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Influence of permeation enhancers on the diffusion and permeation kinetics of anastrazole gels through mouse skin

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ABSTRACT

In the present study efforts were made to prepare transdermal gels of Anasterazole using different concentrations of Carbopol. Based on evaluation parameters values, 0.5% Carbopol938 gels were selected for further studies, as these gels offered high permeability of selected drugs and better pH, viscosity, extrudability and spreadability .Drug reservoir was prepared by incorporating the anastrazole nanoparticles and NSAID in 0.5 % cabopol gel and evaluated for *in vitro* diffusion studies. Various permeation enhancers, namely, SLS, (2% w/w), 2% w/v of PEG400, DMSO and Tween 20 were incorporated into gels with a view to improve permeability of drug. The correlation coefficient values (r) revealed that the diffusion profiles follows zero order kinetics and the mechanism of drug release was governed by peppas model. The diffusion exponent of release profiles (slope) has a value of ($n \geq 1$), which indicates case II transport diffusion. Formulation - GP_1 carbopol+ Tween 20)) shown required release rate in comparison with other formulations and was selected as suitable candidate to be delivered through transdermal route at controlled rate.

KEY WORDS: Polymer, solvents, carbopol, Diffusion, DMSO, Nanoparticles.

1. INTRODUCTION

Anastrozole is a popular effective aromatase inhibitor and there is a necessity for a substitute to the oral route of management to target cancer tissues (Xi, 2010). The development of technology for release of drug at controlled rate into systemic circulation using skin as a port of entry has become popular for various reasons (Chein, 1976). The transdermal entry of drug in to systemic circulation at a desired rate can be achieved by using a suitable rate controlling membrane and a drug reservoir (Chowdary, 1992). Earlier studies proved that Eudragit RL100 films could be used as rate controlling membranes for the design of TDD systems (Gopala krishna murthy, 2006). With a view to design a suitable drug reservoir, various types of gel formulations were prepared. The gels are becoming more popular due to ease of application and better percutaneous absorption, than other semisolids preparations. Gels can resist the physiological stress caused by skin flexion, blinking and mucociliary movement, adopting the shape of the applied area, and controlling drug release (Panigrahi, 2006). To enhance the permeability of anastrazole, various permeation enhancers were incorporated into the gels. The invitro skin permeation experiments are known for their value in studying the rate and mechanisam of percutaneous absorption of drugs. To study the effect of permeation enhancers on the release and permeation kinetics of anastrazole gels, those are evaluated by studying drug diffusion through Eudragit RL100 membrane and mouse skin.

2. MATERIALS AND METHODS

Anastrazole was obtained as a gift sample from Celon Laboratories Pvt. Ltd, Eudragit RL100 (S.D. fine-chem Ltd.; Mumbai) and Carbopol 934(Arihanth traders; Mumbai) were obtained commercially. All materials were used as received.

Preparation of Drug Free Films: Solvent casting method was used for the preparation of Eudragit RL 100 films. The films were prepared with Eudragit RL 100 by employing ethyl acetate as casting solvents. To provide plasticity, n-Dibutyl phthalate at a concentration of 15% w/w of the polymer was used as a plasticizer. An aliquot of 8 ml of the 8% w/v casting solution was gently poured in glass bangle (6.2 cm diameter) placed on mercury. The rate of evaporation was governed by inverting a funnel over the Petri plate. After 24 hours the dried films were taken out and stored in a desiccators until their use.

Formulation of drug reservoir gels: Drug containing nanoparticles and one selected NSAID reservoir gels were formulated as per the composition. The gels are prepared by carbopol 934 in different ratios (0.5%, 1%,1.5%), specified ratios of carbopol 934 was soaked in 20 ml of water over night. Specified amount of Anastrazole suspended nanoparticles and NSAID (Aceclofenac), methylparaben and propylparaben were weighed accurately and dissolved in glycerine. The resulting drugs solution was incorporated into the polymer dispersion with stirring at 500 rpm, by a magnetic stirrer for 1 h. The P^H of above mixture was adjusted to neutral with tri ethanolamine (0.5%). The gel was transferred in to a measuring cylinder and the volume was made up to 100 ml with distilled water. The resulting gels were filled in collapsible tubes.

Preparation of Gels containing permeation Enhancers: Four different permeation enhancers namely Sodium lauryl sulphate (SLS),(2% w/w) , 2% w/v of , Tween 20 , Dimethyl sulfoxide(DMSO) and Poly ethylene glycol - 400(PEG400) were incorporated into the carbopol gels.

Evaluation of Drug Reservoir Gels:

In vitro* Diffusion Study:** ***In vitro diffusion study was carried out using Franz diffusion cell (Franz, 1975). The receptor compartment was filled with 15 ml of phosphate buffer having pH 7.4 as diffusion media. Polymeric film was mounted on the donor compartment with the help of an adhesive. The anastrazole gel (1 gm containing 1 mg of anastrazole and 100 mg of Aceclofenac) was placed into the donor compartment. Magnetic stirrer was set at 50 rpm and whole assembly was maintained at 32 $\pm$ 0.5 ^{0}C. The amount of drug released was determined by withdrawing 1 ml of sample at regular time intervals for 3 hours. The volume withdrawn was replaced with equal volume of fresh buffer solution. Samples were analyzed for drug content using a U V spectrophotometer at 221 nm.

Permeability Coefficient: From the drug diffusion data the permeability co efficient for various films was calculated using the equation (Fites, 1970). $P_m = (K_{app.} H)/A$, Where, K_{app} is Diffusion rate constant (mg/h) calculated from the slope of the linear drug (d/p) diffusion profiles , H is thickness of the film (cm), A is surface area of the film (cm^2).

The diffusion rate and the mechanism of drug diffusion through the transdermal films were analyzed by subjecting the diffusion data into (Salomon, 2002), zero-order equation, $Q=Q_0 - k_0t$,where Q is the amount of drug diffused at time t, and k_0 is the diffusion rate. First order equation, $Ln\ Q=Ln\ Q_0 - k_1t$, where k_1 is the diffusion rate constant and Higuchi's equation, $Q= k_2t^{1/2}$, where Q is the amount of the drug diffused at time t and k_2 is the diffusion rate constant. The diffusion data was further analyzed to define the mechanism of diffusion by fitting the diffusion data following the empirical equation , $M_1/M_\alpha=Kt^n$, where Mt/M_α is the fraction of drug diffused at time t. K is a constant and n characterizes the mechanism of drug diffusion from the formulations during diffusion process.

***In vitro* skin permeation studies:** Male wistar rats weighing between 130-160g and free from any visible sign of disease were selected for the *in vitro* studies. The hair on abdominal region was removed using a depilatory preparation one day prior to experiment. On the day of experiment, animals were sacrificed by cervical dislocation and abdominal skin was excised. The fatty material adhere to the dermis was carefully peeled off. Freshely excised rat skin of thickness (2mm) was mounted on the donor comportment (Rao, 1997). Formulations GP_1, GP_2, GP_3 and GP_4 were evaluated by studying drug diffusion through Eudragit RL100 membrane and mouse skin.

3. RESULTS AND DISCUSSION

In the present study efforts were made to prepare gels using different concentrations Carbopol 934 . Gels prepared with Carbopol 934 were found to be off white and homogenous. The gels were evaluated for drug content, pH, viscosity, extrudability, spreadability and *in vitro* skin permeation studies .Based on evaluation parameters values, 0.5% Carbopol 934 gels were selected for further studies, as these gels offered high permeability of selected drugs and better pH, viscosity, extrudability and spreadability. Drug reservoir was prepared by incorporating the anastrazole nanoparticles and NSAIDs in 0.5 % cabopol gel and evaluated for *in vitro* diffusion studies.

In vitro skin permeation experiments were known for their value in studying the rate and mechanism of percutaneous absorption of drugs. The skin permeation showed a similar pattern as that of the diffusion profile across rate controlling membrane and dialysis membrane, but the amount of drug permeated through the skin was not satisfactory.

The stratum corneum has evolved primarily for barrier function. This creates difficulties in the formulation of TDDS which aims to deliver the drug via skin in therapeutic quantities. The search for solutions to this problem led investigators to employ several enhancement techniques. One approach is the co-administration of skin permeation enhancers. Ideally, permeation enhancers are a chemical entity which reduces reversibly the barrier resistance of the stratum corneum without damaging the viable cells. A large number of substances have been evaluated as permeation enhancers and research is extending with the growing need for safe, effective accelerants. The permeation enhancers such as 2% w/w of sodium lauryl sulphate (SLS), 2% w/v of poly ethylene glycol 400**(**PEG 400), dimethyl sulfoxide (DMSO) and tween 20 were incorporated into gels with a view to improve permeability of selected drugs.

Table.1. Characteristics of anastrazole nanoparticles gels containing Aceclofenac with various concentrations of carbopol 934

Formulation	%Drug content		Viscosity (cps)	Extrudability (N)	Spreadability (gm.cm/sec)	pH		Homogeneity	Appearance
	Anastrazole	Aceclofenac				Before drug incorpor	After incorporation		
AN-AC1	99.67	99.56	18246	15.12	11.8	7.42	7.24	***	Translucent
AN-AC2	97.45	98.82	19643	16.18	16.6	7.62	7.53	***	Translucent
AN-AC3	98.31	98.65	18832	17.32	5.8	7.25	6.99	***	Opaque

Table.2. Characteristics of Anastrazole nanoparticles loaded Gels Containing NSAID with Permeation Enhancers

Formulation		AN-P1(Tween 20)	AN-P2(SLS)	AN-P3(DMSO)	AN-P4(PEG400)
%Drug content	Anastrazole	99.67	97.45	98.31	99.01
	Aceclofenac	99.56	98.82	97.65	99.32
Viscosity (cps)		1724	1964	1983	2385
Extrudability (N)		16.22	17.38	17.32	19.14
Spreadability (gm.cm/sec)		28.8	21.6	15.8	26.88
pH	Before drug incorporation	7.43	7.32	7.54	7.45
	After incorporation of drug	7.39	7.23	7.29	7.42
Homogeneity		***	***	***	***
Appearance		Translucent	Translucent	Opaque	Opaque

Table.3. Comparative Diffusion Characteristics of Anastrazole nanoparticles from various concentrations of carbopol 934 gels to the optimized gel concentration through Eudragit RL 100 films by using mouse skin

Formulation	Diffusionrate constant (k) value(mg/h)	Permeability Coefficient ($P_m X10^4$ mg/cm.h)
AN-AC1 (0.5%)	0.039	0.271
AN-AC2 (1.0%)	0.035	0.243
AN-AC3 (1.5%)	0.031	0.215
AN-AC2 (0.5%)*	0.032	0.222

***Diffusion data through mouse skin**

Table.4. Diffusion Characteristics of NSAID from various concentrations of carbopol 934 gels through Eudragit RL 100 films by using mouse skin

Formulation	Diffusionrate constant(k) value (mg/h)	Permeability coefficient ($P_m X10^4$ mg/cm.h)
AN-AC1 (0.5%)	3.141	21.842
AN-AC2 (1.0%)	3.010	20.935
AN-AC3 (1.5%)	2.916	20.28
AN-AC2 (0.5%)*	2.849	19.81

***Diffusion data through mouse skin**

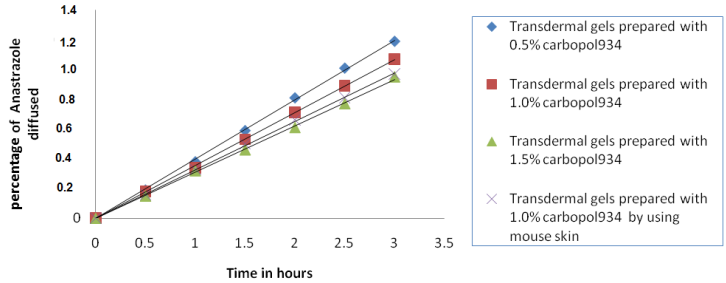

Figure.1. Comparative Diffusion profiles of Anastrazole nanoparticles from various concentrations of carbopol 934 gels to the optimized gel concentration through Eudragit RL 100 films by using mouse skin

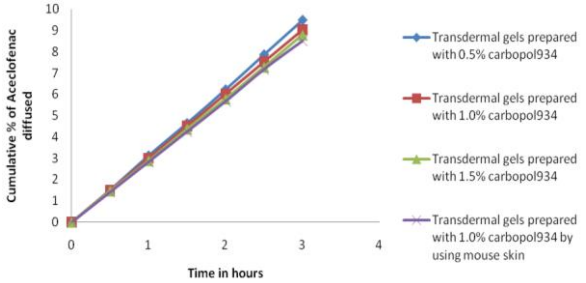

Figure.2. Comparative Diffusion Profiles of NSAID(Aceclofenac) from various concentrations of carbopol 934 gels to the optimized gel concentration through Eudragit RL 100 films by using mouse skin

4. CONCLUSION

The permeation enhancers used for increasing the permeation of drug could be arranged in the following increasing order according to their permeation rates:

Tween 20> SLS> DMSO > PEG 400.

The increased permeation rate in all these enhancers may be due to surfactant action .These results indicated that the non ionic surfactant tween 20 improves the permeability characteristics of selected drugs when compared with the other permeation enhancers. Hence the formulations containing tween 20 were used in further studies.

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