**INTRODUCTION**

Mefenamic acid or 2-((2,3-dimethylphenyl) amino)-benzoic acid belongs to non-steroidal anti-inflammatory drugs (NSAIDs) therapeutic class. It is frequently utilized in treating acute to moderate pain that include headache, fever, dysmenorrheal ache, osteo-arthritis, rheumatoid arthritis and swelling [1]. This drug is categorized in class II according to the Bio-pharmaceutical classification system (BCS) which has lower water solubility but higher permeability [2].

MA causes an extensive range of GIT disturbances, for instance GI-bleeding and gastric distress. It possesses weak solubility over pH range of 1.2-7.5. The systemic half-life of MA is 2 to 4 h. MA inhibits Cyclooxygenase-1 and COX-2 receptors. By blocking COX-1 receptors, it leads to persistent gastric bleeding and peptic ulceration. It can cause serious cardio-vascular undesirable effects via inhibition of COX-2 receptors. Due to shorter half-life, repeated administration of the drug is desired that could originate missing of drug dose and hence resulting in under-dose. Thus topical dosage forms of MA such as emulgel, Microsphere and ointment might increase the dose frequency and hazardous outcomes. Currently, many efforts were made to elevate the dissolution properties of MA to perk up its bio-pharmaceutical presentation [5]. It is traditionally obtainable in a tablet, capsule, and suspension for oral intake. The absolute Fractional bio-availability of MA is approximately 90–100 percent by this; the dissolution is the crucial factor for drug absorbance [6].

**ABSTRACT**

Objective: The aim of study was to formulate and evaluate Mefenamic acid ointment by the addition of penetration enhancer’s clove oil.

Methods: 1%, 2% and 3% formulations of Mefenamic acid ointment formulated as per B. P, by melting hard paraffin 4.75g at 60 °C initially and to this 4.75 g wool fats was incorporated, followed by addition of soft paraffin 80.75g and then adding Cetostearyl alcohol 4.75g and 1.2 and 3 ml clove oil by continuous stirring later on ointment being cooled at room temperature. These formulations were checked for consistency, Spreadability, homogeneity, PH, viscosity, skin irritation, drug content, UV absorbance, Differential scanning calorimetry (DSC) and XRD (X. ray diffraction) studies. *In vitro* pattern via using Franz cells besides with the use of dialysis cellulose membrane was done.

Results: All the synthesized formulations illustrated fine physicochemical characteristics. SEM and XRD Studies expressed that there were no physicochemical incompatibilities among active ingredient (Mefenamic acid salt) and additives combined as drug permeation enhancers (clove oil).3% formulation showed maximum released 65.199%.

Conclusion: In the present study, it was noted that clove oil can enhance the permeation of Mefenamic acid topical ointment.

Keywords: Mefenamic acid, Ointment, Cetostearyl alcohol, Clove oil

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**REFERENCES**

[1] Youssuf, V. (2019). Development and Evaluation of Mefenamic Acid Ointment Using Penetration Enhancers, *Journal of Pharmacy and Pharmacology*, 2, 893-898.

[2] Youssuf, V. (2019). Formulation and Evaluation of Mefenamic Acid Ointment Using Penetration Enhancers, *Journal of Pharmacy and Pharmacology*, 2, 893-898.

[3] Youssuf, V. (2019). Evaluation of Mefenamic Acid Ointment Using Penetration Enhancers, *Journal of Pharmacy and Pharmacology*, 2, 893-898.

[4] Youssuf, V. (2019). Enhancing the Permeation of Mefenamic Acid Ointment Using Penetration Enhancers, *Journal of Pharmacy and Pharmacology*, 2, 893-898.

**Fig. 1: Structure of mefenamic acid**
cell, Refrigerator, an Incubator, water bath, Oven, Soxhlet equipment and Brookfield digital viscometer of model DV-III+.

Preparation of Mefenamic acid ointment

A general B. P ointment being formulated by melting the hard paraffin 4.75g at 60 °C firstly and to this 4.75 grams wool fat added and mixed then 80.75 grams of soft paraffin added and ultimately adding the Cetostearyl alcohol 4.75g and lastly mixed with 1.2 and 3 ml clove oil by agitating thoroughly. Afterward the manufactured ointment was being cooled at a normal temperature [10].

Evaluation of mefenamic acid ointment

Physicochemical determination of mefenamic acid ointment

To check out the appropriateness of Mefenamic acid ointment for topical usage and its physicochemical features were elaborated as given under.

PH

PH scales for Mefenamic acid ointment calculated by means of a titrated pH scale [10, 11].

Viscosity

Brookfield RVDV ultra programmed Rheometer (Brookfield Engineering Labs Middleboro, MA) with spindle CP41 was chosen to estimate viscosity of many formulations in triplicate by revolving the spindle at 10 cpm at 25 °C. The interpretations were noted as triplicate and average was derived [12, 13].

Spreadability

The spread of all preparations was inspected by calculating the diameter of the formation of 0.5 g subsequent to compression between 02 glass slices 10 g [11].

Consistency

The consistency of Mefenamic acid ointment was assessed by conical protrusion procedure. In this technique, cone is connected to a 10 cm attaching rod which was dropped in center of the ointment-filled cup for the sake of finding ointment consistency; the over 50 seconds distance covered is recorded [10, 11].

Homogeneity

Visual surveillance was applied to examine out homogeneity of the ointment. Narrow transparent glass tubes were filled with ointment and seen under light to look for any lumpy entities [14].

Scanning electron microscopy (SEM)

An electron microscope [Maker FEI software (Hillsboro, Oregon, USA) was used for the reason declared over [11].

X-ray diffraction (XRD)

For verification of the purity of drug and ointment (i.e. to search out whether amorphous or crystalline), X-rays diffraction studies of pure powder drug salt (Mefenamic acid) and ointment formulations were carried out by employing a soft-ware PAN analytical (*Netherlands). An anode made of Cu-Ka with a voltage of 30 kV and an electric current of 15 mA was used for determination of measurements. Then the diffract-grams were taken at a rate of 2 min whilst sustaining the temperature at normal. A step width of 0.02 ° and 20 h/2 the 2 ° and that of 60 ° was utilized for this aim [11].

Drug content

10 mg content of each sample was liquefied, stirred in 100 ml of methanol solvent that has been filtered through 0.2m filtering membrane and examined using a visible UV calibrated SM in order to measure the quantity of Mefenamic acid in the ready ointments. The fractions of mefenamic acid were determined [11, 14].

Stability study

Ointment formulated samples were looked for stability as per ICH guideline for pH, spread-ability, viscosity, and drug content for the time of three months [15].

In vitro diffusion study

The Franz diffusion cell equipment by the popular Perm Gear USA, dialysis cellulose membrane and nylon membranes were selected in laboratory propagation studies. The membranes were allotted to future and the owner of the donor’s apparatus for Franz operation cells. 5 ml phosphate buffer having pH 7.3 was added to the receptor chamber/compartment, manufactured mefenamic acid oint, added to chamber the ointment consisting 1%, 2,%, and 3% clove oil at 37 °C solvent temperature. At 0.5 then 1 and 1.5 on and on 2, 3, 4, 8, 12, 16, 20, and 24 h. The samples of 2.0 ml were collected from cells; cells were filled with buffer instantly at 37 °C. Samples had been filtered via Millipore filter sieves kind Whatman, Germany150 mili meters filter paper, and the mefenamic acid estimation of the concentration was completed through UV visible spectrophotometry process [16, 17].

Kinetic analysis of mefenamic acid release in vitro

In vitro diffusion studies were assessed regarding the quantity of Mefenamic acid released. Drug release aspects and linear regression were examined where the “correlation coefficient” was measured to find out which of particular kinematic models matched with that of the release of drug via dialysis cellulose and nylon films [10, 11].

Statistical analysis

The data was analyzed by performing Anova test on SPSS Software. Different kinetic modes was used with DD solver for drug release kinetic for transdermal mefenamic acid ointment [17].

RESULTS AND DISCUSSION

Organoleptic characteristics

The organoleptic attributes like appearance or texture and homogeneity of the ointment preparations are discussed in table 1. Consequences expressed that the ointments had a good homogeneity and yellowish-white appearance and smooth texture. pH of all formulations was found in range 6.51±0.143- 7.12±0.163, with-in the prescribed limit and lies in the normal pH range of skin as given in table 1. Viscosity of all the formulations was noted and found in the range of 2314±6.13 –2651±9.93 CPS at 10 r. p. m as revealed in table 2. Ointment spreading capability of formulations was measured by measuring the diameter of the preparation of 0.5 gram following to pressing b/w 0.2 glass slices 10g as mentioned in table 2. The drug content of mefenamic acid was in the range of 97.13 to 99.11% shown in table 2. In this study, dialysis cellulose membrane was taken; statistically, it was observed that the membranes have good releasing. The formulation (F3) showed the maximum released (65.19%). This study is compatible with earlier works of Gul et al. [11], who gave a detailed account in words about the discharge of ephedrine in semi solid dosage forms. Discharge of mefenamic acid from the transdermal formulation, and its release through the membrane of dialysis cellulose, are indicated in fig. 3. Stability study of Ointment formulated samples were looked for stability as per ICH guidelines and outcomes are given in table 3. Results showed that the outward show of ointment was fine and no marked deviation in pH, spread-ability, viscosity, and drug content for the time of three months.

| Formulation code | pH         | Homogeneity | Texture and Appearance       |
|------------------|------------|-------------|------------------------------|
| F(1%)            | 6.51-7.12  | Good        | Smooth yellowish white       |
| F(2%)            | 6.81-7.02  | Good        | Smooth yellowish white       |
| F(3%)            | 6.60-7.12  | Good        | Smooth yellowish white       |
Table 2: Evaluation parameters of ointment formulations

| F. code | Viscosity | Spreadability (g/cm/s) | Drug content (%) | Skin irritation |
|---------|-----------|------------------------|------------------|----------------|
| F1%     | 2314      | 5.1                    | 99.11            | Nil            |
| F2%     | 2474      | 5.3                    | 98.07            | Nil            |
| F3%     | 2651      | 5.2                    | 97.13            | Nil            |

Table 3: Stability studies of ointment F1%, F2% and F3%

| S. No. | Factor    | Before S. tests’ (mean±SD) | After S. tests’ (mean±SD) |
|--------|-----------|-----------------------------|---------------------------|
|        |           | Month 1                      | Month 2 | Month 3 |
| 1.     | pH        | 6.51-7.12                   | 6.16   | 6.43   | 6.70   |
| 2.     | Viscosity | 2314                        | 2309   | 2307   | 2297   |
| 3.     | Drug content | 99.01                | 98.65  | 98.02  | 97.73  |

Fig. 3: Release of mefenamic acid ointment formulations 1, 2 and 3% (W/V) via dialysis cellulose membrane

SEM

Morphology and size of the prepared mefenamic acid ointment was determined by using scanning electron microscopy. SEM images of different prepared were taken. mefenamic acid ointment. SEM images had shown that mefenamic acid fig. 1(A). Ointment had big crystal like shape in most of the pure drug, while shape of fig. 1(B) as shown In inside ointment formulation 1% showed small white spots were present in formulation, which indicate that drug was loaded in ointment fig. 1(C and D) formulation 2 and 3 % showed the drug distributed within ointment formulations.

XRD studies

To observe physical and chemical properties of mefenamic acid X-ray diffraction studies were applied and polymeric matrix of ointment formulation showed sharp peaks of diffraction at an angle of 2θ value of 20.12 °, 21.23 °, and 24.10 °, etc. X-ray diffractograms are shown in (fig. 2, A) that show the crystalline nature of mefnamic acid. While the fig. 2(d) drug formulation
showed no peaks, displayed peaks having lesser intensity, while the fused peaks were present in diffractograms of the ointment. Irregular peaks of formulation fig. 2, B and C demonstrated that drug changed into an amorphous type in polymeric drugs with molecularly discrete nature. Which was reported by sandal et al. previously [18].

Fig. 2: X-ray diffract grams of (A) pure mefenamic acid (B, C and D) mefenamic acid formulations 1,2 and 3 % respectively
CONCLUSION
This research discloses that Mefenamic acid is a hydrophobic drug having low water solubility but on the other hand having high permeation rate and available in oral dosage forms of suspension and tablet in the pharmaceutical market but along with several adverse effects. Therefore for better patient compliance and appropriate dose frequency Mefenamic acid topical ointment formulation in combination with proper concentrations of convenient permeation accelerators thus may encourage more investigation and assurance towards designing dermal dosage forms of said drug in future.

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CONFLICT OF INTERESTS
We assure that this article paper has no conflict of interest.

REFERENCES
1. Kumar M, Singh D, Bedi N. Mefenamic acid-loaded solid SMEDDS: an innovative aspect for dose reduction and improved pharmacodynamic profile. Ther Delivery 2019;10:21-36.
2. Nurhidmah W, Sumirtapura YC, Pamudji JS. Dissolution profile of mefenamic acid solid dosage forms in two compendial and biorelevant (FaSSIF) media. Sci Pharm 2016;84:181-90.
3. RGS Maheshwari, RK Tekade, PA Sharma. Ethosomes and ultra deformable liposomes for transdermal delivery of clotrimazole: a comparative assessment. Saudi Pharma J 2012;20:161-70.
4. X Liu, H Liu, J Liu. Preparation of a ligustrazine ethosome patch and its evaluation in vitro and in vivo. Int J Nanomed 2011;6:241-7.
5. Sriumomsak P, Limmatvapirat S, Piriyaprasarth S, Mansukmanee P, Huang Z. A new emulsifying formulation of mefenamic acid with enhanced drug dissolution. Asian J Pharm Sci 2015;10:121-7.
6. Modi SV, Patel NJ. Development and evaluation of self-emulsifying drug delivery of a poorly water-soluble NSAID. World J Pharm Pharm Sci 2015;4:462-79.
7. Ajazuddin, Alexander A, Khichariya A, Gupta S, Patel RJ, Giri TK, et al. Recent expansions in an emerging novel drug delivery technology: Emulgel. J Controled Release 2013;171:122-32.
8. Gupta H, Babu R. Transdermal delivery: product and patent update. Recent Pat Drug Delivery Formul 2013;7:184-205.
9. Vasconcelos T, B Sarmento, Costa P. Solid dispersion as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discovery Today 2007;12:1068-75.
10. Gul R, Jan SU, Ahmad M, Faridullah S, Akhtar M. Formulation and evaluation of topical carbamazepine semi solid dosage forms for transdermal drug delivery. Lat Am J Pharm 2019;1:121-7.
11. Gul R, Jan SU, Ahmad M, Faridullah S, Akhtar M. Formulations, characterization, in vitro and ex vivo release of ephedra extract from topical preparations using dialysis cellulose membrane and natural rabbit skin. Dissolution Technologies 2017;4:24-30.
12. Vedavathi T, Srinivasa RB. Formulation and evaluation of terbinafine hydrochloride microsponge gel. Int J Appl Pharm 2019;6:4.
13. AVISH DM, Swaroop RL. Formulation and evaluation of ointment containing sulfowax wax. Asian J Pharm Clin Res 2019;8:115-20.
14. Abid H, Gul MK, Syed UJ, Shefaat US, Kifayatullah S, Muhammad A, et al. Effect of olive oil on transdermal penetration of flurbiprofen from topical gel as enhancer Pak. J Pharm Sci 2012;2:365-9.
15. Anindya HI, Mahdi J. Formulation and physical stability test of griseofulvin micro emulsion gel Int J Appl Pharm 2017;9:22-6.
16. Pattanayak S, Nayack SS, Dinda SC, Panda D, Naval KP. Evaluation of herbal ointments formulated with methanolic extract of cajanus scarabaeoides. J Pharm Allied Health Sci 2011;2:47-59.
17. Rahman G, Syed UJ, Mahmoud A, Muhammad A, Muhammad MQ. Formulation, characterization and in vivo evaluation of hedera helix l., topical dosage forms Pak. J Pharm Sci 2019;6:2603-8.
18. Samiullah, Syed UJ, Rahman G, Syed J, Asmathulla. Formulation and evaluation of transdermal patches of pseudoephedrine hcl. Int J Appl Pharm 2020;3:121-7.