
Effect of Plasticizers on the Permeability and Mechanical Properties of Eudragit Films for Transdermal Application

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The present investigation was taken up to prepare and evaluate Eudragit RS100 films as rate controlling membrane for transdermal use and to study the effect of different concentrations of various plasticizers on the permeability and mechanical properties. Drug free films of Eudragit RS100 were prepared by the casting method on mercury surface employing chloroform as a solvent and dibutyl phthalate (DBP) and polyethylene glycol-400 (PEG) as plasticizers. These films were evaluated for thickness uniformity, tensile strength, percentage of elongation and water vapor transmission. Permeability characters of these films were studied using verapamil hydrochloride (VPH) as a model drug. The thickness of the films was found to be uniform. Tensile strength of the films prepared using DBP as plasticizer was high compared to the films plasticized with PEG. Water vapor transmission and drug diffusion through films followed a pattern closed to zero order type and it was decreased with increase in the film thickness. Films plasticized with PEG showed higher permeability to verapamil hydrochloride. The permeability of the drug was decreased as the concentration of dibutyl phthalate was increased. Whereas increase in the concentration of PEG enhanced the permeability characteristics of the films.

The transdermal route of drug delivery has become popular recently and its importance including physico-chemical considerations has been extensively pointed out by Chien and Zatz¹⁻³. To achieve controlled and constant release of drug into the systemic circulation, transdermal systems require suitable rate controlling membranes and drug reservoirs. Preparation of polymeric films for transdermal use requires plasticizers for various reasons, such as to reduce the brittleness, to impart flexibility, to increase strength and also to improve adhesiveness of films with the surfaces or membranes⁵. Plasticizers interpose themselves between the polymer chains and interact with the forces held together by extending and softening the polymer matrix⁴. The commonly used plasticizers in the formulation of films are phthalate esters, phosphate esters,

fatty acid esters and glycol derivatives⁶. The selection of a suitable plasticizer and its concentration has a profound influence on the mechanical properties as well as permeability of drugs⁷.

In the present study, attempts have been made to prepare plasticized drug-free films of Eudragit RS100 and to evaluate their thickness uniformity, tensile strength, percentage of elongation and water vapor transmission. Plasticizers used were dibutyl phthalate and polyethylene glycol-400 in various concentrations. These films were subjected to permeability studies using verapamil hydrochloride, a model drug to find out the effect of plasticizers on the permeability characteristics of the films.

EXPERIMENTAL

Eudragit RS100 (ED) was obtained as a gift sample from Rohm Pharma, Germany. Verapamil hydrochloride IP

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(VPH) was a gift sample from Torrent Pharmaceuticals, Ahmedabad. Chloroform IP, dibutyl phthalate IP (DBP), polyethylene glycol-400 IP (PEG) were purchased from Qualigens (P) Ltd, Mumbai.

Preparation of drug free films:

Films were prepared according to the method described by Munden⁸. The polymer (8%w/v) was dissolved in chloroform and plasticizers (PEG and DBP) in different concentrations were incorporated. The polymeric solution was mixed thoroughly with the help of magnetic stirrer for 20 min and 5 ml of polymeric solution was poured within a glass bangle placed on mercury surface. The rate of evaporation was controlled by inverting a cut funnel over the petridish. After 24 h, the dried films were taken out and stored in desiccator at room temperature. Thickness uniformity⁹ and water vapor transmission (WVT)¹⁰ of these drug-free films were evaluated following earlier described procedures.

Tensile strength and percentage of elongation determination:

Tensile strength and percentage of elongation were determined using Universal Testing Machine (Shimadzu, Singapore). Drug-free films of 15 mm width and 40 mm length were cut and fixed to the machine jaws. Then load on the film was increased gradually to a maximum, at a speed of 50 mm/s and tensile strength and percentage of elongation was noted.

Drug diffusion through films:

Drug diffusion study was conducted using vertical type diffusion cell. The receptor compartment was filled with 20 ml distilled water as diffusion media. Polymeric film was mounted on the donor compartment with the help of an adhesive. One milliliter of the drug solution in distilled water (3 mg/ml) was poured into the donor compartment. Magnetic stirrer was set at 100 rpm and whole assembly was maintained at $37 \pm 1^\circ$. The amount of drug released was determined by withdrawing 5 ml of samples at specific time intervals for 24 h. The volume withdrawn was replaced with equal volume of fresh and pre-warmed (37°) distilled water. Samples were analyzed for drug content using a UV Spectrophotometer (Hitachi-U-2000) at 229 nm^{11} . From the drug diffusion data, permeability coefficient and diffusion rate constants were calculated.

Skin irritation test:

The primary skin irritation test was performed on seven healthy albino rabbits, weighing between 2.0 to 3.5 kg.

Drug-free films of 3.63 cm^2 area were prepared and were used as test patches, while adhesive tape (USP) was used as control. The test was conducted on unbraided skin of the rabbits. The control and test patches were placed on the left and right dorsal surfaces of the rabbit respectively. The patches were removed after 24 h with the help of alcohol swab and the skin was examined for erythema and edema¹².

RESULTS AND DISCUSSION

Eudragit RS100 has good film forming property¹³. Casting method on mercury surface was found to be satisfactory to get thin and transparent films. Films plasticized with 10% DBP and 2.5% PEG were found to be brittle and tougher and those with 20% DBP and 7.5% PEG were too soft. But the films prepared by using 15% DBP and 5% PEG were found to be optimum with respect to smoothness, flexibility and transparency. The uniformity in thickness was maintained with all the prepared films. The films plasticized with DBP possessed high tensile strength and low percentage of elongation compared to the films prepared using PEG. The tensile strength of the films was decreased in the order of DBP 10% > DBP 15% > DBP 20% and PEG 2.5% > PEG 5% > PEG 7.5%; whereas the order of percentage of elongation was DBP 20% > DBP 15% > DBP 10% and PEG 7.5% > PEG 5% > PEG 2.5% (Table 1). These results indicate that, the films prepared by using DBP were more tougher compared to PEG films and also show that as the concentration of plasticizer was increased the tensile strength was decreased and percentage elongation was increased. It indicates that plasticizer molecules are interacting with forces held together by polymer chains leading to softening of the polymer matrix⁴. All the films were permeable to water vapor at 84% RH and room temperature and followed nearly zero order kinetics. The water vapor transmission (WVT) rate was high in case of PEG films compared to DBP films as shown in fig. 1. As the concentration of DBP was increased, the WVT rate was decreased. But enhanced WVT rate was observed with increase in the concentration of PEG. As the thickness of the film was increased, the WVT rate was decreased irrespective of plasticizer concentration. The WVT rate was in the decreasing order of PEG 7.5% > PEG 5% > PEG 2.5% and DBP 10% > DBP 15% > DBP 20%. Fig. 2 depicts the permeation profiles of verapamil hydrochloride through plasticized Eudragit RS100 films. Results indicated that the films were permeable to verapamil hydrochloride and diffusion pattern was close to zero order kinetics. It is obvious from the permeation profile that, films plasticized with PEG have higher permeability coefficients compared to DBP films; but de-

TABLE 1: EVALUATION OF EUDRAGIT FILMS PLASTICIZED WITH DBP AND PEG.

Evaluation Parameters	Eudragit films plasticized with					
	DBP 10%	DBP 15%	DBP 20%	PEG 2.5%	PEG 5.0%	PEG 7.5%
Thickness (μ)*	150 \pm 0.57	150 \pm 0.42	150 \pm 0.81	150 \pm 0.91	150 \pm 0.52	150 \pm 0.66
Tensile strength (N/mm ²)*	0.461	0.383	0.301	0.391	0.303	0.212
% Elongation*	11.2	18.7	25.3	31.1	38.9	45.5
Water vapor transmission rate. (g.cm/cm ² .24 h)**	2.56X10 ⁻²	2.04X10 ⁻²	7.45X10 ⁻³	4.25X10 ⁻²	1.05X10 ⁻¹	1.15X10 ⁻¹
Diffusion rate constant (mg/cm ² /h)**	2.07X10 ⁻²	1.94X10 ⁻²	1.64X10 ⁻²	2.28X10 ⁻²	2.86X10 ⁻²	3.00X10 ⁻²
Permeability coefficient (mg/h.cm)	7.49X10 ⁻³	7.05X10 ⁻³	5.96X10 ⁻³	8.25X10 ⁻³	1.04X10 ⁻²	1.09X10 ⁻²
Skin irritation	—	+	+	—	—	—

Table summarizes the data obtained from evaluation of Eudragit films plasticized with different concentrations of dibutyl phthalate and polyethylene glycol 400. *Indicates average of five observations. **Indicates average of three observations. +Indicates negligible erythema and - denotes absence of erythema.

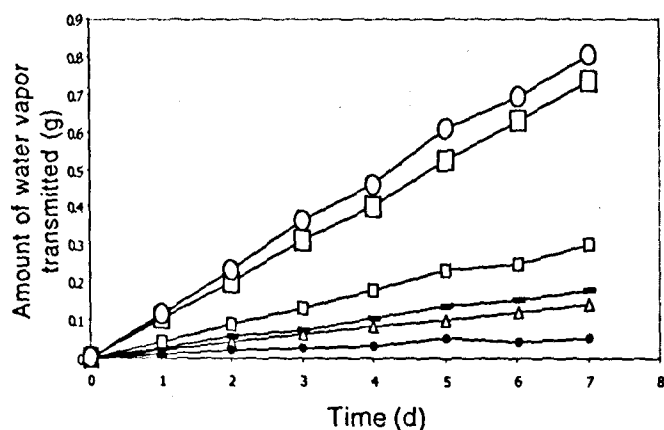


Fig. 1: Water vapor transmission through plasticized Eudragit films.

Water vapour transmission profiles through Eudragit films plasticized with PEG 7.5% (—○—), PEG 5% (—□—), PEG 2.5% (—△—), DBP 10% (— — —), DBP 15% (—△—) and DBP 20% (—●—).

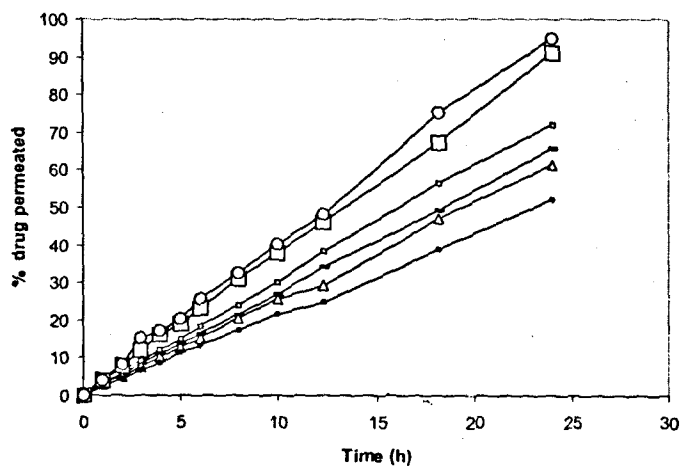


Fig. 2: Permeation of verapamil hydrochloride through Eudragit films with different plasticizers.

Permeation of verapamil hydrochloride through Eudragit films with different plasticizers that include PEG 7.5% (—○—), PEG 5% (—□—), PEG 2.5% (—△—), DBP 10% (— — —), DBP 15% (—△—) and DBP 20% (—●—).

Increased permeability coefficient was observed as the thickness of the film was increased. Among the DBP films, as the concentration of plasticizer was increased, decreased diffusion rate of the drug was observed (diffusion rate of DBP 10% > DBP 15% > DBP 20%). In case of PEG films, as the concentration of PEG was increased, the diffusion rate was also increased and it was in the order of PEG 7.5% > PEG 5% > PEG 2.5%. The higher diffusion rate of drug in case of PEG films might be due to the leaching out of PEG fraction from the films, which might have led to the formation of small pores and hence high permeability. Among the two plasticizers used, PEG (5% w/w) was found to possess satisfactory mechanical and permeability characteristics. The results of skin irritation test showed negligible erythema with prepared films when compared to control. The absence of edema indicated that these polymeric films were compatible with the skin and hence can be used for transdermal application.

In conclusion, the present study showed that, the type of the plasticizer and its concentration has considerable influence on the mechanical and permeability properties of the polymeric films. Compared to DBP films, PEG films were found to be smooth, flexible and possessed higher permeability to water vapor and verapamil hydrochloride. The diffusion of drug was extended over a longer period at

a controlled rate and no edema was observed in skin irritation test. Hence, these films can be used as rate controlling membrane in the preparation of transdermal films.

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