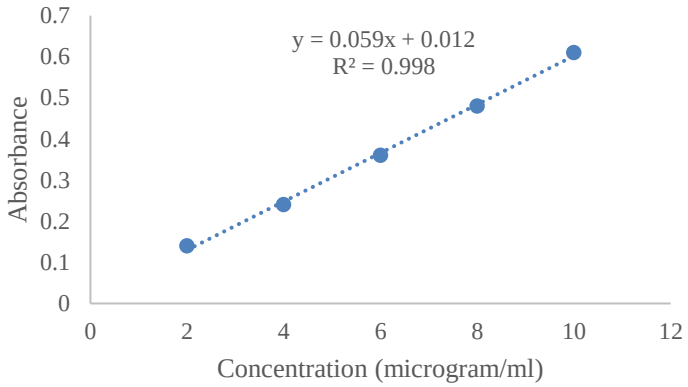

Figure 2: Standard calibration curve.

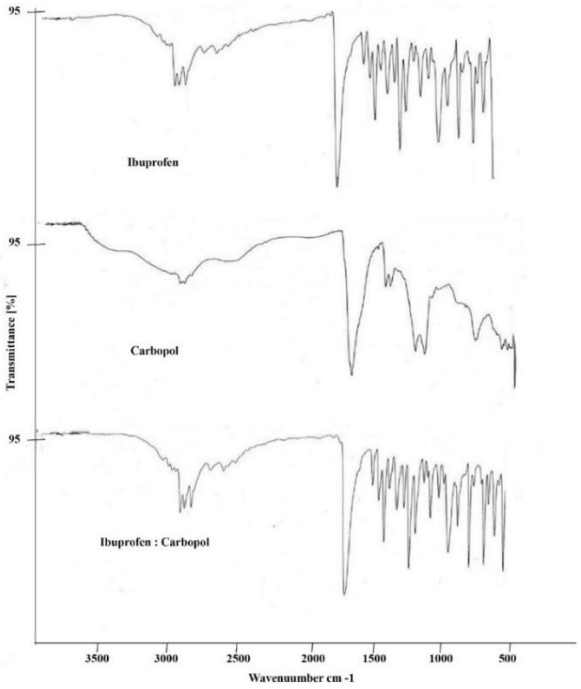

Figure 3: FTIR of ibuprofen, carbopol, ibuprofen: carbopol

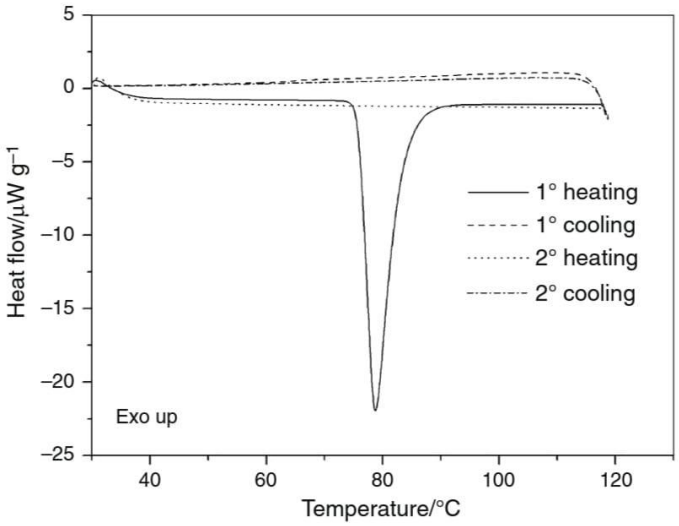

Figure 4: DSC analysis results of Ibuprofen.

Permeability of Microemulgel

Table 4: Kinetic analysis.

	F1	F2	F3	F4
Zero Order				
k0	2.405	2.186	2.006	1.804
Rsqr_adj	0.2848	0.3764	0.5569	0.6334
AIC	87.2104	84.1949	80.2038	76.4800
MSC	0.1353	0.2722	0.6139	0.8036
First Order				
k1	0.085	0.059	0.045	0.034
Rsqr_adj	0.8549	0.8033	0.8556	0.8633
AIC	71.2568	72.6535	68.9942	66.6146
MSC	1.7306	1.4263	1.7348	1.7901
Higuchi Model				
kH	14.726	13.295	12.058	10.764
Rsqr_adj	0.9277	0.9465	0.9777	0.9924
AIC	64.2885	59.6347	50.3299	37.7847
MSC	2.4274	2.7282	3.6013	4.6731
Korsmeyer Peppas Model				
kKP	21.411	18.382	14.442	11.969
n	0.383	0.399	0.444	0.467
Rsqr_adj	0.9797	0.9817	0.9854	0.9947
AIC	52.4060	49.7310	46.9082	34.9783
MSC	3.6157	3.7186	3.9435	4.9538

AIC=Akaike Information Coefficient

Drug Release from Microemulgel

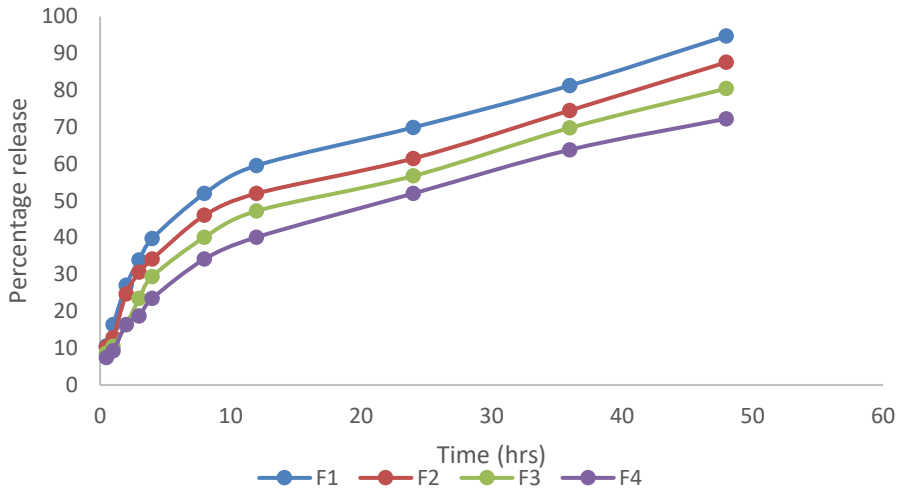

Figure 5: Drug release of F1, F2, F3, F4 formulations of ibuprofen.

DISCUSSION

The microemulsion was prepared with the ingredients given in **Table 1**. Developed micro emulsion system then converted to emulgel, provide the solubilization of drug, ibuprofen, thus helpful in increasing the bioavailability of drug **[11].** The overall results from post formulation studies showed that the drug has poor flow properties and has melting point nearly equal to that of pure ibuprofen.

The particle size of the emulgel showed that it was within the range of micro emulsion and also showed that it is good to be absorbed within the skin when applied topically **[12]**. In the clarity test confirmed the smooth texture and homogeneity of the formulation. The drug was evenly distributed across the system as the drug content results were satisfactory.

The formulation F1 showed the highest permeability followed by the F2 in drug permeability test. The higher the permeability, the more drug will be absorbed across the skin. Also, higher bioavailability is the characteristic of topical microemulgel which distinguishes it from other dosage forms such as oral tablets or topical gels or creams **[13].**

Comprehensive Fourier Transform spectroscopy was used for the determination of interactions of ibuprofen with carbopol and other ingredients used in preparation of microemulsion. The FTIR analysis of pure drug, in **Fig. 1** showed characteristic peak at 3000 cm-1 indicating carboxl group. This peak exhibited the specificity and accuracy for pure ibuprofen. **Fig. 2** indicated principal peak for pure carbopol used as gel forming agent in preparation.

There was no redistribution, superimposition, or change in length of the ingredients when the microemulsion preparation was tested through FTIR spectroscopy, which clearly indicates that the components of microemulsion did not overlap or interact. A very narrow broad absorption band was discovered, indicating the existence of H - bonds between the polymer and the medication. This confirms the efficacy of our formulation since the drug is successfully incorporated into the gel without changing its physicochemical nature **[14]**.

The dissolution modeling analysis in vitro was run using the DD solver, the analysis of formulations was performed by using DD solver excel sheet. By applying following models i.e., zero order, first order, Higuchi and Korsmeyer peppas model **[15]**. **Zero order** kinetics shows that a constant amount of drug is eliminated per unit time and it is concentration independent. **First order** kinetics shows that a constant proportion of drug is eliminated per unit time and it is concentration dependent, higher the concentration greater the amount of drug is eliminated per unit time **[15]**. **Higuchi Model** describes the drug release as a diffusion process based on Fick's Law of diffusion which is square root time dependent. It is concentration independent nearly zero order. **Korsmeyer-Peppas Model** describes the drug release from polymeric systems **[16].** After testing formulation F1, F2, F3 and F4 didn't fall in the zero order and

first order model as R square adj, AIC and MSC values didn't fall in the acceptable range. The R square adj value in Higuchi and Korsmeyer Peppas model were higher than 0.95 showing that all these models were followed by F1, F2. F3, F4 (i.e., for Higuchi and Korsmeyer Peppas, R square adj values were within acceptable range). For F1 Korsmeyer Peppas model was acceptable as the n value obtained were closer to acceptable range. Acceptable range for ACI values was it must be lower than 50, for Higuchi AIC value of F3 and F4 was in acceptable range, which was F3= 50.3299 and F4= 37.7847 and for Korsmeyer Peppas model, the AIC values of all formulations was within range except for F1 **[17]**. For F1, the value is slightly higher i.e., 52.4060. It can also be considered as acceptable. AIC values for other formulations was F3= 45.13 and F4= 34.9783. When we talk about acceptable range for MSC, its value must be greater than 3 and less than 5. Higuchi model was not followed by F1 and F2, while F3 and F4 fall in acceptable range (F3= 3.4 and for F4= 4.6731) **[18]**. In Korsmeyer Peppas model MSC values were within range. The n vale for F1 was 0.383 and for other formulation it was slightly higher. So, it showed that these formulations lie under Fickian drug release (concentration dependent drug release system) **[19].**

Among all these formulations, F1 was selected as the best one because it showed highest drug release percentage i.e., 94.6 percent. This formulation also followed the Korsmeyer Peppas model **[20]**. The prepared microemulsion can be considered as cost-effective formulation, because of the reduction in topical dose of ibuprofen in formulation.

CONCLUSION

Amongst all the formulations, the F1 emulgel was better in all aspects and qualities. The developed micro emulgel showed drug highest solubility and stability of system. The prepared emulgel could be cost effective formulation as it helps in reducing the topical dose, frequency and showed highest bioavailability of 94 percent. when compared to the other marketed products. Formulation F1 was compatible with skin as well. Thus, all the results clearly indicated that the system developed for the loading of ibuprofen i.e., emulgel is stable and compatible with the drug as well. The emulgel helps to treat arthritis and sports injuries by providing quick relief from pain and ensure patient compliance. Also, it showed the promising potential of ibuprofen emulgel as an alternative to the conventional dosage forms.

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DECLARATION OF INTERESTS

The authors report no conflict of interest and are sole responsible for the data provided.

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