FORMULATION AND OPTIMIZATION OF PIROXICAM FOR TRANSDERMAL DRUG DELIVERY

Ms. VAMAKSHI THAKER

[1]Asst. professor, School of pharmacy, Sage university Bhopal, M.P.

Abstract :- In developing a transdermal delivery system, two criteria are considered: one is achieving adequate flux across the skin and the other is minimizing the lag time in skin permeation. Transdermal drug delivery system facilitates the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects. Topical administration of drug with systemic effect can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first-pass metabolism of the drug and related toxicity effects, controlling the rate of delivery and modulating distribution of drug in the systemic circulation.

Keywords :- Microemulsion, Piroxacam, Antifungal drug, Co surfactants, Transdermal drug delivery system.

Introduction:- The Transdermal drug transport is one of the most promising method for drug delivery utility. Increasing numbers of drugs are being delivered to the listing of therapeutic retailers that may be introduced to the systemic move through skin. Transdermal drug transport structures (TDDS) may be defined as self contained discrete dosage bureaucracy which, when carried out to the intact skin, can provide the medicine via the pores and skin at a managed price to the systemic circulation. The capability of the use of intact skin as the path of drug management has been recognised for several years. The suggestion of the use skin for shipping of drug is from historic time. Ebers papyrus used the husk of castor oil plant bark imbibed with water placed on aching head. Historically, the medicated plaster may be viewed because the first development of transdermal drug shipping; this medicated plaster became very popular in japan as over the counter pharmaceutical dosage from Transdermal shipping now not only presents controlled, constant administration of the drug, however also allows non-stop enter of drugs with brief organic 1/2-lifestyles and gets rid of pulsed access into systemic move, which frequently undesirable aspect impact. TDDS facilitate the passage of therapeutic portions of medication substance via the pores and skin and into the general stream for his or her systemic results. In growing a transdermal delivery system, two criteria are taken into consideration; one is achieving adequate flux throughout the skin and the other is minimizing the lag time in skin permeation. One approach overcoming this constraint is the incorporation of numerous chemical skin enhancers into the automobile.

Materials :- Piroxicam, Chloroform, Tween 20, Ethanol, Methanol, Castor oil, Oleic acid, Potassium dihydrogen orthophosphate, Sodium hydroxide, Propylene glycol.

Methods :-

PREFORMULATION STUDIES

Preformulation may be described as a sage of development process during which the researches characterize the physical, chemical and mechanical properties of the drug substance to form effective, stable and safe dosage form. Hence, preformulation studies are essential to characterize the drug for proper designing of the drug delivery system . The preformulation studies which were performing in this project include.

Description:- Organoleptic characters of drug was observed and recorded by using descriptive terminology.

Melting point:- Capillary tube, which is sealed at one end is charged with sufficient amount of dry powder to form a column in the bottom of tube 2.5mm to 3.5mm, and packed down as closely as possible by moderate tapping on a solid surface. The apparatus is operated according to the standard operating procedure. The block is heated until temperature is about 30°C below the expected melting point. The capillary tube is inserted into the heating block, and the heating is continued at a rate of temperature increased of about 1°C to 2°C per minute until melting is completed.

The temperature at which the detector signal first leaves its initial value is defined as the beginning of melting, and the temperature at which the detector signal reaches its final value is defined as the end of melting, or the melting point. The two temperature fall within the limits of the melting range.

Solubility Studies :- The spontaneous interaction of two or more substance to form a homogenous molecular dispersion is called as solubility.10mg of drug was a suspended separately in 10ml of different solvents at room temperature in tightly closed tubes and shaken. The solubility profiles of two drugs in various solvents are shown in the table.

Hygroscopic nature:

Procedure :- 2gm of the test specimens were weighed accurately in petridish and the weight were noted down. Then the test specimens were exposed to 75% RH at 40°C in environment stability testing camber and the other was kept at room temperature for 7 days period. The specimen was weighed after 7 days and the difference in weight was noted down.

Identification of drug sample

Finding the absorption maxima (λ max) :- The absorption maxima were found for drug identification. Ultraviolet visible spectrophotometry has been used to obtain specific information on the chromophoric part of the molecules. Organic molecules in solutions when exposed to light in the visible/ultraviolet region of the spectrum absorb light of particular wavelength on the type of electronic transition associated with the absorption.

The drug solution (10, 20, 30, 40, 50, 60 µg/ml) in phosphate buffer pH 7.4 was taken in standard curvette, and scanned in the range of 200-300 nm in a UV spectrophotometer. It exhibits maxima at 377nm. UV spectrum of

drug taken in phosphate buffer pH 7.4 also exhibits maxima at 377nm. Therefore, further all measurements were taken 377nm.

FORMULATION DEVELOPMENT

The pharmaceutical development studies have to be carried out with the purpose of selecting right dosage form and a stable formulation. These studies give detailed description of all the steps involved in the process of development of the finished procedure. Such details are intended towards identifying critical parameters involved in the process, which have to be controlled in order to give reliable and reproducible quality product.

Dose calculation:- The total dose of drug, D, in a prolonged action preparation comprises the normal (prompt) dose, D_n and the sustaining dose D_S i.e. $D_t = D_n + D_S$ if the first order elimination rate constant is K, the rate at which drug is eliminated when a normal dose is given is D_n K which is the rate at which drug is replaced if the peak blood level is to be maintained. Given a maintenance period 't' the maintenance dose (D_s) is D_n k_t. The total dose is therefore:

$$\mathbf{D_t = D_n + D_s}$$
$$= D_n + D_nK_t$$
$$= D_n(1+K_t)$$
$$= D_n(1 +0.693t/tl/2)$$
$$\mathbf{D_t = D_i\ (1+\ 0.693\ x\ t_{m/}t_{1/2})}$$

Calculation of HLB value for O/W type of Microemulsion:- The HLB of a non-o-ionic surfactant whose only hypdrophilic portion is polyoxyethylene is calculated by using the formula

$$\mathbf{HLB = E/5}$$

Where, E is the percentage by weight of ethylene oxide. A number of polyhydric alcohol fatty acid esters, such as glyceryl monosterate, can be estimated the formula

$$\mathbf{HLB = 20(1-S/A)}$$

Where, S is the saponification number of the ester and A is the acid number of the fatty acid. The HLB of polyoxyethylene sorbitan monolaurate (tween-20),

For which S= 5.5 and A= 276, is

$$\mathbf{HLB = 20(1-45.5/276) = 16.7}$$

The HLB values of some commonly used amphiphilic agents are given in table 13

The oil phase of an oil- in water (o/w) emulsion requires a specific HLB, called Required Hydrophile- Liphophile Balance (RHLB). A different RHLB is required to form water-in oil (w/o) emulsions have been determined empirically for a number of oil and oil-like substance

Selection of oils:- To find out the suitable oil, which can be used as oil phase in microemulsion, and provide excellent skin permeation rate of piroxicam. The solubility of piroxicam in various oils including olive oil, castor oil, isopropyl myristate, isopropyl palmitate, oleic acid was measured at 25°C. The solubility of olive oil, castor oil, isopropyl myristate, isopropyl palmitate, and oleic acid in oily mixtures was also measured.

Procedure:- About 10 gm of oil was accurately weighed in 25 ml glass beaker and 100mg of piroxicam was added into it, followed by stirring on magnetic stirrer at moderate speed to dissolve the drug. When drug was dissolved completely another 10mg piroxicam was added and stirring was continued. Addition of drug was continued until the saturated solution is obtained. Finally, the total amount of drug consumed was determined by using UV-spectrophotometer at 377nm. It was found that, oleic acid has consumed maximum amount of piroxicam and thus chosen as a vehicle for microemulsion oil phase.

Selection of surfactants and co-surfactants:- The non-ionic surfactants do not ionize at any great extent in the solution, they are greatly compatible with both anionic and cationic substances; various nonionic surfactants like, span20, tween-20 and co-surfactants like, propylene glycol, isopropyl alcohol and b-butanol were subjected to titration. Finally, Tween-20 and propylene glycol were selected as an ideal surfactant and co-surfactant for the system.

Trial formulations:- Different trial formulation were formulated and studied for their physiochemical characterization and visual observation. Finally get the optimized formulation

Different percentage of surfactant and co-surfactant have been used in each trial formulation and studied to have controlled effect for period of 24 hours.

Trial Batch-I:- The first trial formulation of piroxicam microemulsion were prepared by employing drug and oil phase same concentration varying the percentage of surfactant and co-surfactant (Tween-20 and Propylene glycol, 1:1 ratio).

Trial Batch-II:- In the second trial formulation, Piroxicam microemulsions were prepared by employing drug and oil phase same concentration and varying the percentage of surfactant and co-surfactant (Polysorbate-20 and Propylene glycol,2:1 ratio).

Table: Formulation of trial batch I (F1-F3)

S.no.	Ingredients	F1	F2	F3

1	Piroxicam (mg)	10	10	10
2	Oleic acid(%w/v)	2	2	2
3	Tween-20(%w/v)	1	2	3
4	Propylene glycol (%w/v)	1	2	3
5	Distilled water (%w/v)	26	24	22
6	Final volume (%w/v)	30	30	30

Table: Formulation of trial batch II (F4-F6)

Surfactant : co-surfactant (2:1)

S. no.	Ingredients	F6	F7	F8
1	Piroxicam (mg)	10	10	10
2	Oleic acid (%w/v)	2	2	2
3	Tween-20(%w/v)	2	4	6
4	Propylene glycol (%w/v)	1	2	3
5	Distilled water (%w/v)	25	22	19
6	Final volume (%w/v)	30	30	30

Table: Compositions of the selected microemulsion formulation

S.no.	Formulations	Piroxicam (mg)	Oleic acid (%w/v)	Tween-20 (%w/v)	Propylene glycol (%w/v)	Distilled water (%w/v)	Final volume (%w/v)
1	ME-1	10	2	6	3	19	30
2	ME-2	10	4	6	3	17	30
3	ME-3	10	6	6	3	15	30
4	ME-4	10	8	6	3	13	30
5	ME-5	10	10	6	3	11	30

CHARACTERIATION OF MICROEMULTIONS

Optical Transparency:- Optical transparency of the formulation was determined by inspecting the sample in clear and transparent container under the presence of good light against reflection into the eyes, and viewed against black and white illuminated background.

Determination of pH:- pH is measured using a pH meter of a glass electrode. pH fundamentally represents the value of hydrogen ion activity in solutions. It is defined by the equation given below. This value well accords with the logarithm of the reciprocal of hydrogen ion concentration in dilute solutions.

Viscocity Measurements:- This procedure determines the viscosity of a fluid by the use of a Brookfield viscometer. Viscosity is the measure of fluid friction which can be considered as the internal friction resulting when a layer of fluid is made to move in relationship to another layer. Viscosity is a measure of the ratio of shearing stress to rate of shear.

$$\frac{\textbf{Shear Stress (dynes)}}{\textbf{Rate of shear (cm/sec)}} = \textbf{Poise}$$

- Check to confirm that the viscometer has been calibrated. If not, calibrate using software.
- The sample container and quality should be approximately the same as for the calibration standard. Equilibrate the temperature of the sample to the temperature designated in the specification (±1°C).
- Confirm that the viscometer is using the bubble level on the back of the instrument. For the Brookfield LV-II, the instrument with spindle attached and the speed set as designated in the product specification. The main display will flash 00.0 after 10 sec.
- Immerse the spindle designated in the product specification into the sample to the groove on the spindle shaft. Do not allow air bubbles to be formed. Attach the spindle to the viscometer.
- The spindle should not touch the bottom or sides of the container and should be centered. Reconfirm that the viscometer in level.
- The spindles were rotated at a speed of 60 rpm. Samples of microemulsions were allowed to settle over 30 min at room temperature before the measurements were taken.
- For the LV-II, choose the units by pressing the desiredunits key(cps for centipoises).
- Set the speed as designated in the product specification, start the viscometer and read at constant reading. For manual models, use the conversion chart to convert the dial readings to centipoises.
- When done, turn motor and power off. Clean spindles and place in spindle holder.

Mechanical stress study:- The chemical and physical stability of microemulsionwith lornoxicam were evaluated via phase separation by mechanical stress study.

The different microemulsion formulation (ME-1 to ME-5) were centrifuged (Remi centrifuge) at 2000 rpm for different time interval (10 min, 30 min, 60 min) and noted down the volume of phase separation of formulation.

Particle shape and Surface Morphology

(a) **Transmission Electron Microscopy (TEM):-** Morphology and structure of the microemultion were studied using transmission electron microscopy with Topcon 002B operating at 200kv (Topcon,Paramus,NJ) and capable of point-to-point resolution. In order to perform transmission electron microscopy observations, a drop of microemulsion was suitably diluted with water and applied on a carbon-coated grid, then treated with a drop of 2% phosphotungstic acid and left for 30s. The coated grid was dried under vacuum and then taken on a grid holder and observed under the transmission electron microscope

Particle Size Measurement

(a) **Determination of particle size distribution by particle size analyzer:-** The selected best piroxicam microemulsion formulations were subjected to laser particle counting method. Here the sample was injected into the sample delivery and controlling champer. Then, suitable solvent was pumped through the chamber. Now a beam of laser light was allowed to fall on the sample cell. After required number of runs, they were directed towards the detector. From this the particle size range nd the average mean particle size of the formulation can be studied. The average particle size of microemulsion formulations can be determined using particle size analyzer.

(b) **Drug content analysis:-** 1ml of microemulsion formulations was transferred into a beaker containing 10 ml methanol. The content of the beaker were stirred for 30 min and then kept for 2hrs. After 24hrs the content of beaker were transferred into centrifuge tube and centrifuged at the 3000 rpm for 10 min. Supernatant was separated and filtered. Then 0.1 ml of the supernatant was diluted appropriately with Phosphate Buffer Saline (PBS) pH 7.4 and assayed Spectrophotometrically for drug constant.

Summary :- In developing a transdermal delivery system, two criteria are considered: one is achieving adequate flux across the skin and the other is minimizing the lag time in skin permeation. Transdermal drug delivery system facilitates the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects. Topical administration of drug with systemic effect can have advantages over other methods for several reasons, one of which is the avoidance of hepatic first-pass metabolism of the drug and related toxicity effects, controlling the rate of delivery and modulating distribution of drug in the systemic circulation. Transdermal delivery of microemulsion system which composed of non-irritating, pharmaceutically acceptable ingredients. Microemulsion was prepared by water titration method using oleic acid as oil phase, tween-20 as surfactant and propylene glycol as co-surfactant. Different oils, surfactants and co-surfactants were screened to select ideal components of microemulsions with good solubility and excellent skin penetration of piroxicam. The use of oleic acid is advantageous because it increase skin permeability by two mechanistic

scenarios of the enhancer; (a) lipid fluidization, and (b) lipid phase separation, oleic acid is a model skin permeation enhancer, oleic acid facilitates penetration into the skin by disrupting the fluidity of the stratum corneum. The thermodynamic activity of drug in the formulation is a significant driving force for the release and penetration of the drug into skin. In microemulsion, the co-surfactant lowers the interfacial tension of the surfactant film, resulting in a more flexibility and dynamic layer system. The thermodynamic driving force for the release reflects shows the relative activities of the drug in different phase. Since drug can be release from the internal phase to external phase and then from external phase to the skin, the relative activities may monitor the skin permeation flux.

The permeation capability of the microemulsion formulation were evaluated by conducting the *in-vitro* skin permeation experiments. ME (1-5) piroxicam microemulsion were studied for *in vitro* skin permeation through excised goat skin. The amount of piroxicam permeated through excised goat skin over 24-hour period was plotted against the function of time (fig. 4), the permeation fluxes (µg/cm^2/hour) for all these microemulsions through the goat skin were determined. The determined permeation fluxes are given in Table 30. Among all formulation, the highest permeation flux of µg/cm^2/hour was observed in case of formulation ME-3.

References :-

1. Chien YW. Transdermal Drug Delivery and Delivery Systems, in: Y.W. Chien, Novel Drug Delivery Systems, 2nd ed, Chapter 1, Marcel Dekker, New York, 1992: 301-380.
2. Vyas SP and Khar RK. Targetted and Controlled Drug Delivery Novel Carrier System 1st ed., CBS Publishers and Distributors, New Delhi, 2002; 411-447.
3. Hadgraft J, Guy R. In; Transdermal Drug Delivery , Marcel Dekker, Inc., New York and Basel,35,296.
4. Prausnitz MR, Mitragotri S, Langer R. Current Status and Futyre Potential of Transdermal Drug Delivery. Nature reviews, Drug Discovery, 2004;(3): 115-124.
5. Govil SK, In; Tyle, P., Eds., Drug Delivery: Fundamentals and application, Marcel Dekker, Inc., New York, 1988: 385-406.
6. Jain NK. Controlled and Novel Drug Delivery, Cbs Publisher and distributor, 1st ed, 100.
7. Jayaswal SB, Sood R, the Eastern Pharmacist, 1987; 30(357):47-50.
8. Hoar TP,Schulman JH, Transparent Water-IN-Oil Dispersions, The Oleopathic Hydro-Micelle, Nature, 1943:152; 102-103.
9. Schulman, JH, Stoeckenius, W Prince, L.M, Mechanism Of Formulation and structure of microemulsions by Electron Microscopy, J. Phys. Chem, 1959: 63, 1677-1680.
10. Cordero J, Alarcon L, Escribano E, Obach R, Domenech J. A Comparative Study of the Transdermal Penetration of A Series Of Nonsteroidal Anti-Inflammatory Drugs, J. Pharm. Sci, 1997, 86:503-508.
11. Holmberg, K., Handbook of Applied Surface and Colloid Chemistry. 2002: Chichester, New York, Wiley.

12. /www.wikipedia.org/Rheumatoid arthritis
13. Googman and Gilman's The pharmacological basis of Therapeutics, 11th edition, 2005.P.1415, Unit II, "'Disease of organ system " 1304-1309.
14. Abd-Allah FI, Dawaba HM, Ahmed AM. Preparation, characterization, and stability studies of piroxicam-loaded microemulsions in topical formulations. Drug Discov Ther. 2010; 4(4); 267-75.
15. Lopes LB, Scarpa MV, Pereira NL, De Oliveira LC, Oliveira AG. Interaction of sodium diclofenac with freeze-dried soya phosphtidylcholine and unilamellar liposomes. Revista Brasileira de Ciencias Farmaceiticas/Brazilian Joural of Pharmaceutical Sciences, 2006;42(4):497-504.2. Park ES, Cui Y.
16. Yun BJ, Ko IJ, Chi SC. Transdermal delivery of piroxicam using microemulsions. Arch Pharmacal Res. 2005;28(2): 243-8.
17. Khossravi M, Kao Y-H, Mrsny RJ , Sweeney TD. Analysis methods of polysorbate 20:a new method to asses the stability of polysorbate 20 and established methods that may overlook degraded polysorbate 20.
18. Arulanantham K, Genel M. Central nervous system toxicity associated with ingestion of propylene glycol, J Pediatr1978;93:515-516.
19. Microemulsion System with Improved loading of piroxicam: A study of microstructure Muhammad Faizan Nazar, Asad Muhammad Khan and Syed Sakhawat Shah 30 october 2009.
20. Y. Bindu Vani, C. Haranath, C. Surya Prakash Reddy, E. Bhargav Formulation and in vitro evaluation of Piroxicam Emulgel Int. J. Pharm. Sci. Drug Res. July-August, 2018, Vol 10.
21. Kulkarni Parthasarathi Keshavarao, Dixit Mudit, D. Lavanya, L. Naga Vamsi Krishna, R. Prudhvi development and evaluation of piroxicam loaded biopolymer based transdermal film, international research journal of pharmacy, 2(11),2011.
22. Nilesh Mishral, Dr. Ashish Mahamuni a comparative study of dicloferac sodium with piroxicam in patients undergoing surgical removal of third molar Dr. Journal of critical reviews Vol 7, Issue 7, 2020.
23. Pavani Vengalal, Cvs Subrahmanyam 1, M Gangaraju2 In vitro and in vivo evaluation of piroxicam loaded Ceramic Nanoparticles International Joural of Pharma Science and Research (Ijpsr) Vol. 7 No. 7 Jul 2016.
24. SH Girish, C Surabhi, S Meenakshi, KS Nithin, DV Gowda formulation and evaluation of solid self micro emulsifying dispersible tablet of piroxicam, International Journal of applied Pharmaceutics, 127-133, 2021.
25. Boonme, Nattakit Molee, formulation and characterization of piroxicam-loaded microemulsions, progess in applied Science and technology 10(2), 43-49,2020.