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Original Article

FORMULATION AND EVALUATION OF METFORMIN HCL RELEASE FROM TOPICAL PREPARATION USING TWO DIFFERENT TYPES OF MEMBRANE

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ABSTRACT

Objective: Present study was carried to formulate and evaluate the transdermal ointment containing the metformin HCl active ingredient and to assess their Physicochemical studies.

Methods: Metformin HCl ointment was prepared with various thymol oil concentrations. Ointments were assessed with different characterizations; Physical appearance**,** viscosity, pH, drug content, Consistency, homogeneity, consistency. Differential scanning calorimetry analysis, XRD studies. It was used *in vitro* via using Franz cells along with the use of two membranes i.e. Nylon and cellulose membrane.

Results: SEM and XRD studies showed that there were no physical and chemical interactions between excipients and drug. All the formulations showed good physicochemical characteristics. The formulation showed different releases. It was observed that nylon had better release properties as compared to cellulose.

Conclusion: In the study conducted here, it was observed that Nylon membrane showed better discriminating power to compare among the formulation. This indicates that it has gotten prime importance to watch the effect of the membrane upon the release pattern of the various formulations. In order to improve the formulation, we can use *in vitro* diffusion cell experiments of transdermal drug delivery.

Keywords: Transdermal ointments, Thymus oil, Metformin, Nylon and cellulose membrane

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INTRODUCTION

Metformin was discovered in 1922 (Fischer, Ganellin *et al.* 2010) [1]. Metformin is primarily used for type 2 diabetes, although predominantly anti-diabetic, has been shown by playing an important role in a number of skin pathologies. Due to its role in improving erythropoiesis, it has been shown to be helpful to treat the hormonal acne, hidradenitis supportive (HS) and acanthosis nigricans. There has been sharp increase in the prevalence of DM in developed nation, most importantly due to obesity and lifestyle changes. Due to altered metabolism leading to atherosclerosis due to dyslipedemia and hyperglycemia, chronic kidney disease, and which exert much burden on the healthcare system where patients with DM are treated [2]. An estimated 20.8 million. World wide prevalence of diabetes for all groups of ages estimated in 2000 (2.8%) in future 2030 it would be (4.4%) Centers for sickness control and cure predicts that diabetes will go up by the year 2025, (37.5%) [3].

Its anticancer properties also serve as a supplement to the conventional treatment of hirsutism associated with polycystic ovary syndrome. Recently, the use of systemic metformin for psoriasis and skin tumors has shown encouraging results. The ointment preparation for metformin is under progression and *in vivo in vitro* studies required for development; therefore current study will focus on the formulation development of *in vitro* studies of ointment loaded with metformin HCl. It is also used in polycystic ovary syndrome.

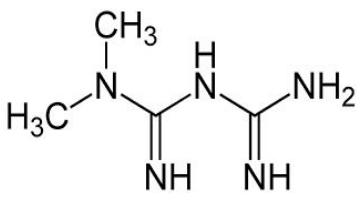


Fig. I: Metformin HCl structural formula

MATERIALS AND METHODS

Chemicals

Metformin HCl was received from Global Pharmaceuticals (Pvt) Ltd, White Petrolatum (Quetta, Local market), Methyl paraben and Propyl paraben (BDH labs, England) Cetostearyl Alcohol (BDH Labs, England), wool fat, Liquid Paraffin (Quetta) Polyoxyethylene (80) Sorbitan monooleate (Tween 80) (Merck, Germany), and De-ionized water (Medilines Diagnostic division) the Nylon membrane filter hydrophobic with 0.22 µm, 125-µm thickness along with a diameter of 25-mm and ester membrane mixed with cellulose filter with properties such as that it is hydrophilic and 0.025 µm with 180-µm thickness with 25-mm diameter Millipore Corp provided.

Apparatus

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

Instruments

UV-Visible Spectrophotometer, Weighing balance Analytical grade origin, Magnetic stirrer/Hotplate, pH meter, Homogenizer Brookfield Engineering Laboratory USA Franz diffusion cell, Refrigerator, an Incubator, water bath an Oven and Soxhlet Apparatus and Brookfield digital viscometer of model DV-III+.

Metformin HCl calibration curve

Metformin HCl standard curve can be obtained such that by dissolving 10 milligrams metformin HCl powder, a stock solution was made wherein 50 ml d/w and agitation that for several minutes until 100 ml is obtained with a phosphate buffer with a pH of 7.4. Dilutions, 0.032, 0.0160, 0.0080, 0.0040, and 0.0020 mg/ml were shaped from solution. All the dilutions were assessed for absorptions on 242 nm through Ultraviolet-visible spectrophotometer type-1601 Shimadzu, Japan. Fig. 2 shows the linearity graph of this finding [4].

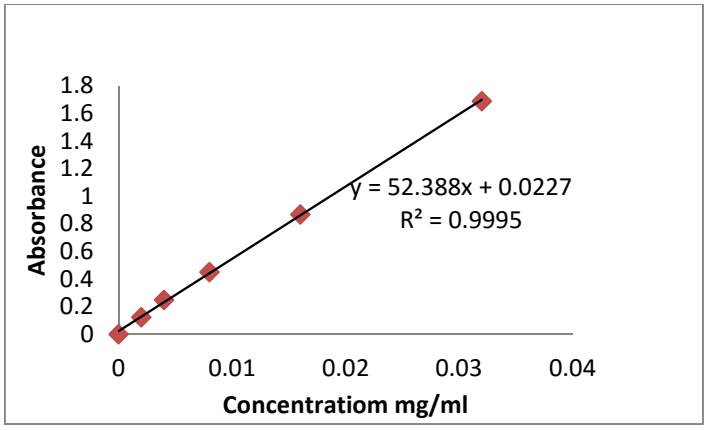


Fig. 2: Calibration curve of metformin HCL

Formulation of metformin HCl ointment

The simple B. P ointment being prepared by Gul et al. [5]. Whereby melting the hard paraffin 4.75g at 60 °C first and to which 4.75 grams, wool fat was included and finally, by adding cetostearyl alcohol 4.75g. Stirred and cooled the prepared ointment at ambient temperature. Metformine hcl (1.0g), thymol oil with various concentrations and white soft paraffin 78.75g were added and measure the characterization.

Physicochemical determination of metformin Hcl ointment

To fig. out the suitability of metformin HCl ointment for transdermal use its physical-chemical properties were explained as shown below.

pH

pH scales for metformin ointment were evaluated using a titrated pH scale [4, 5].

Consistency

The consistency of the metformin in ointment form which was evaluated by conical projection technique In which cone is attached to a 10 cm connecting rod being was dropped in the center of the ointment-filled cup in order to find out ointment consistency the over 50 seconds the distance covered is observed [4, 5].

Viscosity

Brookfield RVDV ultra, programmable Rheometer (Brookfield Engineering Laboratories Middleboro, MA) with spindle CP41 was taken to measure viscosity of several formulations in triplicate by rotating the spindle at different speeds at 25 °C. The readings were taken as triplicate and average of readings was acclaimed [6, 7].

Spreadability

The prevalence of all preparations was evaluated by finding the diameter of the formation of 0.5 g after pressing b/w 02 glass slices 10 g [4].

Homogeneity

Visual observation was used to find out the homogeneity of the ointment. Narrow transparent glass tubes filled with ointment and observed under light to check for any lumps or particles [8].

Scanning electron microscopy (SEM)

An electron microscope was used for SEM. Maker FEI software (Hillsboro, Oregon, USA) was used for the purpose stated above [9].

X-ray diffraction (XRD)

For confirmation of nature of the pure drug and that of ointment (i.e., to determine whether it is amorphous or crystalline), X-rays diffraction studies of the pure drug (metformin) and matrix (metformin) were conducted using a software 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 determining measurement. Then the diffractograms were captured at a rate of 2 min while keeping the temperature at ambient. A step width of 0.02 °and 2Φ between the 2° and that of 60° was used for this purpose [9].

Drug content

A sample of 10 mg each was dissolved, stirred in 100 ml of a hydrochloric acid solvent, which has been filtered via 0.2m membrane filter and evaluated using a visible UV calibrated SM in order to measure the amount of metformin HCl in the prepared ointment. The proportion of metformin Hcl was calculated [8, 9].

Skin irritation study

Skin irritation study was performed for metformin topical ointment on human volunteers to check out any irritation problems which may reject its suitability for topical application. This test was performed on volunteers. Approximately 1 gm ointment was applied topically near the wrist to a 2 square inch area and was examined for any irritation or lesions followed by redness [10].

***In vitro* diffusion the study protocol**

The Franz diffusion cell equipment by the famous Perm Gear USA Metformin Hcl cellulose membrane and nylon membrane was used in laboratory proliferation studies. The membranes were assigned to the future and the holder of the donor's equipment for Franz deployment cells. 5 ml phosphate buffer with pH of 7.4 was added to receptor chamber; prepared metformin hcl were added to the chamber a blank and the ointment containing 1.0%, 2.0%, and 3.0% thyme oil. 37 °C was the temperature of the solvent. 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 mili Liters were taken from cells, cells were filled with buffer immediately at 37 °C. Samples were being filtered through Millipore filters type Whatman, Germany150 mm filter paper, and the metformine HCL, c assessment of the concentration was done via UV visible spectrophotometer on 242 nm [10-12].

Kinetic analysis of metformine HCL release *in vitro*

In vitro diffusion studies were assessed regarding the quantity of metformin HCL released. Drug release parameters, and linear regression were assessed where the "correlation coefficient" was calculated to determine which specific kinematic models corresponded to that of release the drug via cellulose and nylon films. Kinetics equations are below given in table 1. Were used in order to calculate important readings [5, 9].

Model equation

- Zero-order Qt = Qo+Kot
- First order In Qt = lnQo+K1t
- Higuchi Qt = K H√t
- Korsmeyer-Peppas plot Mt/M∞ = Ktn

• Hixon-Crowell Qt/Qo=Kktn

Stability findings

Regarding the stability of the metformine hcl formulations under various storage conditions which were studied and the Samples analyzed after three months storage at 8±.1 °C, 25±.1 °C (incubator), 0±1 °C (freezer), and 40±.1 °C and the Formulations are tested for alterations in appearance along with the pH and consistency with homogeneity [13].

Statistical analysis

DD Solver (Microsoft Excel 2007) was used for statistical analysis.SPSS version 18.0, [9].

RESULTS AND DISCUSSION

Characterization of metformin based on its pH, spreadability, homogeneity, consistency, viscosity and drug content of metformin formulations being characterized in table 1. There were no differences in ointment in terms of their pH, Colour, phase separation and other important features. The ointment all with pH b/w 5.2 and 6.1 pH is observed. Formulations of metformin hcl ointment and wit human skin pH which ranges from 4.5–6.5 [14]. The spread ability, along with. Consistency was observed over 90 d' time span. The spread ability differ b/w 4.8 and 5.1 g/cm/s, which indicates the ointments were with minute shear pressure were spreadable. Excellent similar texture was seen in all ointment formulations lumps were not seen or any visual particles. The viscosity was observed in the range of 14222 to 15350 cps. After the ointment used to the skin of human volunteers no signs and symptoms of redness, lesions and itching were observed. The drug content of metformin HCl was in the range of 98.09 to 99.80%, and the ointments demonstrated good uniformity. Physical parameters were watched indicated that the metformin HCl being good for transdermal application.

In this study two types of membranes were used table 2. Indicates the nylon membrane had the highest release rate [15], which is also shown in fig. 3. It can be due to 125 µm of thickness and the porous nature of the membrane [4]. There was 10 fold smaller pore size and 180-micron meters thick when we came to cellulose membrane. There was a different marker release in both of the membranes (p<0.05)]. The formulation is fit to Korsmeyer-Peppas model as shown in table 2. Describing the release of caffeine in w/o emulsion. The release was also affected by the nature of the membrane. Gul *et al.* Stated that nylon membrane had better release properties than that of cellulose membrane [16]. Release from the vehicle are affected by a multitude of factors to name some quantities of marker in vehicle along with the marker solubility, its, diffusion coefficient and partition coefficient of the marker b/w the vehicle and membrane nature of the membrane with a thickness and pore size too. In our study it was seen that the membrane with a pore size smaller then that showed additional discriminatory strength to differentiate among the tested formulations. There is a need of studies to find out whether it is due to pore size or also the nature of the membrane to play a part.

Table 1: Physical parameters values for metformin Hcl formulations

S. No.	pH	Spreadability (g/cm/s)	Homo geneity	Irritation of skin	Viscosity	Drug content (%)
1	5.9	4.8	Good	NO	15350	98.09
2	6.1	4.9	Good	NO	14222	99.31
3	5.2	5.1	Good	NO	14333	99.80

Table 2: Metformin hcl release from the formulations by using nylone and cellulose-based membrane

Drug being released after 24 h (%)	Membrane	Amount of drug which is released at each time point (mg/1.5 cm²)								
		0.5 h	1 h	2 h	3 h	4 h	5 h	6 h	12 h	24 h
49.92	Cellulose	0.8320	1.1123	2.0291	2.7747	2.9186	3.7818	3.971	4.6177	4.9997
64.74	Nylon	0.9575	1.9211	2.6325	2.8414	3.5765	4.1647	4.5348	5.0088	6.4741

(R^2) is the coefficient correlation

Formulation type	Zero (0) order	First(1st) order	Higuchi	Hixon-crowell	korsmeyer peppas	Best-fitting model
Cellulose	0.8070	0.8124	0.9193	0.8016	0.9499	Korsmeyer-Peppas
Nylone	0.8844	0.8890	0.9634	0.8874	0.9777	Korsmeyer-Peppas

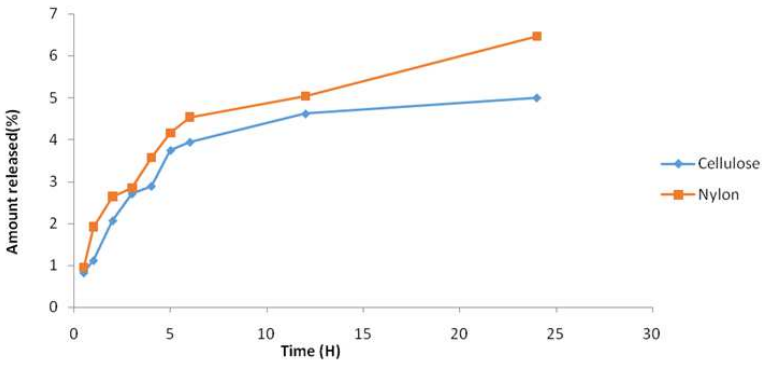
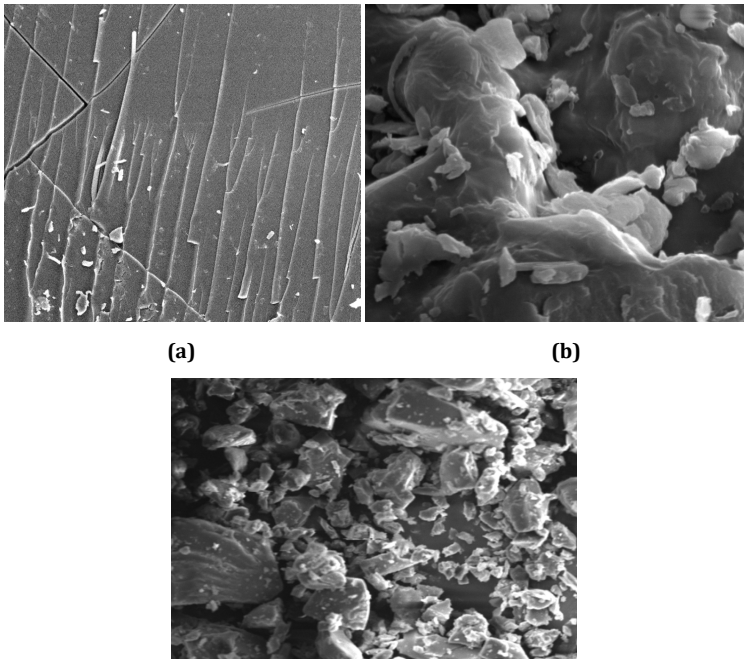


Fig. 3: Release profiles of metformin HCl ointment from nylon and cellulose membrane

SEM

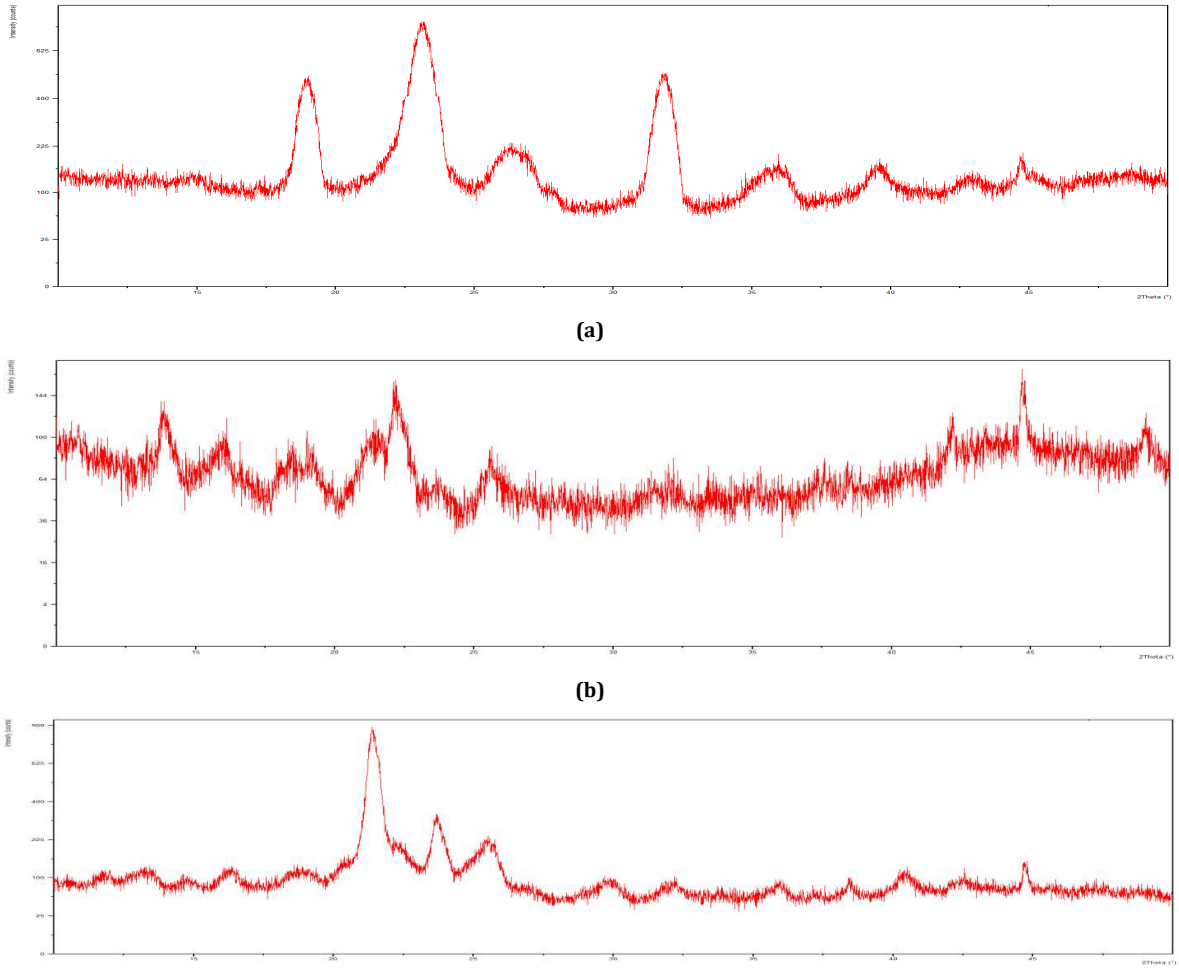
The drug was released and after then, the surface morphology of the drug was studied under an electron microscope. Gapes having irregular shapes were observed under an electron microscope. SEM results showed that the drug indeed had elasticity in its nature. The drug position is clearly visible in the formulations as shown in fig. 4



(a) **(b)**

(c)

Fig. 4: Illustrates surface morphology of the base (a) displays surface morphology of the formulation (b, c)



(a)

(b)

(c)

Fig. 5: X-ray diffractograms of metformin Hcl pure(a), blank as a base(b) loaded metformin hcl with base (c)

XRD studies

X-ray diffraction study was performed to confirm the physi-cochemical characteristics of metformin hcl in the matrix of the transdermal ointment where pure ointment showed prominent peaks of diffraction with angle of 2θ value, of 13.51°, 18.13°, 20.10° et cetra. As in fig. 5 indicating the presence of crystalline ointment. Diffractograms regarding physical mixture of ointment and excipients also showed some peaks of decreased intensity, while in the diffractograms of the ointment, fused peaks were seen instead of, sharp and intense peaks. The drug was molecularly dispersed as shown by the lack of festered peaks and altered to amorphous form [17].

Stability studies

The stability of the metformin hcl ointment for 3 months when stored at temperatures of 08, 25 and 40 C, was studied. In topical ointment preparation no previous publish data was found. Being a prime role in the stability of topical dosage form [11]. With limitation of oxidation, our product was stored as such and it was found stable.

CONCLUSION

Metformin hcl Ointment with high *in vitro* release rate was made with success. Penetration to the artificial membrane was enhanced by use of thyme oil through the transdermal route with increased concentrations. Moreover, further studies can be carried to evaluating the efficacy of metformin hcl ointment *in vivo*

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

None

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