JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Formulation and Characterization of an Emulgel for Topical delivery of Hydrophobic Drug.

R.P.Ade[1]., A.S.Pratapwar[2].,V.S.Amle[1]V.K.Pawar[1]

1) Department of Pharmaceutics, SBNM college of Pharmacy Hatta.Tq.basmath Dist-Hingoli
2) Department of Pharmaceutics SNIOP Pusad, Dist-Yavatmal Maharashtra

Corresponding Author-
Rajkumar P.Ade
Department of Pharmaceutics,
SBNM college of Pharmacy Hatta.Tq.basmath Dist-Hingoli

Abstract

In Present study, a microemulsion based gel (emulgel) system was constructed for transdermal delivery of ibuprofen. The formulations consists of oleic acid 6%, tween 80 20%, ethanol 10%, water phase 59% (w/w) and ibuprofen 5%, with different gelling agents i.e. Carbopol 934, HPMC K15M, Xanthun gum in 1% & 1.5% respectively. Similarly in the study, topical emulgels of ibuprofen were formulated and subjected to physicochemical studies i.e. pH, rheological studies, spreading coefficient & extrudabilitystudies, skin irritation study, in vitro release studies, anti-inflammatory study. In vitro release of the tests formulations were performed to determine drug release from emulgel rate and duration of drug release. Formulated emulgel showed acceptable physical properties, drug content, drug release, and anti-inflammatory activity, which remained unchanged upon storage for 3 months. The physical appearance was milky white, pH was in between 6-6.5, formulations showed better spreading coefficient & extrudability. However, the Carbopol 934 based Emulgel in its low concentration with the formulation code F2 proved to be the formula of choice, since it showed Viscosity of the optimized batch F2 was found to be 26687 cps and 93.69% drug content, the highest drug release i.e. 87.45% in 6 hrs and incase of albumin induced paw edema it showed very good anti-inflammatory activity.

Keyword-

Emulgel, Rheological studies, spreading coefficient, Carbopol 934, transdermal delivery

Introduction

Topical drug delivery systems have been used for centuries for the treatment of local skin disorders and relieve the pain. One side the topical applications of the drug offer the potential advantages of delivering the drug directly to the site of action and delivering thedrug for an extended period of time at the effected site that mainly acts at related regions. On the other hand, the topical delivery system increases the contact time and mean

resident time of the drug. Most widely used drugs when given by oral route have side effects like gastric irritation, nausea, bleeding in gastrointestinal tract etc. In order to minimize such side effects and systematic toxicities and also achieve better therapeutic effects one of the promising method is to administered drug via skin or, in short by topical drug delivery system Topical DDS is a localized drug delivery system anywhere in the body through ophthalmic rectal vaginal & skin as topical routes Topical drug delivery, system has several advantages such as ability to deliver drug more selectively to a specific site, avoidance of gastro intestinal incompatibility and metabolic degradation associated with oral administration more over topical deliveries provide increased bio availability by avoiding first pass metabolism by liver and consistent delivery for extended period.[1-3]

Emulgels are emulsions, either of the oil-in-water or water in oil type, which are gelled by mixing with a gelling agent. Emulsified gel is stable one and superior vehicle for hydrophobic or poorly water-soluble drugs. In short emulgels are the combination of emulsion and gel. In spite of many advantages of gels a major limitation in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approaches being used, so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels. In recent years, there has been great interest in the use of novel polymers which can function as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, greater shelf life, bio-friendly, clear & pleasant appearance.[4,5]

Materials And Methods

Materials

Diclofenac Sodium was obtained as kind gift sample from MEB Parma kurum, Amravati India. Oleic acid purchased from Research-Lab Fine industries, Mumbai, India, Carbapol 934 & Tween 80was purchased from Corel Pharma Chem, Mumbai India. All other materials used of analytical grade.

Methods

Drug Polymer Compatability Study

The FTIR of pure drug and physical mixture of formulation ingredients of optimized batch was measured using Fourier transform infrared spectrophotometer (Model FTIR- 8400S, Shimadzu, Japan). The amount of each formulation ingredient in the physical mixture was same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400cm-1.[6]

Formulation of Emulgel

Determination of ibuprofen solubility in selected oils

Diclofenac solubility test was performed to select the oil for preparation of microemulsion. The 1 g of ibuprofen was added into each flask containing 5ml of selected oils such as castor oil, oleic acid, isopropyl myristate, liquid paraffin and the mixtures were shaken for 24 hours at temperature 250 C and next were centrifuged at 3000 rpm during 5 min. In thesupernatant ibuprofen content was determined by UV spectrophotometric method.

Pseudo ternary phase diagrams

Diclofenac showed maximum solubility in oleic acid as compared to other oils; hence, it was selected for further studies. Tween 80, as a surfactant, and ethanol, as cosurfactant, showed better solubility for ibuprofen and good emulsifying properties with oleic acid. Pseudo ternary phase diagrams were constructed using water titration method. Surfactant and cosurfactant (Smix) were mixed in different weight ratios (1:1, 1:2, and 1:3, 2:1 and 3:1). Oil and Smix mixture were mixed thoroughly in different weight ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3 8:2 and 9:1) Distilled water was added drop wise to the different mixtures of oil/Smix until cloudy dispersion was obtained. Pseudo ternary plots were constructed using Chemix School Software and microemulsions were prepared based on ternary phase diagram

Method of Preparation

Different formulations were prepared using varyingamount 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 in distilled water separately with constant stirring at a moderate speed using mechanical shaker. Formulations F1 and F2 were prepared by Carbopol 934 and F3, F4 by xanthun gum, F5, F6 by HPMC K15 M and , F8by Carbopol 934 & Xanthun gum, F9,F10 by Xanthun gum and HPMC K15M, F11,F12 by Carbopol 934 & HPMC K15M as gelling agent. The gel prepared by dispersing the gelling agent in heated distilled water (75 degrees * C) and the dispersion was cooled andleft overnight. The pH of all the formulations was adjusted to 5.5 to 6.5 using tri ethanol amine (TEA) The oil phase of the emulsion was prepared by dissolving methyl and propylparabens in ethanol and it was added to oleic acid. Then ibuprofen was added to oil phase. The aqueous phase was prepared by incorporating Tween-80 into distilled water, then bothphase were mixed using constant stirring to get microemulsion. The obtained emulsion wasmixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel

Table 1: Composition Of Emulgel Formulations.

Ingredients(% w/w)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Diclofenac	5	5	5	5	5	5	5	5	5	5	5	5
Oleic acid	6	6	6	6	6	6	6	6	6	6	6	6
Tween 80	20	20	20	20	20	20	20	20	20	20	20	20
Ethanol	10	10	10	10	10	10	10	10	10	10	10	10
Methanol	1	1	1	1	1	1	1	1	1	1	1	1

Methyl paraben	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**	**0.03**
Propyl paraben	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**	**0.01**
Water	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**
Carbopol 934	**1.5**	**1.5**	**-**	**-**	**-**	**-**	**0.5**	**0.75**	**-**	**-**	**0.5**	**0.75**
Xanthum gum	**-**	**-**	**1**	**1.5**	**-**	**-**	**0.5**	**0.75**	**0.5**	**0.75**	**-**	**-**
HPMC K15M	**-**	**-**	**-**	**-**	**1**	**1.5**	**-**	**-**	**0.5**	**0.75**	**0.5**	**0.75**
Triethanolamine	**0.7**	**0.7**	**0.7**	**0.7**	**0.7**	**0.7**	**0.7**	**0.7**	**0.7**	**0.7**	**0.7**	**0.7**
Water	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**

Evaluation of micro-emulsion :

Phase separation:

Microemulsions were subjected to centrifugations at 3000rpm for a period of 60 min and observed for any phase separation.

Evaluation of emulgel:

The above formulated emulgel formulation was subjected to evaluation of followingparameters:

Physical observation

Physical parameters such as color, appearance, consistency, grittiness on application andother visual factors like clarity and color of formulation are first thing decides quality offormulation Any change in physical observation with time reflect physical instability of formulation and make the product cosmetically unacceptable. Physical instability refers to the change in colour, texture, gloss, appearance; feel and othervisual factors are generally in dispersion system like emulsion, physical instability is caused by phase separation of emulsion as the effect of temperature. time and other dependent factors which may try to affect the separation immediately after preparation of emulsion. This unwanted separation of phases makes the product cosmetically inelegant and unacceptable. Physical parameters such as colour, homogeneity, consistency, grittiness, and phase separation were recorded.[7-9]

Determination of pH

The pH value can be considered as an indicator to possible instability as any deterioration of ingredient/s due to varied climatic conditions during storage and incompatibility of ingredients can lead to change in viscosity. pH of all formulations was determined by a pH meter (Digital pH meter). The pH meter was calibrated with a standard buffer solution having pH 4 and 7 before use, 1 g of the formulation was dissolved in distilled water and stirred until it forms a uniform suspension, kept it aside for 2 h. The volume made up to 100 ml and pH of the suspension was measured with the help of calibrated pH meter.[10-11]

Viscosity

Viscosity is the most important parameter in the evaluation as it governs many properties of the formulation such as spread ability, pourability of the product from the container etc. As there are various factors which can

affect the viscosity like change in temperature, change manufacturing conditions, quality of raw materials etc. The viscosity of emulgel was determined by LVT Brookfield viscometer. The sample was placed in a clean and dried container and viscosity was checked as per standard operating procedure of viscometer by using spindle no. 4 at speed 30 rpm. After recording the dial reading viscosity was calculated in the centipoises (cps).[13-14] Following formula is used for the calculation of the viscosity:

Viscosity in centipoises (cps) = Dial reading x Factor.

Rheological Studies

Rheological properties (study of deformation and flow of matter) are required in various pharmaceutical areas. For studying rheology of emulgel Brookfield viscometer LV dial type was used. For obtaining nature of system and rheograms, both ascending and descending readings were noted down. i.e. firstly, by increasing shear stress and then by decreasing.Rheograms obtained were plotted by taking RPM on Y- axis and Dial reading on X axis.[15]

Determination of spreadability

The spreadability was determined by parallel plate method.[17] Two glass slide of 10x 20 cm were selected. The formulation whose spreadability had to be determined was placed over one slide. The other slide was placed upon the top of the formulation such that the cream was sandwiched between the two slides across a length of 14.5 centimeters along the slide [71-72). Two slides are fixed to stand so that lower slide was remained fixed to stand so that lower slide was remained fixed allowing the upper slide to slip off freely with the help of 50 gm weight. The time required for the upper slide to separate out from lower slide was noted and spreadability was calculated as follows.

$$S=WXL/T$$

Where, S = Spreadability

L= Length of the glass plate (14.5 cm)W-Weight tied to upper plate (50g)

T= Time taken to separate the slide completely from each other

Extrudability test

In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in percentage of emulgel and emulgel extruded from lacquered aluminium collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. More quantity extruded better is extrudability. The measurement of extrudability of each formulation is in triplicate and theaverage values are presented. The extrudability is than calculated by using the following formula:[18]

Extrudability = Weight applied to extrude Emulgel from tube (in gm) / Area (in cm2).

Drug content determination

Diclofenac content in emulgel was measured by dissolving quantity of jellified emulsionin solvent (methanol) by sonication. Absorbance was measured after suitable dilution at 221 nm in UV-spectrophotometer and % drug content was calculated.

$$\text{Content uniformity} = \frac{\text{conc in mcg/ml} \times 100 \times \text{Dilution Factor}}{1000}$$

The percentage content uniformity is calculated by:

$$\text{\% Content Uniformity} = \frac{\text{Practical Yield} \times 100}{\text{Theoretical yield}}$$

Ex vivo diffusion study

Cellophane membrane previously soaked in the respective dissolution medium overnight was used as the permeation membrane. 200 ml of Phosphate buffer pH 7.4 was placed in abeaker (receptor compartment). An accurately weighed quantity (1 g) of the formulated Emulgel was then uniformly spread on the cellophane membrane (donor compartment) andthis membrane was tied to the diffusion tube (a hollow tube open on both sides). One sideof the cellophane membrane was kept in contact with the medium (Phosphate Buffer pH7.4). The medium was constantly agitated using a magnetic stirrer and the temperature wasmaintained at a constant of 371 °C throughout the operation. Samples of 10 ml volume were then withdrawn from the receptor compartment at intervals of 1 hour over a period of8 hours and the amount withdrawn was replaced with fresh volume of the medium. The samples withdrawn were then analysed for the amount of Ibuprofen released by UV spectrophotometric method by measuring the absorbance of the samples at 221 nm againstPhosphate Buffer pH 7.4 taken as blank.[19]

Determination of total microbial count in formulated emulgel

Microbial evaluation is essential to check the limits of microbial contamination and extentof pathogenicity. This evaluation has direct correlation with the quality of products. The total microbial count was determined by the plate count method.

Stability study

Stability may be defined as the ability of the drug to retain its property within specified limits throughout its shelf life. Improper storage of cosmetic product can lead to their physical deterioration & chemical degradation resulting in reduced activity &occasionallyin the form of toxic degradation product The arrehemics equation is widely applied to the cosmetic product for the Accelerated stability studies. The stability of the medicinal product at room temperature is comparedwith that of evaluated temperature.[20-21]

Results and Discussion

Drug Polymer Compatability Study.

Ibuprofen FTIR of Ibuprofen exhibits characteristic peaks for carboxyl group at 29561m-1 and 1721cm-1 due to N-H and C-O stretching respectively, at 1273cm -1(Benzene), 1107.9 cm -1 (Hydroxyl group, Bending).

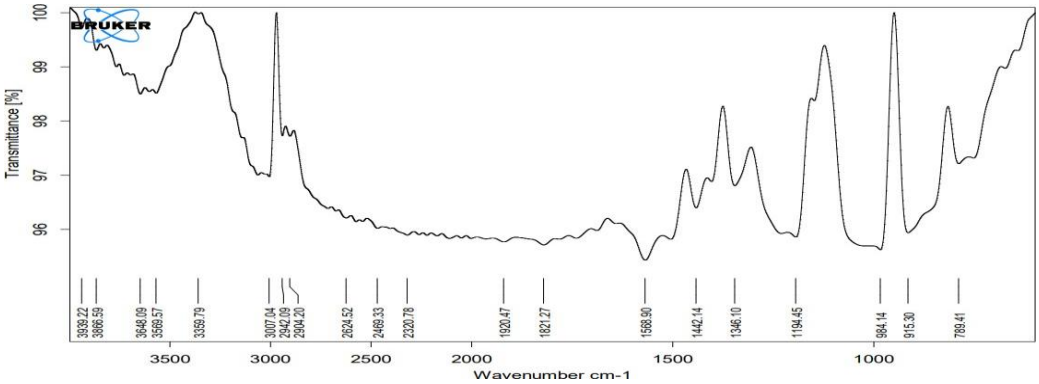

Fig.1 FTIR of Diclofenac sodium.

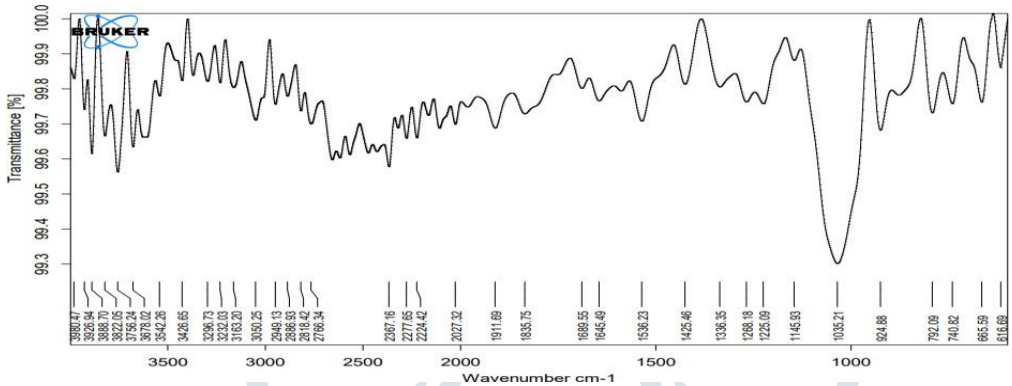

Fig.2 FTIR of Physical Mixture

Pseudo ternary phase diagram:

From all four-phase diagrams i.e. 1:1, 1:2, 2:1 and 3:1 the ratio of 2:1 S/Cos concentration showed good self microemulsifying region hence selected for formulation of microemulsion. Right part from boundary line in phase diagram shows us the region in which self microemulsifying region exists. A larger microemulsion region is responsible for the higher microemulsifying potential of the combination. Thus, it is helpful in finding regions having better ability at lower proportion of cosurfactants and having higher drug loading potential.

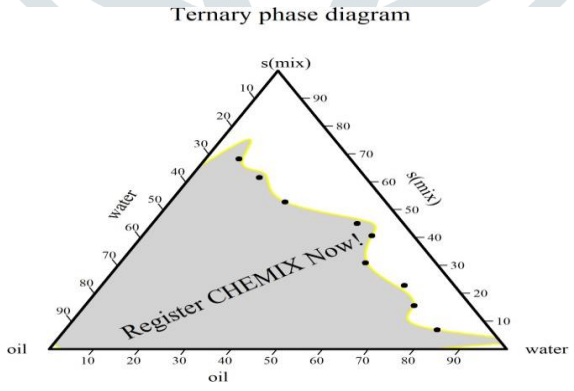

Fig.3 Pseudo ternary phase digram

Physical appearance of emulgel formulation:

The prepared emulgel formulations were inspected visually for their color, homogeneity andconsistency.

Table 2. Determination of physical properties of formulated Emugel

Batch	Colour	Homogenicity	Consistency	Phase separation
F1	Milky white	Homogeneous	Cream	No
F2	Milky white	Homogeneous	Cream	No
F3	Milky white	Homogeneous	Cream	No
F4	Milky white	Homogeneous	Cream	No
F5	Milky white	Homogeneous	Cream	No
F6	Milky white	Homogeneous	Cream	No
F7	Milky white	Homogeneous	Cream	No
F8	Milky white	Homogeneous	Cream	No
F9	Milky white	Homogeneous	Cream	No
F10	Milky white	Homogeneous	Cream	No
F11	Milky white	Homogeneous	Cream	No
F12	Milky white	Homogeneous	Cream	No

Determination of physical properties of formulated Emugel.

The pH of the topical formulations should be compatible with skin pH. A change in the pH may cause skin irritation or disruption. The pH of the all emulgel formulations was modified with the help of triethanolamine and when checked it was found in between the range 6 and 6.5, which is acceptable for skin preparations. The formulation F2 showed more spreading coefficient, i.e.21.96, as compared to other formulations, this is because formulation contained optimum concentration of Carbopol 934, i.e. 1.5%.

Table 3.Determination of physical properties of formulation.

Formulation	pH	Spreadability (gm.cm/s)	Extrudability	Drug content (%)
F1	6.06±0.024	18.14±0.12	Very good	76.69
F2	6.02±0.016	21.96±0.34	Excellent	93.69
F3	6.15±0.017	19.15±0.22	Excellent	77.19
F4	6.04±0.020	17.67±0.61	Excellent	96.83
F5	6.06±0.012	18.44±0.15	Excellent	82.59
F6	6.05±0.021	17.76±0.29	Excellent	76.59
F7	6.18±0.016	16.06±0.19	Very good	92.45

F8	6.04±0.20	19.07±0.27	Very good	71.71
F9	6.15±0.017	20.05±0.85	Excellent	91.54
F10	6.02±0.012	18.67±0.43	Excellent	83.21
F11	6.08±0.008	15.89±0.27	Very good	78.54
F12	6.10±0.008	16.97±0.39	Very good	83.90

(n=3)

Spreadability

Spreadability is the term expressed to denote the extentof area to which the gelreadily spreads on application to the skin. One of the essential criteria for an emulgel is that it should have good spreadability. It depends upon the type and concentrations of polymers used in the formulation. More viscous formulation would have poor spreadability. The formulation F2 showed more spreading coefficient, i.e.21.96, as compared to other formulations, this is because formulation contained optimum concentration of Carbopol 934, i.e. 1.5%.

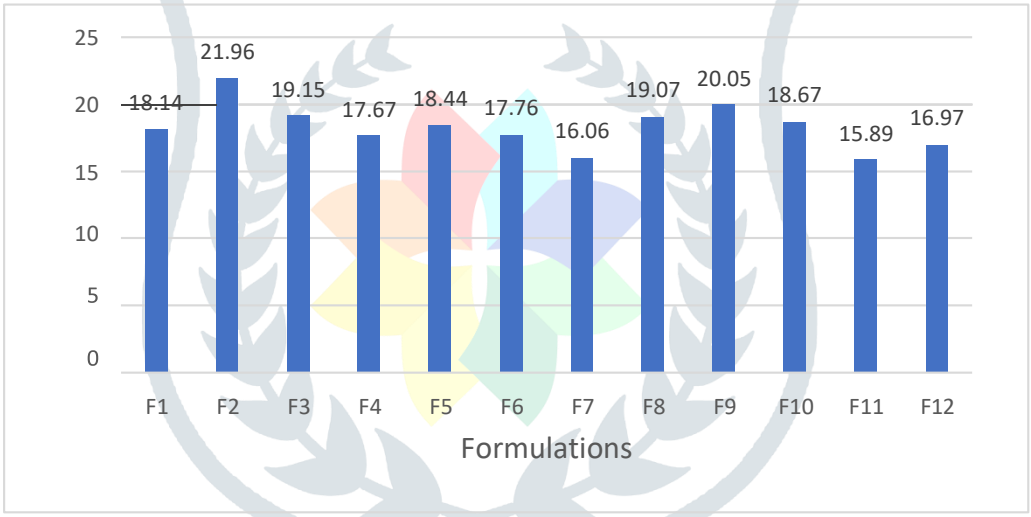

Figure 3. Bar Graph showing Spredability of Formulated Emugels.

Viscosity:-

Rheological behavior of the emulgel formulations exhibitednon-Newtonian shear thinning pseudo plastic type of flow, i.e. decreases in viscosity at increasing shear rates. As the shearstress is increased, the disarranged molecules of the gelling material are caused to align their long axes in the direction of flow. Viscosity for respective emulgelswas found to be

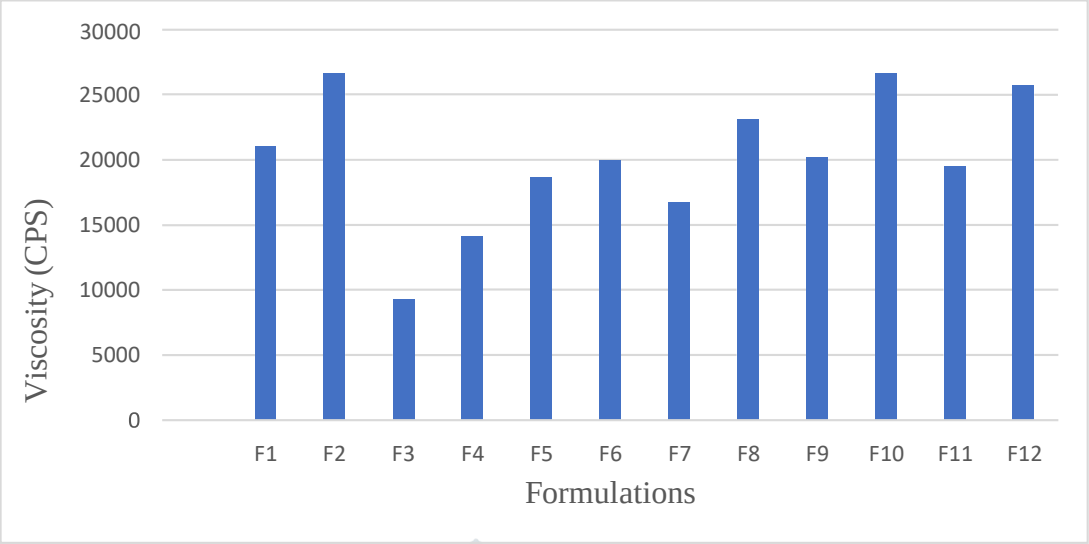

Figure 4. Bar Graph showing Viscosity of Formulated emugels.

In vitro drug release

The release of active pharmaceutical ingredient (ibuprofen) from the emulgel was varied according to polymer concentration. The drug release from its emulsified gel formulation can be categorized in the following ascending order:F12<F11 <F8 <F10angle F9<F3<FI<F4<F7<F5<F6<F2 , Where the amounts of release of drug after 6hours were 46.51\%,48.30\% 51.01\% 52.37%, 56.21%, 59.93%, 56.15\% 73.7\% 74.53%,75.36%, 75.36%, 87.45% respectively.

The progressive augment in the amount of drug diffusion through membrane from formulation credited to gradual dwindle in the concentration of polymer. It has beenrecapitulated that, if we amplify the concentration of polymer, the diffusion of drug through the membrane also diminishes. The cumulative % of drug release profile ofall the formulation batches has been shown below:

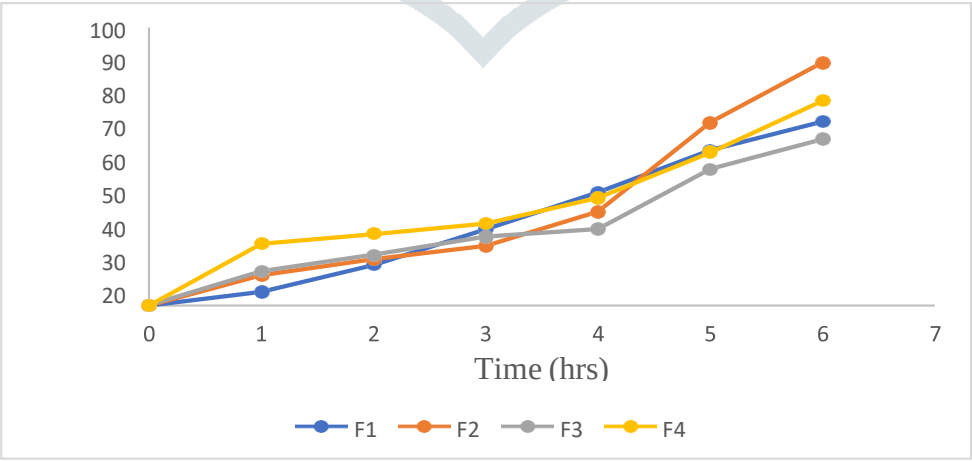

Fig. 4 % cumulative drug release of formulations F1 TO F4

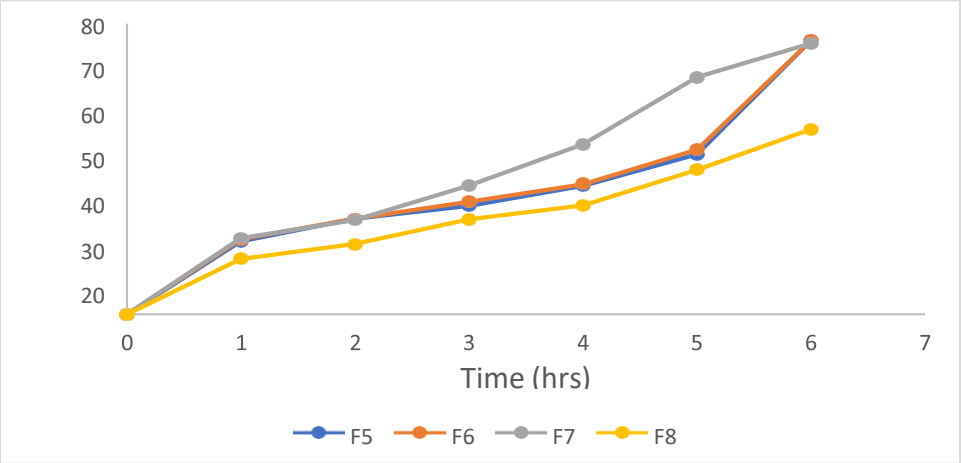

Fig. 5 % cumulative drug release of formulations F5 TO F8

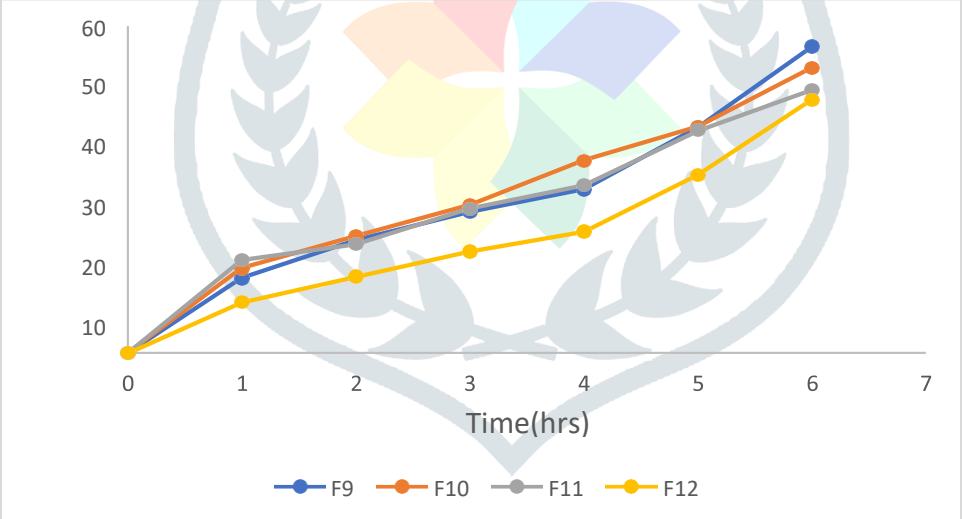

Fig. 6 % cumulative drug release of formulations F9 to F12

Stability study:

The stability test was carried out for three months and results revealed that all theshowed better stability at 40 degrees * C and 30 degrees * C There was not any changes found in physical properties of emugel.

Conclusion

Formulated emulgel showed acceptable physical properties, drug content, drug release, and anti-inflammatory activity, which remained unchanged upon storage for 3 months. The physical appearance was milky white, pH was in between 6-6.5, formulations showed better spreading coefficient & extrudability. However, the Carbopol 934 based Emulgel inits low concentration with the formulation code F2 proved to be the formula of choice,

since it showed Viscosity of the optimized batch F2 was found to be 26687 cps and 93.69% drug content, the highest drug release i.e. 87.45% in 6 hrs.

References-

1. Jain A, Deveda P, Vyas N, Chauhan J et al. Development of Antifungal Emulsion BasedGel For Topical Fungal Infection(S). UPRD 2011;2(12).
2. Mishra A.N., Controlled and Novel Drug Delivery, 4th edition, CBS Publisher and Distributers. (1997) 107-109.
3. James Swarbrick, Encyclopedia of Pharmaceutical Technology, 3rd edition vol-1 Informa Healthcare.(2007);1311-1323
4. Upadhyaya Supriya, chauhan bishtSeema, Kothiyal Preeti, emulgel: a novel approach for topical delivery of hydrophobic drugs, International Journal of Universal Pharmacy andBio Sciences 3(2): March-April 2014.
5. B. W. Tekade, U. T. Jadhao, Formulation and evaluation of diclofenac sodium effervescent tablet. Innovations in Pharmaceuticals and Pharmacotherapy. 2 (2), 350-358, 2014.
6. Sanjay, Jain BD, Padsalg A, Patel K, Mokale V, Formulation, development and evaluationof Fluconazole gel in various polymer bases, Asi. J. Pharm., 2007; 1: 63 -68.
7. Fariyaz Shakeel., Sanjula Baboota., Alka Ahuja., Javed Ali., and Sheikh Shafiq.. Skin Permeation Mechanism and Bioavailability Enhancement Of Celecoxib From Transdermally Applied Nanoemulsion. Journal Of Nanobiotechnology. (2008);6(8):1-11.
8. Kasliwal N, Derle D, Negi J, Gohil J. Effectof permeation enhancers on the release and permeation kinetics of meloxicam gel formulations through rat skin. Asian Journalof Pharmaceutical Sciences 2008, 3 (5): 193-199
9. U T. Jadhao, B W. Tekade, Formulation and in-vitro evaluation of oral Hydrogel containing miconazole nitrate., AJPER October – December 2017;6, (4) ;45-56.
10. Swapnil Suresh Walekar, Micro emulsions Based Gel System: A Novel Approach for Topical Drug Delivery, An International Journal of Advances in Pharmaceutical SciencesVolume 5, Issue 1, 2014:1776-1782.
11. Umesh Jadhao, Harshal Tare., "Development and Evaluation Of Herbal Ethosomes Of Passiflora Foetida Linn For The Treatment Of Psoriasis" IJBPAS, October, Special Issue,2023,12(10):535-549.
12. Bali, V., Ali, M., & Ali, J. (2010). Study of surfactant combinations and development of a novel nanoemulsion for minimising variations in bioavailability of ezetimibe. Colloidsand Surfaces B: Biointerfaces, 76(2), 410-420.
13. Doh, H. J., Jung, Y., Balakrishnan, P., Cho, H. J., & Kim, D. D. (2013). A novel lipid nanoemulsion system for improved permeation of granisetron. Colloids and Surfaces B: Biointerfaces, 101, 475-480
14. Jadhao U.T, Rathod S. P,.Formulation and critical evaluation of piroxicam gel., The Pharma Innovation Journal 2021; 10(3): 89-94.,
15. Gupta GD, Gaud RS. Release rate of Nimesulide from different gellants. Ind J Pharm Sci 1999; 61:229-234.
16. Chakole CM, Shende MA, Khadatkar SN, Formulation and development of novel combined halobetasol propionate and fusidic acid ointment. Int J Chem Tech Res 2009; 1:103-116.

17. U.T. Jadhao, Rathod S.P, Dhembre G.N, Formulation and evaluation of nanosponge gel containing ketoconazole. Innov Pharm Pharmacother 2021;9(1):15-24.

18. Stable topical formulation of Clarithromycin. Appln no- 10/498, 407.ICH Harmonized Tripartite Guidelines, Stability testing of new drug substances and products, ICH Committee. Federal register 2003; 68: 6571718.

19. Bacchav Y, Patravale V B. Formulation of Meloxicam gel for topical application: in-vitro and in-vivo evaluation, Acta Pharmaceutica 2010; 60: 153 163.

20. Patel C J, Tyagi S, Gupta A K, Sharma P, Prajapati, P.M, Potdar M P, Emulgel: A combination of emulsion and gel, Journal Drug Discovery and Therapeutics 2013;1(6): 72-76.

21. Vijaya Bhanu P, Shanmugam V, Lakshmi P V, Development and optimization of noveldiclofenac emulgel for topical drug delivery, Pharmacie Globale (IJCP) 2011; 9(10):1-4. 64.