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Original Article

FORMULATION AND EVALUATION OF MEFENAMIC ACID OINTMENT USING PENETRATION ENHANCERS

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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 fatwas 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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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 decrease the dose, dose frequency and hazardous outcomes. Currently, no transdermal preparation of Mefenamic acid is at hand in market as per literature analysis [3, 4]. Its physical and chemical characters, particularly the very little solubility in water (<<1 mg ml–1) and distinct adhesive properties, give rise to major challenges during dosage form development and manufacturing. Hence, great efforts were made to elevated 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].

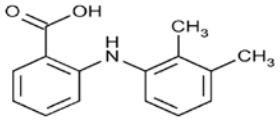


Fig. 1: Structure of mefenamic acid

Topical preparation is another probable formulation used for the localized result at site of its application. Ointment and emulgel are capable topical preparations for the liberation of hydrophobic drug moieties like Mefenamic acid, diclofenac, ketoprofen, ketoconazole [7].

The possible merits of transdermal drug delivery are well recognized, which consist of evasion of hepatic 1st-pass metabolism, keeping balanced maintained plasma concentration of drug, self-intake and decreasing dose rate, less side-effects, and improved patient compliance [8].

Numerous biopharmaceutical methods are established for the improvement of solubility and dissolution speed of weakly water-soluble medicinal agents. Amongst these novel processes, micronization, nano-suspension, super-critical fluid procedure, sono-crystallization, co-solvent mechanism and hydro-trophy in uplifting the solubilization of inadequately soluble medicines are prominent for rising the dissolution, absorption and therapeutic efficiency of drugs [9].

MATERIALS AND METHODS

Chemicals

Mefenamic acid salt was received from Pliva Pakistan PVT Limited, Karachi Pakistan. Clove oil (From Local market Quetta) and Cetostearyl alcohol (B. D. H Laboratory, Britain), wool fat, Soft Paraffin, hard paraffin (Quetta), and De-ionized water (Medilines Diagnostic division) the dialysis cellulose membrane having characters such as hydrophilic and 0.025 µm with 180-µm thickness with 25-mm diameter Millipore Corp given.

Apparatus

'Conical flask 50 ml, 100 ml Pipette 10 ml (Preciclolor *Germany), with glass jar (Amber colored), Aluminum foil with 100 ml tubes (Pyrex, *England) with Glass beaker 50 ml alongside White-colored glass jar.

Instruments

UV-Visible Spectrophotometer, weight measuring balance of analytical grade origin, Magnetic agitator/Hot-plate, pH meter, Homogenizer Brookfield Engineering Labs America Franz diffusion

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 Middle-boro, 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 2Φ b/w 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 spectro-photometery 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 formulated 1%, 2% and 3% ointment by measuring the diameter of the preparation of 0.5 gram following to pressing b/w 02 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 released. 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 soild 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.

Table 1: Physical parameters of ointment formulations

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

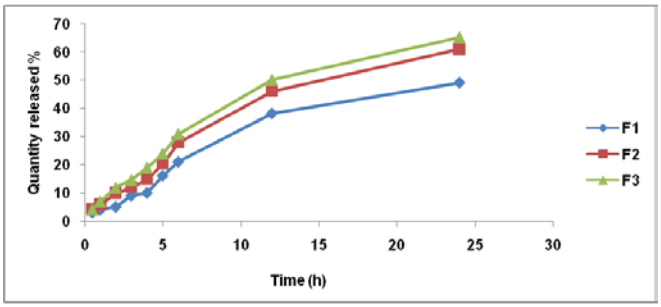
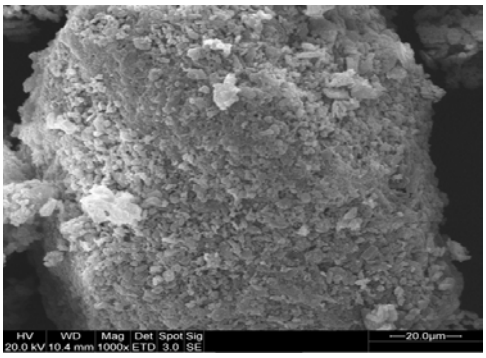


Fig. 3: Release of mefenamic acid ointment formulations 1, 2 and 3% (W/V) via dialysis cellulose membrane

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 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.



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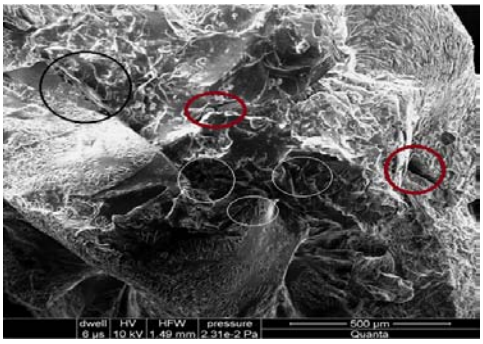

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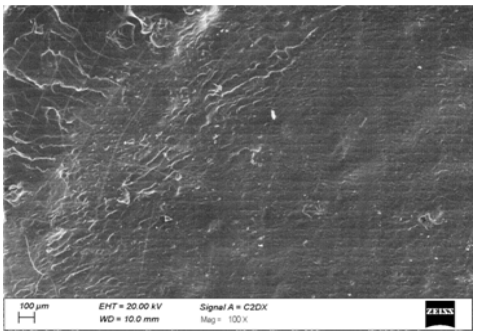

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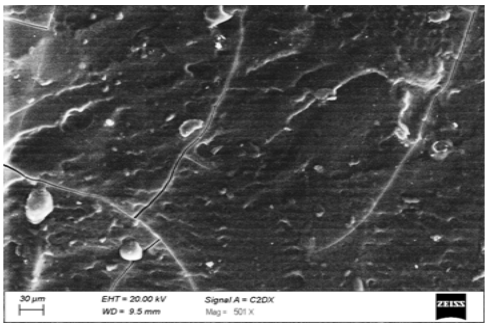

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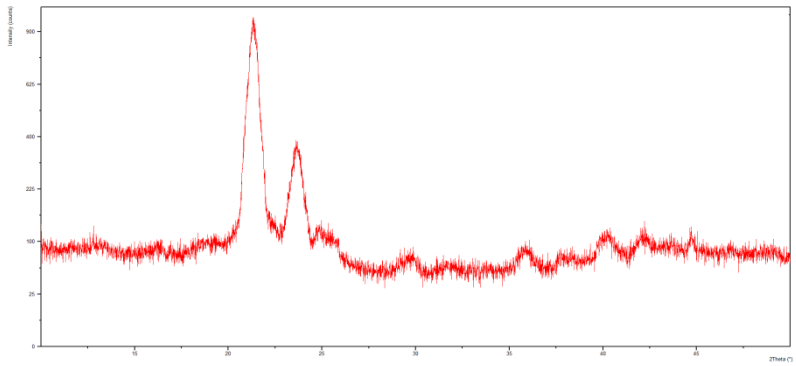
Fig. 1: (A) Illustrates surface morphology of the drug, while (B, C and D) display surface morphology of mefenamic ointment at different magnification powers stability studies of mefenamic ointment

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]



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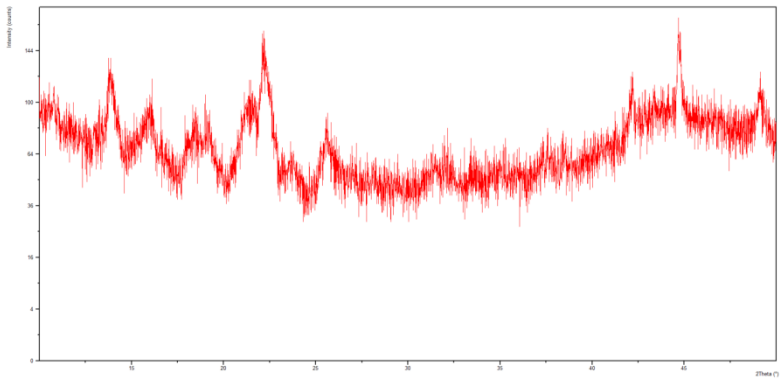

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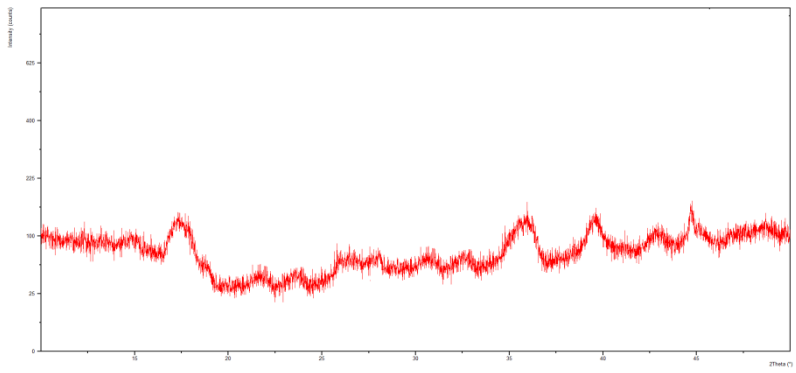

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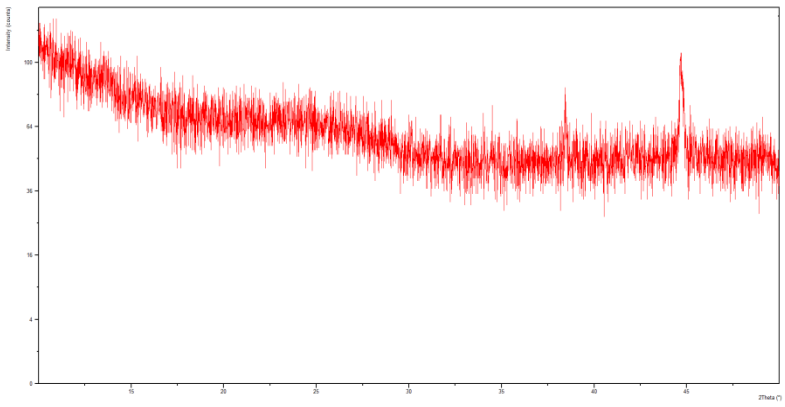

D

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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Nil

AUTHORS CONTRIBUTIONS

We put forward a document entitled: "Formulation and evaluation of Mefenamic acid Ointment Using Different Penetration Enhancers" author by Yousaf Khan, Syed Umer Jan and Rahman Gul for the contemplation as a research paper in the International journal of current pharmaceutical research. Yousaf Khan, Rahman Gul scrutinized the laboratory work, examined the data, and wrote the manuscript. All writers have interpreted and acknowledged the manuscript as well as are guarantors.

CONFLICT OF INTERESTS

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

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