IJMPR 2022, 6(2), 62-68

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article
SJIF Impact Factor: 5.273

FORMULATION AND EVALUATION OF PIROXICAM EMULGEL USING PERMEATION ENHANCERS FOR TOPICAL DELIVERY

***Poonam Yadav, Durga Pandey, Praveen Tahilani and R. B. Goswami**

Sagar Institute of Research and Technology-Pharmacy Bhopal, MP.

Received on: 26/12/2021
Revised on: 16/01/2022
Accepted on: 06/02/2022

***Corresponding Author**
Poonam Yadav
Sagar Institute of Research and Technology-Pharmacy Bhopal, MP.

ABSTRACT

The objective of this work was to prepare and evaluate emulgel of Piroxicam which will increase skin penetration of drug due to penetration enhancers in comparison with marketed preparations of the drug. Droplet's size of emulsion was found 759 µm. The drug content found to be 98.1 in the gel and viscosity 20211 ± 0.43 cP spreadibilty of formulation was more than marketed formulation. Optimized formulation showed 83.1 % release in 8 hours which is little more than marketed preparation. Emulgel are more comfortable than cream and ointments. Materials selected for preparation are biocompatible in nature. Piroxicam will be highly effective drug in the treatment pain, swelling, and joint stiffness from arthritis. Its analgesic activity can be improved by adding methyl salicylate, mentha oil and clove oil in the formulation. Mentha oil and clove oil used for permeation enhancers in the formulation for better drug absorption. More drug will be absorbed by emulgel than conventional formulation and reduces dosing frequency. We can conclude that Piroxicam is more effective when entrap as microemulsion and given in emulgel form as compared to conventional dosage form of the same drug.

KEYWORDS: Emulgel, Piroxicam, permeation, Spreadility, Microemulsion.

INTRODUCTION

Piroxicam is a potent anti-inflammatory drug. It is used in treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and acute gout disease. It has prolonged half-life of about 45 hrs. It is a poorly water-soluble drug and when administered orally it may cause bioavailability problems due to its poor solubility and dissolution rates in biological fluids. It also possesses analgesic and antipyretic properties. Although the drug is well absorbed following oral administration, gastric irritation is still the most serious adverse effect associated with conventional route of drug administration. Piroxicam is weakly acidic and highly lipophilic anti-inflammatory drug available for oral, parenteral and topical administration. The drug inhibits the synthesis of prostaglandins in inflammation.[1]

Advantages of microemulsion and emulgel over other dosage forms
Increases the rate of absorption, Eliminates variability in absorption, Helps to solubilize lipophillic drug, Provides an aqueous dosage form for water insoluble drugs, Increases bioavailability, Various routes like topical, oral and intravenous can be used to deliver the product, Rapid and efficient penetration of the drug moiety, Helpful in taste masking, Provides protection from hydrolysis and oxidation as drug in oil phase in o/w microemulsion is not exposed to attack by water and air. Liquid dosage form increases patient compliance. Less amount of energy requirement.[2,3]

Ingredients selected for formulation • Methyl salicylate is an external analgesic that temporarily relieves minor body aches and muscle and joint pain associated with backache, arthritis, strains, sprains. • Carbopol 940 will be used as gelling agent. • Oleic acid as oil, Tween-80 and Span-80 as emulsifiers and ethanol as co-surfactant will be selected for preparation of emulgel. Water will be used as aqueous phase • Mentha oil and clove oil were used as penetration enhancers. The emulsion will be prepared and it will be incorporated in gel base using Carbapol gelling agent.[4,5]

Rationale for selection of emulgel system The hydrophobic moieties cannot be added directly to the gel bases because of the improper release shown by drug as of lack of solubility. The emulgel allows the addition of such hydrophobic drugs in the oil phase which leads to the dispersion of oil globules in aqueous phase resulting in formation of o/w emulsion. Further this emulsion can be simply added to the gel base, thereby providing good stability and better release of drug. [6] Gels show greater loading capacity than other novel delivery systems due to the lesser entrapment efficiency shown by them because of their nano size. Majority transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or

breaking and ointment shows rancidity due to oily base but emulgel showing better stability.[7]

The objective of this work is to prepare and evaluate emulgel of Piroxicam which will increase skin penetration of drug due to penetration enhancers in comparison with marketed preparations of the drug. We used Oleic acid as oil phase Tween-80 and Span-80 as emulsifiers and ethanol as co- emulsifiers. Carbopol 940 as gelling agent and water will be used as aqueous phase. Mentha oil and clove oil will be used as penetration enhancers. In addition, we use methyl salisylate in oil phase to give additive effect to Piroxicam.

MATERIALS AND METHODS

Various sensory characters observed which are White to off white colour, doorless appearance and crystalline powder.

Solubility

An excess amount of piroxicam was added to each solvent and was stirred magnetically. After stirring for 24 hours at 37ºC, the equilibrated sample was centrifuged for 10 min at 5000 rpm (rotations per minute) to remove excess amount of piroxicam. The supernatant was filtered and properly diluted with phosphate buffer pH 7.4. The concentration of piroxicam was determined by UV spectrophotometry.[8,9]

Table 1: Solubility of Piroxicam.

S.N.	Components	Solubility (mg/ml)
1	Water	0.13
2	Linseed oil	5
3	Oleic acid	13.2
4	Phosphate buffer	0.20
5	Propylene glycol	6
6	Tween 80	16
7	Span 80	3.2

Melting point

Melting points of drug was determined by using capillary method where drug placed in the capillary tube fused at one end tied to thermometer. The thermometer was dipped in Thiele's tube containing paraffin oil. The tube was heated with the help of burner and the melting point was noted when the drug just started melting. The melting point of Piroxicam was ound 205- 208℃.[8]

Identification Test

Determination of λ_{max} for the drug in phosphate buffer (pH-7.4)

The UV spectrums were recorded in the range 200-400 nm by using UV-Visible double beam spectrophotometer. An absorption maximum of Piroxicam in phosphate buffer pH 7.4 was recorded at 354 nm when scanned between 200-400 nm as shown in figure.

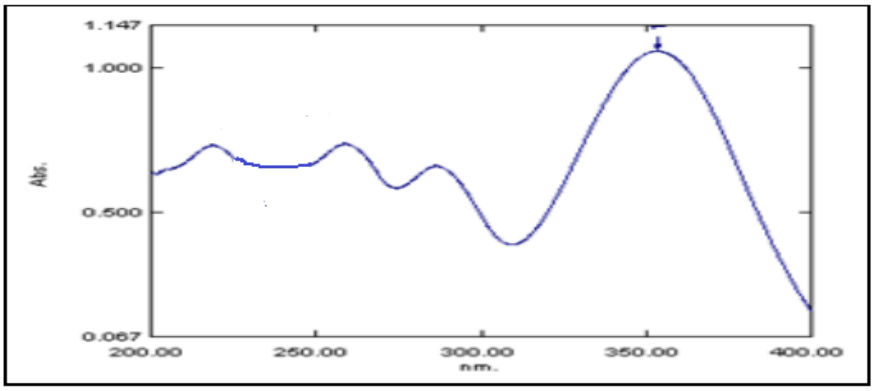

Fig. 1: Maximum Absorbance of Piroxicam

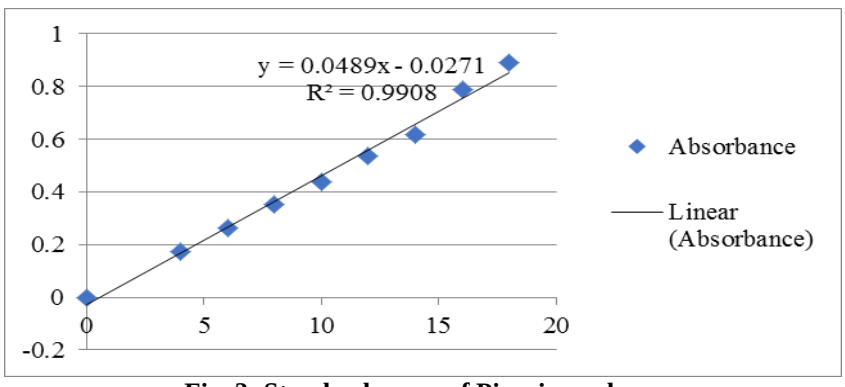

Fig. 2: Standard curve of Piroxicam drug.

FTIR

Spectra of pure drug were recorded by KBr method by using Fourier transform infrared spectrophotometer. In the present study, the potassium bromide disc method was employed. The powdered sample was intimately mixed with dry powdered potassium bromide. This mixture was then compressed in to transparent disc under high pressure using special dies. This disc was placed in IR spectrometer and spectrums were recorded. The scanning range was 400-4000 cm^{-1} and the resolution was shown in result and discussion section.

Chemicals Used

Drug received from SIFC, Clove oil received from Chemdyes carporation , Rajkot, Ethanol from Changshu yangyuan chemicals, Tween 80 Suvidhinath laboratories,(sulab), Baroda, Triethanolamine from Suvidhinath laboratories,(sulab), Baroda, Carpobol 940 from Oxford lab, Methyl salicylate and Mentha oil received from S.D Fine Chemicals Ltd., Mumbai (India) All other chemicals and reagents used were of analytical grade. Distilled water was used throughout the study.

Preparation of emulgel

Preparation of gel base by using Carbopol

Various batches prepared by changing composition of Carbopol, Span 80 and Tween 80. Carbopol is dissolved in distilled water using mechanical stirrer at optimum RPM and TEA is added to adjust the pH. Carbopol is pH sensitive polymer forms gel in particular pH. The effect of carbopol 940 on pH is that the higher the concentration of carbopol 940, the more acidic the pH of the gel produced because carbopol 940 has acidic properties. Carbopol 940 can form a good and stable gel matrix at a neutral pH around 6-11. When carbopol 940 is dispersed it will have an acidic pH and still not form a good matrix gel. After being neutralized by alkylating agents (e.g. NaOH and Triethanolamine) the polymer will absorb and hold water, the polymer chains are interconnected with cross bonds to form a good gel mass.[9]

Preparation of emulsion

Oil phase

Span 80 was dissolved in oleic acid and 0.5 % piroxicam was added to the above phase. Clove oil and Methyl salicylate also added in measured quantity in the oil phase.

Aqueous phase

Tween 80 is dissolved in distilled water, and then ethanol mixed. Heat both the phases separately to 70- 80°C. Mix both phases slowly at the constant stirring untill cooled to room temperature, which results in formulation of o/w emulsion.

Preparation of emulgel Emulsion and Gel base are mixed in 1:1 proportion with constant stirring, which results in piroxicam emulgel.

Table 2: Composition of formulation by changing % of surfactant & Co-Surfactant.

Ingredients(%w/w)	F1	F2	F3	F4	F5	F6
Piroxicam	0.5 %	0.5 %	0.5 %	0.5 %	0.5 %	0.5 %
Oleic acid	20	20	20	20	20	20
Ethanol	5	5	5	5	5	5
Clove Oil	2	2	2	2	2	2
Mentha Oil	2	2	2	2	2	2
Span 80	0.9	1.8	2.8	0.9	1.8	2.8
Tween 80	1.1	2.1	3.2	1.1	2.1	3.2
Methyl salicylate	10	10	10	10	10	10
Carbopol 940	0.5	0.5	0.5	0.75	0.75	0.75
Triethanolamine	qs to adjust pH					
Water	58.9	57	56.8	58.9	57	56.8

Table 3: Composition of optimized emulgel formulation by using Carbopol 940.

S. No	Ingredients	% w/w
1	Piroxicam	0.5
2	Oleic acid	18
3	Ethanol	5
4	Clove Oil	2
5	Mentha Oil	2
6	Span 80	2.8
7	Tween 80	3.2
8	Methyl salicylate	10
9	Carbopol 940	0.5
10	Triethanolamine	qs
	Water	56

Characterization of Emulgel

Physical Appearance

The prepared emulgel formulations were inspected visually for their color, homogeneity, consistency and pH.

pH

The pH values of 1% aqueous solutions of the prepared gellified emulsions were measured by pH meter (Digital pH meter).

Rheological Study

The viscosity of the different emulgel formulations was determined at 25°C using Brookfield viscometer with spindle 52 Brookfield Engineering Laboratories.

Drug Content Determination

Drug content of emulsion was measured by UV spectrophotometer. 1 ml of emulsion was diluted to 20ml with methanol and volume was made up to 100ml using phosphate buffer 7.4. A volume of 2ml of this solution was further diluted to make 10 µg/ml solution of piroxicam

In vitro drug Release Study by Franz diffusion cell

Gellified Emulsion (500 mg) was applied evenly to the surface of egg membrane which was clamped between the donor and the receptor chamber of diffusion cell. Franz diffusion cell (with effective diffusion area 3.14 cm2 and 15.5 ml cell volume, Temperature 37 ± 0.5ºC, Speed 50 rpm) was used for the drug release studies. The receptor chamber was filled with freshly prepared PBS (pH 7.4) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time intervals. Samples were analyzed for drug content by UV/VIS visible spectrophotometer after appropriate dilutions. The cumulative amount of drug released across the egg membrane was determined as a function of time. same in-vitro drug release study performed for marketed formulation (Pirox Gel, Cipla Pharmaceuticals) and compared with optimized formulation.[10]

Photomicrography

Morphology of emulsion was studied under light microscope. Optimized batches of the emulgel were viewed under light microscope to study their shape. The emulgel was suitably diluted, mounted on glass slide and viewed by light microscope under magnification of 40 X.

Scanning electron Microscopy by SEM

Sample for scanning electron microscopy was performed in SEM model Ultra Plus, software, ZESIS (Germany).

Spreadability

One of the criteria for an emulgel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreadability. Spreadability of emulgel and marketed gel was measured in terms of diameter of emulgel circle produced when emulgel is placed between two glass plates of definite weight. A weighed quantity (350 mg) of emulgel or gels was taken on one glass plate and another glass plate was dropped from a distance of 5 cm. The diameter of the circle of spread emulgel was measured. 47, 48 Stability study Stability study of the selected formulation was done at room temperature for 1 m [11,12]

Stability study

Stability study of the selected formulation was done at room temperature for 1 month and formulation was finally evaluated for appearance, drug content and pH. [13-14]

RESULTS AND DICUSSION

Preformulation studies shows that drug is pure. FTIR of drug shown in figure and interpretation shown below. The calibration curve of Piroxicam was constructed by using UV/vis spectrophotometer in phosphate buffer pH 7.4. The curve was shown in the Figure and there is an increase in the absorbance with an increase in the concentration range of 4-18 µg/ml with the R^2 value is 0.990.

Solubility

Highest solubility of piroxicam was found in oleic acid amongst oils, Tween 80 amongst surfactants and ethanol amongst co-surfactants. Hence these components are selected for preparation of emulgel system.

Appearance of emulsions and emulgels

All formulation batches were found to be homogenous yellowish milky emulsions while emulgels were found to be yellowish white viscous creamy preparation.

Drug content

The drug content of the formulated emulgel was estimated spectrophotometrically at 354 nm. The drug content found to be 98.1 % in 1.0 gram of the gel. Amount of drug in the emulgel indicates the suitability of the system for high entrapment in the internal phase.

Droplet Size

The results indicate that globule size of droplet varies from 700 to 3 µm. Droplets size of emulsion was 759 µm shown in figure

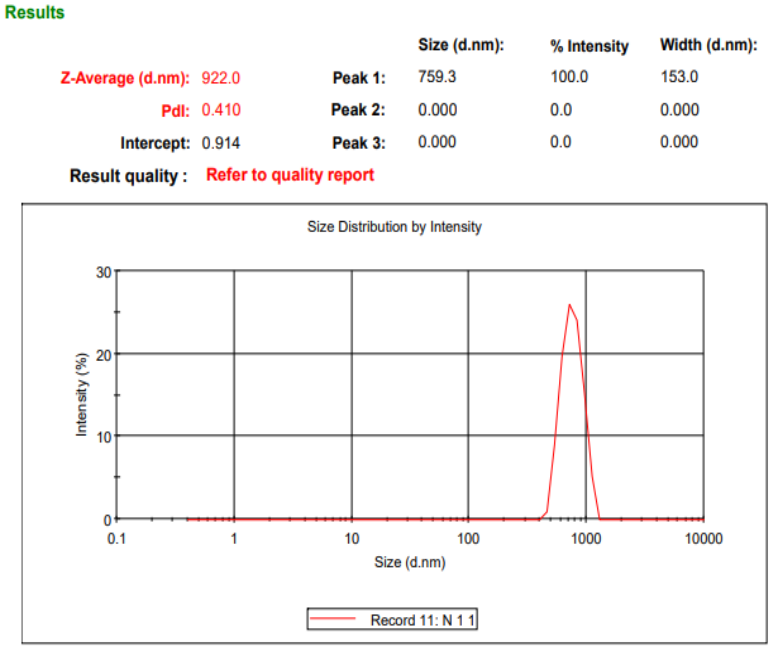

Fig. 3: Particle size of optimized formulation.

Viscosity

Viscosity of optimization batch of the emulgel was found to be 20211 ± 0.43 cP.

Interpretation of FTIR of Piroxicam

FTIR spectrum of pure Piroxicam exhibited characterized by the peak at 3332.16 cm-1 and 1347.00 cm-1 for pyridine2-yl amino stretching and saturated methyl group respectively. The presence of those characteristic peaks of drug observed in the FTIR spectra of formulation, indicates that absence of chemical interaction between the drug and the polymers employed in the study.

3799.34 – OH Stretching, 3332.16 – CH – Stretching (Alkyne)2235.55 – C = N (Stretch) 2119.35 – C= N 1972.64 – C – H (Bending) 1625.01 – N – H (Amine) Stretch 1523.34 – No (Nitro) Stretch 1431.01- OH (Carboxylic) Bend 1347.00 – S=O (Sulfone) 1297.67- C – N (Aromatic amine)1177.33 - C – O (Ester) 1037.54 – S=O (Sulfoxide) 829.55 – C-H (1,4- Disubstituted) 769.73 – C-H (Trisubstituted) 687.65 – C-Br (Stretch) Scanning Electron Microscopy (SEM) SEM Shows size around 1.5 µm for optimized formulation.

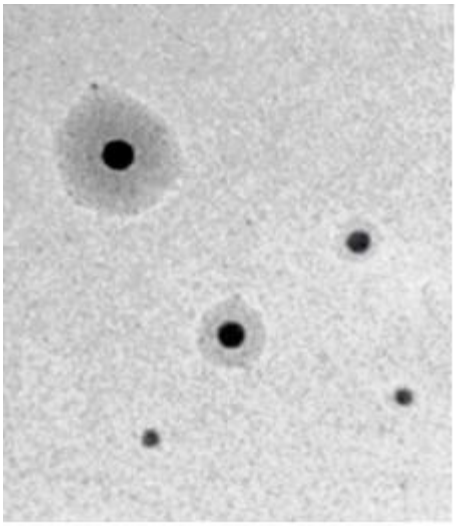

Fig. 4: SEM of optimized Formulation.

Photomicrograph From the photomicrograph, nearly spherical globules of emulsion were observed. Though this study does not give any exact estimate of size however it gives a general idea about formation of emulsion and success of the method used Figure

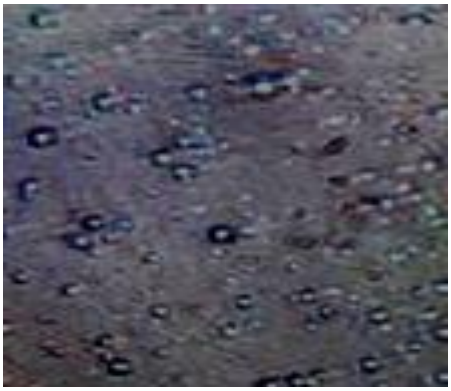

Fig. 5: Photomicrograph of emulsion droplets.

Measurement of pH

pH of the emulgel preparation was found to be 5.3, which is in the normal pH range (4 - 5.5) of skin and would not produce any skin irritation.

In vitro drug Release Study

The in-vitro drug release for the prepared emulgels was evaluated using phosphate buffer pH 7.4 for 8 hrs and results were tabulated in Table 8 and Figure 14. Optimized formulation F3 showed release drug faster than the other formulation due to the lower concentration of Carbopol and higher concentration of emulsifiers. An increase in concentration of Carbopol leads to decreased drug release from formulation due to increase in viscosity of formulation. The topical emulgel of Piroxicam was prepared successfully by using Carbopol 934. The prepared emulgel was subjected to physicochemical studies. The in vitro studies revealed that optimized formulation showed 83.19% of drug release at the end of 8 hr.

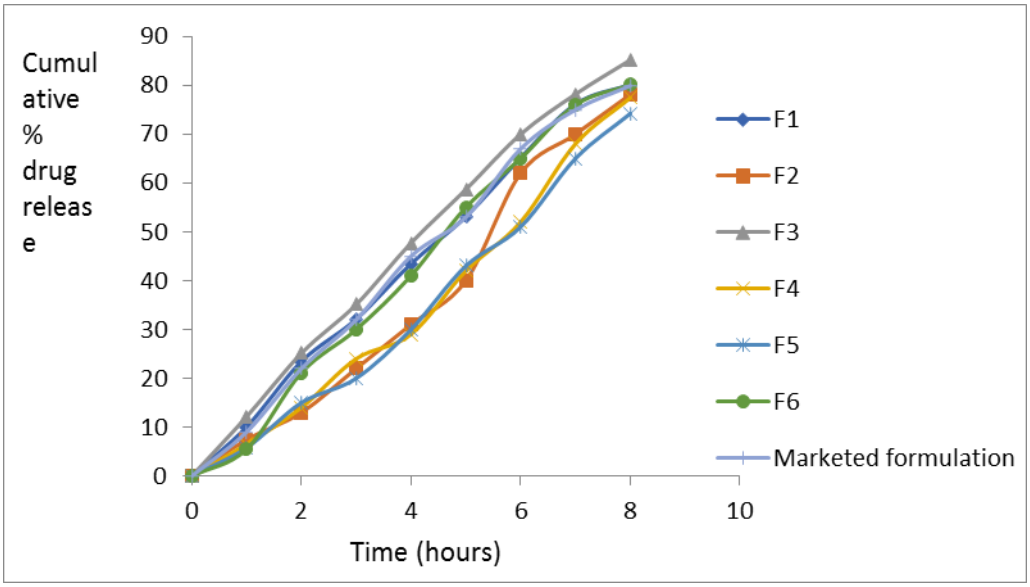

Fig. 6: F3 formulation is optimized formulation and showed 83.1 % release in 8 hours

Table 4: % Drug Content and average globules size.

Batch	% Drug Content	Average globule Size
F1	90.29	13.1
F2	89.23	12.3
F3	98.1	11.5
F4	93.09	14.2
F5	91.13	15.9
F6	88.1.5	14.3

Formulation batches F3 release drug faster than the other formulation due to the lower concentration of Carbopol and higher concentration of emulsifiers. An increase in concentration of Carbopol leads to decreased drug release from formulation due to increase in viscosity of formulation.

Spreadability

Spreadability of the formulations is shown in table 10. Spreadability denotes the extent of area where the gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value. The spreadability of the emulgel formulations is presented in Table10. Spreadability of emulgel is an important parameter. Results of spreadability indicate that spreadability of emulgel is better than the marketed gel.

Table 5: Spreadability of the formulation.

Formulation	Diameter of circule
Optimized formulation	4.10+ 0.12
Marketed Formulation	2.29+ 0.18

Values are average of three determinations

Stability study of optimized formulation

No Major changes noted during one month stability of formulation.

Table 6: Stability study of optimized formuation.

Before			After one month		
Appearance	**Drug Content (%)**	**pH**	**Appearance**	**Drug Content(%)**	**pH**
Yellowish White viscous creamy	98.1	5.4.	Yellowish White viscous creamy	96.95	5.6

Average of average of three determinations

CONCLUSION

Based on the results observed from SEM, Particle size, Viscosity pH and in vitro release study, designed formulation can be a good dosage form for topical delivery of drug for good permeation. However, efficacy of formulation depends on experimentation on animal model.

ACKNOWLEDGEMENT

Author is thankful to SIRT-Pharmacy and SIRTS Pharmacy for successful conduction of experimentation and data compilation of project.

Conflict of Interest

Declared none.

REFERENCES

1. Pandey D, Singh R, Jain S and Jain D. Ofloxacin ion pairing within submicron emulsion: a potential approach for ocular delivery. Indian Drugs, 2019; 56(04): 56-63.
2. Jain V, Gupta S, Garg D, Mishra P. Ciprofloxacin surf-plexes in sub-micron emulsions: A novel approach to improve payload efficiency and antimicrobial efficacy. Int J Pharm, 2011; 56-43.
3. Khunt DM, Mishra AD, Shah DR. Formulation design & development of piroxicam emulgel. Int J PharmTech Res., 2012; 4: 1332-44.
4. Gupta SK, Bansal P, Bhardwaj RK, Jaiswal J, Velpandian T. Comparison of analgesic and anti-inflammatory activity of meloxicam gel with diclofenac and piroxicam gels in animal models: pharmacokinetic parameters after topical application. Skin Pharmacology and Physiology, 2002; 15(2): 105-11.
5. G. S. Canto, S. L. Dalmora & A. G. Oliveira Piroxicam Encapsulated in Liposomes: Characterization and In Vivo Evaluation of Topical Anti-inflammatory Effect, Drug Development and Industrial Pharmacy, 1999; 25(12): 1235-1239.
6. Dalmora ME, Dalmora SL, Oliveira AG. Inclusion complex of piroxicam with β-cyclodextrin and incorporation in cationic microemulsion. In vitro drug release and in vivo topical anti-inflammatory effect. International journal of pharmaceutics, 2001 Jul 3; 222(1): 45-55.
7. Rafiee-Tehrani M, Mehramizi A. In vitro release studies of piroxicam from oil-in-water creams and hydroalcoholic gel topical formulations. Drug development and industrial pharmacy, 2000 Jan 1; 26(4): 409-14.
8. D. Pandey, D. Jain formulation and evaluation of submicron emulsion containing entrapped fluoroquinolone for ocular delivery. Asian Journal of Pharmaceutical and clinical research, 2018; 11(7): 431-35.
9. Garg, Varun, Harmanpreet Singh, Amit Bhatia, Kaisar Raza, Sachin Kumar Singh, Bhupinder Singh, and Sarwar Beg. "Systematic development of transethosomal gel system of piroxicam: formulation optimization, in vitro evaluation, and ex vivo assessment." *AAPS pharmscitech*, 2017; 18(1): 58-71.
10. Patel, Nikunjana A., Natvar J. Patel, and Rakesh P. Patel. "Formulation and evaluation of curcumin gel for topical application." *Pharmaceutical Development and* Technology, 2009; 14(1): 83-92.
11. Esmaeili, Fariba, Saeid Rajabnejhad, Ali Reza Partoazar, Shahram Ejtemaei Mehr, Reza Faridi-Majidi, Mousa Sahebgharani, Leila Syedmoradi, Mohammad Reza Rajabnejhad, and Amir Amani. "Anti-inflammatory effects of eugenol nanoemulsion as a topical delivery system." *Pharmaceutical development and technology*, 2016; 21(7): 887-893.
12. Velam, Vinesha, Prasanna Raju Yalavarthi, C. R. Sundaresan, K. R. Vandana, Thushara Bindu Dudala, Haritha Kodavatikanti, and Harini Chowdary Vadlamudi. "In vitro and in vivo assessment of piroxicam incorporated Aloe vera transgel." *International journal of pharmaceutical investigation*, 2013; 3(4): 212.
13. Shin SC, Cho CW, Choi HK. Permeation of piroxicam from the poloxamer gels. Drug development and industrial Pharmacy, 1999 Jan 1; 25(3): 273-8.
14. Bindu Vani Y, Haranath C,Surya Prakash Reddy C, Bhargav E. Formulation and in vitro Evaluation of Piroxicam Emulgel. Int. J. Pharm. Sci. Drug Res., 2018; 10(4): 227-232.