International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.11 No.11, pp 309-314, 2018

Formulation and Evaluation of Ketoconazole Loaded Transdermal Gel using Natural Penetration Enhancer

Shivani Kala*, Govind Singh Bathyal, Divya Juyal

Himalayan Institute of Pharmacy and Research Atakfarm, Dehradun, Uttarakhand, India

Abstract : Drug delivery via oral route is the most commonly used rote for administration of drug but owing to various imitations of oral administration including GI irritation and other side effects research is being carried out for other routes of delivery Transdermal route is such route which is very easy to administer and without any side effects However the main demerit of the route is that a the drugs can't cross the skin barrier and penetration of drugs is poor To increase the penetration of drugs across the skin absorption promoters or penetration enhancers have been used chemical penetration enhancers are mainly used in topical formulation which may cause various side effects including skin irritation, rashes etc The current research is focused on exploring a natural penetration enhancer for increasing the penetration of the drug across skin using Ketoconazole, a synthetic imidazole antifungal drug used primarily to treat fungal infections as mode drug in emulgel.
Keywords: Ketoconazole, Transdermal Gel, Natural Penetration Enhancer.

1. Introduction :

The transdermal route always provide innovative research area in drug delivery, and many drug delivery products are under clinical evaluation related to transdermal or dermal system. The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect[1]. Owing to some complexities skin have barrier for penetration through it. To enhance the transport of drug through skin various techniques are applied called as permeation enhancement techniques and agents utilized in it are PENETRATION ENHANCERS[2] also called sorption promoters or accelerants) which penetrate into skin to reversibly decrease the barrier resistance [3]

Brief anatomy of the skin: Skin is a complex biological structure consisting of many layers with a thickness of 2.97 ± 0.28 mm. Its function is to safeguard the major internal parts of the body from the external effects, regulation of temperature, sensation and water balance. A normal adult human body skin covers around two square meters surface area and gets about one-third of the blood circulating in the body.

DOI= http://dx.doi.org/10.20902/IJCTR.2018.111133

The skin is considered to have four distinct layers of tissue[4].

1. Non-viable epidermis (stratum corneum)
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue (hypodermis)

Advantages & Disadvantages of penetration enhancers

Various advantages of penetration enhancers include[6]

- They help to provide penetration rate of drug sufficiently high for therapeutic efficiency
- It facilitates the absorption of unabsorbable drugs through skin.
- It can improve transdermal absorption of topical preparation completely.
- It determines the penetration rate of transdermal drug delivery system.
- The terpenes like limonene in propylene glycol solution are effective penetration enhancer for cytotoxic drugs.

Various Disadvantages of penetration enhancers are[7]

- The effective concentration varies from drug to drug.
- The use of various penetration enhancer with various concentrations vary
- Physicochemical properties of enhancers are also affecting the side effects in the body.

Gels are transparent or translucent semisolid preparations consisting of either suspension or dispersion of one or more active ingredients in suitable hydrophilic or hydrophobic bases. Gel consists of either natural or synthetic polymer, they forming a three dimensional matrix throughout a dispersion medium or hydrophilic liquid. After administration of gel, the liquid evaporates leaving the drug entrapped in a thin film of the gel forming matrix physically covering the skin[8].

Several antifungal agents are available on the market in different topical preparations (e.g. creams, ointments, and powders for the purpose of local dermatological therapy. One of these antifungal agents is ketoconazole, which has both antifungal and antibacterial properties. It is applied locally in mild uncomplicated dermatophyte and other cutaneous infections[9].

2. Material and methodology:

Drug (Ketoconazole) was obtained as a gift sample from IPCA Laboratories Ltd, Selaqui, Dehradun.

2.1 Extraction of essential oil:

300 gm of dried crushed rhizomes of plant material of *Zingiber officinale* was taken in 1000 ml of round bottom flask and extracted with distilled water for 6- 8 hr at 70- 80°C using Clevenger apparatus and added a small porcelain chip to avoid bumping, the oil was collected which was light yellow in color with characteristic odour.

2.2 Formulation of transdermal gel:

Purified water BP was filtered through #200 mesh nylon cloth, into the water vessel and heated to about 40° C and weighed amount ofCarbopol – 940 was added slowly in to the vertex to complete the addition within half an hour. Further mix for one hour. The suspension was allowed to stand night with proper cover. Ketoconazole was added slowly into propylene glycol solution with continuous stirring till a clear solution is formed. Keep it aside with proper cover.Transfer the drug solution slowly to Carbopol Suspension with continuous mixing. Dissolve 3 mg of Disodium Edetate BP solution under mixing.Mix 15 mg of Trolamine USP/NF and 300 mg of Menthol to the manufacturing vessel and mix with high speed homogenization.

Table 1: Formulation of transdermal gel

S.NO.	Ingredients	M1	F1	F2	F3
1	Ketoconazole	20	20	20	20
2	Carbomer 940	11.8	11.8	14.8	8.8
3	Polypropylene Glycol	100	100	100	100
4	Trolamine	15	15	15	15
5	Disodium Edetate	0.2	0.2	0.2	0.2
6	Menthol	20	-	-	-
7	Ginger oil	-	20	20	15
8	Purified Water	833	833	830	841
	Total (mg)	1000	1000	1000	1000

3 Evaluation:

3.1 Appearance:

The gel Formulations (M,F1,F2 and F3) was observed on transparent clear watch glass.

3.2 pH Measurement:

pH of Gel for formulation M,F1,F2 and F3 was measured by using digital pH meter in Laboratory. 1g of gel was dissolved in 100 ml freshly prepared distilled water, mixed by stirring and left for 1 hour in ambient temperature.

3.3 Viscosity Measurement:

The viscosity of gel formulations used employed to evaluate by Brookfield Digital viscometer. Viscometer having spindle no. 6 was rotated at 10 rpm The reading, nearer to 100 % torque was observed. Samples were measured at 30 ± 1 °C.

3.4 Spreadibility:

It is the evaluation parameter for a gel to ensure the ideal quantities is that it should possess good spreadability. It expressed the spreading ability of gel to its application site. The therapeutic Potency of a formulation also depends upon its spreading value.

This test consists of a wooden block (fixed) and a glass slide (movable) assembly. The 2 g of prepared gel was added to the pan. The time was noted for movable of upper glass slide.

Spreadability was calculated by using theformula:

S = M.L/T
Where,
S = Spreadability
M = Weight tide to the upper slide
L = Length of a glass slide
T = Time taken to separate the slide completely from each other.

3.5 Extrudability-

it was determined by using aluminium collapsible. The tube was filled with 20g gels and after that it was compressed. The extrudability of the formulation was determined in weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 seconds.

3.6 Drug content-

The prepared formulation of 100 mg was dissolved into 100 ml of phosphate buffer solution having pH 6.8. It was stirrer for 2 hrs and after complete solubilize of drug, the solution were filtered. The solution were measured its absorbance at 273 nm using phosphate buffer (pH 6.8) as blank.

3.7 *In-vitro* diffusion studies-

Franz diffusion cell carrying egg membrane was employed to evaluate the diffusion study of drug from gel. The receptor compartment containing 10 ml of phosphate buffer solution (pH 6.8) and then 100 mg of gel was placed on the membrane.

The temperature were controlled under36 to 37°C and stirred with mechanical stirrer. The solution was withdrawn (3 ml) at interval specific interval (1 hr) and investigated by UV spectroscopy at 273 nm.

3.8 Stability studies-

The stability studies were performed for all formulations. The formulations were kept at temperature 25°C, 40°Cfor 45 days. The formulation was analyzed for the change in appearance, pH and drug content at specific interval**.**

4 Results

4.1 Appearance:

The gel formulations (M,F1,F2 and F3) have shown Translucent appearance with smooth and uniform texture.

4.2 pH Measurement:

ph of various formulations is shown in table no 2.

Table 2: ph of various formulations

Batch No.	pH
M	6.86
F1	6.91
F2	6.78
F3	6.60

4.3 Viscosity Measurement:

The viscosity of transdermal gel of Ketoconazole shows the consistency of the gel. As a results the concentration of Cabopol 940 increases showed increase in viscosity of the formulation, Viscosity impact on in-vitro drug release as well as spreadibility of the formulations.

In F2 the concentration of carbopol 940 was increased hence the viscosity of the formulation also get increased which will gives directly impact on the drug release.In F3 the concentration of Carbopol 940 was decreased hence the viscosity of the formulation also get decreased.

Table 3: viscosity of various formulations

Batch No.	Viscosity(cps)
M	205364
F1	213167
F2	324715
F3	196789

4.4 Spreadibility:

Spreadibility of different formulation were decreases with increase in concentration of Carbopol which is gelling agent in the formulation on the other hand spreadibility also inversely proportional to Viscosity.

Table 4: spreadibility of various formulations

Batch No.	Spreadibility(gm.cm/sec)
M	7.80
F1	7.60
F2	6.34
F3	8.05

4.5 Drug content: Drug content of various formulations is as shown in table:

Table 5: drug content of various formulations

Batch No.	Drug content
M	86.67%
F1	82.72%
F2	88.55%
F3	90.22%

4.6 In- Vitro Drug Release Data:

According to above results it was concluded that the concentration of released Ketoconazole was increased in formulation F1 (Ginger used as a penetration enhancer) but in Formulation M (Menthol used as penetration enhancer) the release concentration of Ketoconazole was less as compared to formulation F1.

On the other hand if the amount of carbopol 940 were increased in formulation F2 Hence the amount of released Ketoconazole was extended for a period of time and Due to increased viscosity because the carbopol interact with the drug as a result the release of drug is decreased in 3 hours with respect to F1.

In F3 case the amount of Cabopol 940 were decreased with decrease in Ginger as Penetration enhancer so the viscosity of the formulation also get decreased but due to lack optimum concentration of Penetration enhancer (Ginger) the release of Ketoconazole was less as compared to F1 and F2 formulations.

Drug permeation study:

Table 6: Rate of drug permeation of prepared gel

Formulation code	R^2	Slope value
M	0.901	18.53
F1	0.883	20.42
F2	0.914	17.28
F3	0.889	20.02

The formulation F1 has higher slope value indicating that the permeation of drug through skin is higher compared to other formulations. Hence F1 is considered best formulation.

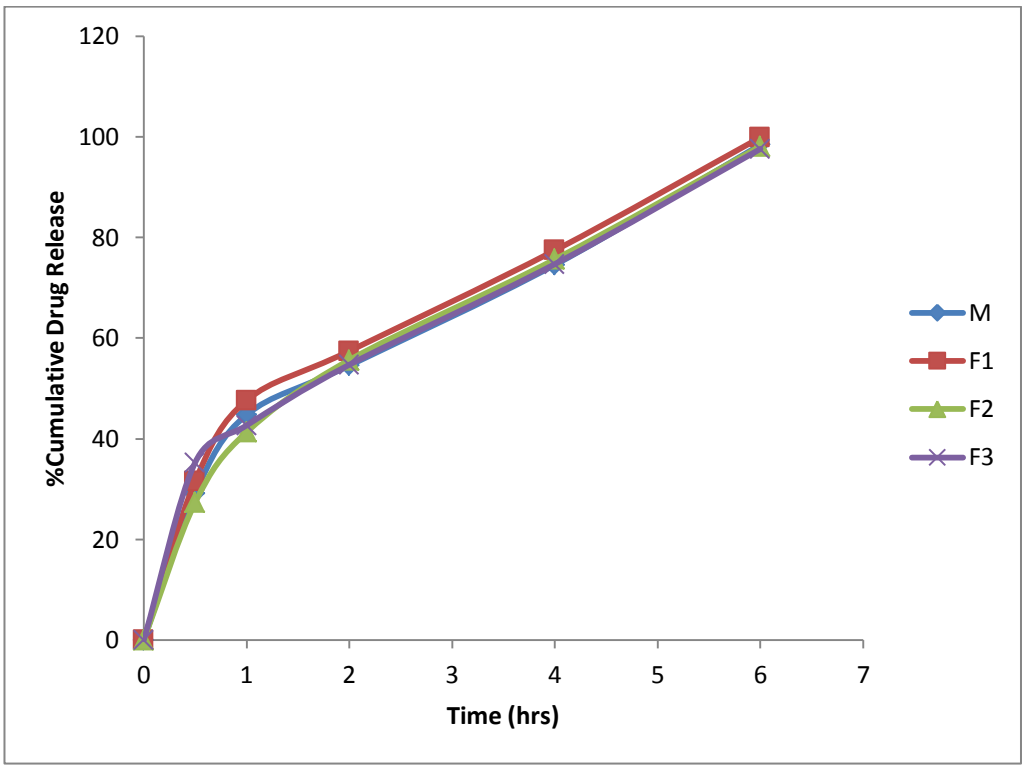

Figure 1: Rate of drug permeation of prepared gel

5 Conclusion:

The results also showed that the formulation containing ginger oil as penetration enhancer showed better release profile than that containing menthol so it can be concluded that Ginger oil can be successfully used as an penetration enhancer in transdermal formulation for efficient delivery of drug

6 . References:

1. Mathur et al: Enhancers in transdermal drug delivery system, Asian Journal of Pharmaceutics. July-September 2010; 173-183.
2. BashayMasarrat, Gulam Ahmed: Chemical Permeation Enhancement Through Skin International Journal of Advanced Research (2015), Volume 3, Issue 8, 644-651
3. Williams AC, Barry BW: Penetration enhancers. Adv Drug Deliv Rev. 2004; Mar 27;56(5):603-18.
4. Kanikkannan N, Kandimalla K, Lamba SS, Singh M: Structures activity relationship of chemical penetration enhancers in transdermal drug delivery. Current Medicinal Chemistry 1999; 6: 593-608.
5. PillaPavani Ganga Bhavani: Formulation And Evaluation Studies On Transdermal Dosage Forms Of Diclofenac Sodium. World Journal of Pharmacy and Pharmaceutical Sciences , Volume 4, Issue 03, 1043-1063
6. Vyas S, Khar RK: Controlled Drug Delivery - Concept and Advances. VallabPrakash. 2002; 418-22.
7. Vyas S, Khar RK: Controlled Drug Delivery - Concept and Advances. VallabPrakash. 2002; 418-22.
8. Fox T.L: Transdermal Drug Delivery Enhancement by Compounds of Natural Origin Molecules .2011 :10507-10540.
9. Thomas ER and Galgiani JN. Antimicro agents and chemo, 1: 418-422, 1986.

*****