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Permeability Enhancement of Carvediolol Using Non-Ionic Surfactant and Different Polymers through Transdermal Film

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Abstract: Study of film properties of available hydrophilic polymer such as hydroxy propyl methyl cellulose E5 and polyvinyl alcohol in combination with polyvinyl pyrrolidone was undertaken. The effect of plasticizers i.e., polyethylene glycol 600 and triethyl citrate on formulation characteristics was also studied. The formulated films were characterized as physical evaluation i.e. weight variation, thickness uniformity, tensile strength, hardness, folding endurance, surface pH, Swallability, and water vapor transmission. Triethyl citrate as plasticizer showed good physical properties at 40% w/w of polymer concentration as compared to polyethylene glycol at same concentration. The hydrophobic surfactant enhanced the permeability of model drug carvediolol through skin. This was because of changes barrier properties of the skin and partition coefficient between vehicle and drug. In vitro drug permeation studies were carried out on guinea pig skin as animal model and result showed that both of the enhancers permeate drug release from polymer matrix. The combination of different hydrophobic vocalizing polymers also retards the permeation rate during in-vivo permeation study. These results indicated that, the nature of enhancers highly influences cutaneous barrier impairment. Skin irritation studies were carried out in guinea pig and did not show any signs of irritation, edema or erythema after a week.

Key words: Transdermal Film · Non Ionic Surfactant · *In vitro* Permeation · Carvediolol.

INTRODUCTION

During the past few years, the interest for the development of novel drug delivery systems on existing drug molecules has been increased by researchers. The development of formulations or newly system has participated for improving the drug's performance as efficacy and safety. This will also help for improving patient compliance and overall therapeutic benefit to get more effectiveness. Transdermal drug delivery is one of the approaches for controlled release of the drug into the patient. Such approaches maintain a blood-level profile and thus reduced systemic side effects with improved efficacy than other dosage forms or system [1]. The transdermal drug delivery system have concept for delivering drugs through the skin, which provide drug directly systemic treatment of diseased states. This delivery system has more importance, because of several important advantages [2]. Such as hepatic first pass metabolism is on limit, therapeutic efficiency is improved, duration of action of used drugs has prolonged action with short plasma half-life, and help for maintaining of steady plasma level of the drug [3]. Transdermal delivery is used for those drugs; those have such properties, i.e., low dosing, melting points low and also low molecular weights, and a solubility of <1mg/ml in both solvent one is water and other mineral oil [4]. Carvediolol is acted by blocking adren-oreceptors and used for treatment of Hypertensive patients. Carvediolol have low bioavailability (20%), this can be avoided by transdermal administration for reduce hepatic first pass metabolism with oral route. The model drug has a short half life and thus requires frequently continuous dosing sequence by the oral route for get more effect. A single application of transdermal film can be possible enhanced duration of action [5]. The aims of the present study was to prepared transdermal films containing carvediolol and investigate the permeation rate, release kinetic pattern of drug and

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achieve a controlled drug release with improved bioavailability for better patient co-operation. The present study was to formulate a series of matrix films with variability of ratio of nonionic surfactants and different polymers i.e. HPMC E5 (cellulose derivatives [6]), polyvinylpyrrolidone K30 (PVP), ERL 100 and chitosan (mucoadhesive mucilaginous polymer [7, 8]). Chitosan is versatile natural polymer [9], which have been used in the different dosage form that helps in the sustain and control release of drug [10]. Chitosan is a polysaccharide polymer having unbranched chains of - (1, 4)-2- acetoamido-2-deoxy-D- glucose. The amino group present in chitosan has a pKa value of ~ 6.5. Chitosan is amorphous solid materials, which is practically insoluble in water, dilute acids, dilute and concentrated alkalies, alcohol and other organic solvents [11, 12]. The prepared films contained carvediolol as model drug and characterized effect of drug permeation rate through guinea pig skin as in-vitro permeation study. The objective of study was also to establish the drug delivery system, which will release the drug in a controlled manner through skin as transdermal drug delivery system. This improves bioavailability of drug in blood and takes help for controlling hypertension for prolonged time.

MATERIALS AND METHODS

Experimental: Carvediolol was provided as a gift sample from Sun Pharmaceutical Industries Ltd., Baroda, India). Hydroxy propyl methyl cellulose (Plethico Pharmaceutical Ltd., Indore, India), Eudragit RL 100 was supplied as a gift sample (Intas Laboratories Pvt. Ltd. Ahmadabad, India). Chitosan and polyvinyl pyrrolidone K30 (Otto Kemi Ltd., Mumbai, India), Polyethylene Glycol 600 (Merck, Ltd., Mumbai, India), Triethyl citrate (Thomas baker Pvt. Ltd., Mumbai, India), Span 80 and Tween 80 polymers (Otto Kemi Ltd., Mumbai, India) were purchased. All the other laboratories chemicals were used as analytical grade.

Methods

Preparation of Transdermal Films: Transdermal films containing drug were prepared by casting solvent method in circular glass molds or glass bengals with 3 cm radius and 1 cm height. This glass mold was kept inside petridishes containing mercury as a substrate, because mercury not adsorb on the surface of backing membrane. The backing membrane was prepared by pouring a 4% (w/v) polyvinyl alcohol (PVA) solution in 5 ml distilled water. The prepared membrane was dried at 65°C for 6 h. The drug reservoir was formulated by dissolving hydroxypropylmethyl cellulose E-5 (10%) in 15 ml distilled water for investigation release profile of drug. PEG 600 40% (w/w) or triethylcitrate 40% (w/w) was used as a plasticizer in different composition (Table 1) with polymeric dispersion used during formulation of film. The accurately weighed 29.25 mg drug content previously mixed in 5 ml methanol and drug containing mixture added into the homogeneous polymeric dispersion containing plasticizer with slow rate of stirring on a magnetic stirrer. The drug containing polymeric dispersion was transfer on a backing membrane with continuous thin layer and dried at 60°C for 6 h. The rate-controlling membrane was developed on surface of drug reservoir system by using 4 % (w/v) eudragit RL 100 or chitosan with 0.10% (w/v) polyvinyl pyyrolidone K30 as film forming agent and triethyl citrate 40% (w/w) as plasticizer of polymer composition in 10 ml distilled water. Tween 80 or Span 80 1% (w/v) as permeation enhancer was incorporated in the drug reservoir system (Table 1). Small patches of 3.14 cm^2 were cut from prepared casted film. Each individual patch contains 3.25 mg of drug and packed in aluminum foil, stored in desiccators until further use [13].

Characterization of Transdermal Films

Weight Variation: Weight variation of films was done by weighing each film individually and the average weight of film was taken as the weight of the film [14].

Table 1: Composition of the transdermal films

Formulation code	Backing layer (4 %, w/v)	Drug reservoir[a] (10 %, w/v)	Rate controlling membrane[b] (w/v)	Permeation enhancer (1 %, w/v)
C 1	PVA	HPMC E5	-	-
C 2	PVA	HPMC E5 +PEG 600	ERL (4 %)	-
C 3	PVA	HPMC E5 +TEC	ERL (4 %)	-
C 4	PVA	HPMC E5 +PEG 600	Chitosan (4 %)	-
C 5	PVA	HPMC E5 +TEC	Chitosan (4 %)	-
C 6	PVA	HPMC E5 +TEC	ERL (4 %)	Tween 80
C 7	PVA	HPMC E5 + TEC	ERL (4 %)	Span 80
C 8	PVA	HPMC E5 + TEC	Chitosan (4 %)	Tween 80
C 9	PVA	HPMC E5 + TEC	Chitosan (4 %)	Span 80

PVA – Polyvinyl alcohol, HPMC – Hydroxypropyl methylcellulose, ERL – Eudragit RL 100, TEC – Triethyl citrate, PEG 600 – Polyethylene glycol 600
[a] With carvediolol (0.292%, w/v), [b] With Polyvinyl pyrrolidone K30 (0.1%, w/v)

Fig. 1: Appratus for testing of tensile strength.

Fig. 2: Appratus for investigation of hardness of carvediolol transdermal films.

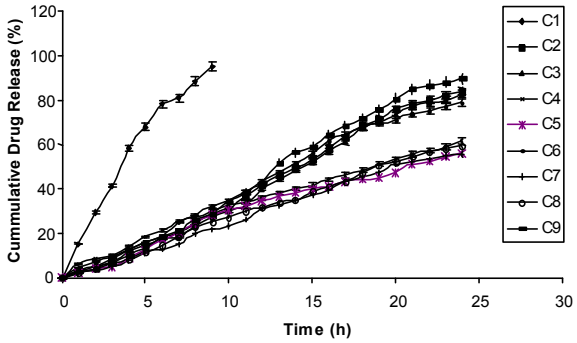

Fig. 3: *In vitro* permeation study of carvediolol transdermal films.

Thickness: The thickness of the films was determined by measuring the thickness at five sites for three films of each formulations using micrometer (Chounmoyto, Japan) and the average thickness was calculated [15].

Tensile Strength: This mechanical property was evaluated using fabricated testing instrument in laboratory (Fig. 1). Film strips in previously discussed dimension about 3.14 cm^2 and free from air bubbles or physical imperfections were held between two clamps positioned at a distance of 3 cm. During measurement, the strips were pulled by the top clamps at a rate of 100 mm/min; the force was measured when the film broke. Results from film samples, which broke at and not between the clamps, were not included in the calculations. Measurements were run in triplicate for each film. Two mechanical properties, namely tensile strength and percentage elongation, were computed for the evaluation of the film [16]. Tensile strength was calculated using the following formula:

A. Tensile strength = break force $(1+\Delta L/L)$

B. Break force = Weight required to break the film (kg)

where A, B and L are width, thickness and length of strip respectively and ΔL is the elongation at break.

Hardness: To determine the hardness of the patches, an apparatus was designed in our laboratory (Fig. 2). It consists of a wooden stand of 15 cm height and top area of 15 cm × 15 cm. A small pan was fixed horizontally to one end of the 2 mm thick steel needle whose other end is reduced to a sharp point. A hole of 0.2 cm was made at the center of tip area of wooden stand, which was supported on the pan rod. An electric circuit was developed through a 6 vt battery in such a way that the bulb glows only when the circuit is completed through the contact of a metal plate and sharp end of the needle. The film was placed between the metal plate and sharp end of the needle. The weights were gradually added at an interval of 20 sec for the stabilization of the force till the bulb glowed. The final weight was considered as a measure of hardness [17].

Folding Endurance: Folding endurance was determined by folding of one film at the same place repeatedly till it was breaks from that specific point. Folding endurance was calculated by calculating number of times required for breaking or cracking of film or could be folded at the same place.

Swellability (%) : Each film of surface area 3.14 cm^2 was weighed and placed in a Petri dish with10 ml of double distilled water. The degree of swelling (% S) was calculated using parameters

$$S\,(\%) = \frac{Wt\ \ Wo}{Wo} \times 100$$

where, S = swellability, W_t is the weight of film at time t and W_o is the weight of film at time zero [18].

Water Vapor Transmission: The glass vials of 5 ml capacity were washed thoroughly and dried to constant weight in an oven. 1gm of calcium chloride (Fused) was taken in vials and the prepared transdermal films were fixed onto the vials rim with the help of surgical white tape. These pre-weighed vials were stored in humidity chamber at RH 80±5% with temperature of 25±1°C for 24 h. The weight gain was determined every hour up to a period of 24 h (Predetermined equilibrium period) to observe the weight gain.

Surface pH: Surface pH was identified by allowed films to swell by keeping them in contact with 0.5 ml of distilled water in glass tubes for 15 min. The pH was noted by using glass electrode came to contact at the surface of the film after equilibrates within 1 min.

Drug Content Uniformity: The patch (3.14 cm^2) was transferred into a graduated flask containing 100 ml of phosphate buffer pH 7.4. The flask was shaken for 4 h in a mechanical shaker. Then the solution was filtered and after suitable dilutions with phosphate buffer pH 6.8 the absorbance was measured at 249 nm using the placebo patch solution as blank and the drug content was calculated [19].

***In vitro* Permeation Studies:** Films with 3.14 cm^2 area were introduced for studying *in vitro* drug permeation study with a modified Keshary-Chein diffusion cell (Capacity 75 ml). Present study was performed by using guinea pigs (Male, 250 to 300 g weight and 6 months of age). All guinea pigs were killed by cervical dislocation and dorsal skin of animal was removing. Now remove hair by shaving, washed and placed it to overnight with phosphate buffer pH 7.4 (Receptor phase) [20]. Dorsal skin of guinea pig was clamped between the donor and recipient compartments of experimented cell. Now film was kept inside the donor compartment over the skin and covered with paraffin wax. Sink condition was maintained at 37±1°C throughout the experiment by maintain temperature of receptor phase. The aliquote was withdrawn at predetermined time intervals and equal volume of pre-warmed buffer introduced to experimented vessel [21]. The samples were analyzed for drug content at 242 nm for determined the amount of drug permeate through skin.

Skin Irritation Study: The guinea pigs were divided into 5 groups (n=3). On the previous day of the study, the hairs on the studying area of guinea pig were removed by razer or shave. The skin was cleared with rectified spirit. The group I of animals was without any treatment and considered as normal. Another group of animals without drug containing transdermal films (Group II, placebo effect) was applied with adhesive surgical white tape (USP, Leucoplast™). The drug loaded prepared films were applied on the dorsal surface of animals of III and IV groups. Group V as a control group, which treat with 0.8% v/v aqueous solution of formalin as a standard irritant and its effect was compared with test one. The animals were kept under observation till to any sign of erythema or paw oedema within a period of 7 days [22].

Ethical clearance for the handling of animals for iiritancy studies was obtained from the institutional animal ethical committee (IAEC) formed for this studying.

RESULTS AND DISCUSSION

The characteristics of drug free films i.e., weight variation, thickness, tensile strength, folding endurance, surface pH, hardness, swellability (%), water vapour transmission (WVT) are discussed in Tables 2 and 3. The weight of the films varied between 20.1 to 27.1 mg. All the films indicated uniformity in weight with low standard deviation values prepared by solvent casting method. The film thickness was varied between 0.532 to 0.935 mm, and the area of the film was 3.14 sq.cm (Table 3). The tensile strength of the film(s) was found varied with the nature of the polymer and plasticizers variability; between 0.686 to 0.928 kg/mm^2. The folding endurance measures the ability of patch to withstand rupture. Folding endurance with plasticizer as TEC was found to be 339.6. The polymer HPMC with plasticizer TEC had maximum folding endurance while film containing PG showed least folding endurance. The polymeric softness and weakness property is characterized by a low tensile strength, folding endurance and percentage elongation, where as hard and tough polymer was characterized by a greater tensile strength, folding endurance and hardness. Formulation C3 and C6 were better in comparison to C2 and C4. Results showed that incorporation of TEC as a plasticizer was imparting enhancement of mechanical properties of the film with containing HPMC as viscolizing agent and Span 80 as permeation enhancer (C7) because the flexibility of polymer. The plasticizer molecules have to interact with the polymer molecules and change the effect of polymeric film was prepared by using polymer alone

Table 2: Study of mechanical properties of the transdermal films

Code	Folding endurance	Tensile strength (kg/ mm^2)	Hardness (gm)	Swellability (%)
C 1	306.4±7.8	0.928±0.029	335±10	41.32±2.13
C 2	332.45±6.4	0.923±0.024	315±9	40.25±3.65
C 3	339.6±5.7	0.731±0.026	285±8	36.21±2.16
C 4	331.78±5.4	0.738±0.029	294±7	37.01±1.97
C 5	332.85±4.5	0.686±0.018	281±9	40.22±2.15
C 6	333.45±4.85	0.798±0.017	305±6	38.55±2.01
C 7	335.8±6.4	0.765±0.025	310±11	34.12±2.01
C 8	338.9±3.5	0.812±0.021	308±7	39.12±1.19
C 9	336.4±4.1	0.856±0.032	299±9	40.87±2.04

Table 3: Study of Physicochemical parameter of the transdermal films

Code	Weight variation (mg)	Thickness (mm)	Surface pH	Water vapor transmission (WVT) (mg/cm^2/h)	Drug content (mg/patch)	Permeation rate (mg/cm^2/h)
C 1	20.1±2.1	0.935±0.63	5.4±0.2	0.172±0.0023	3.25±0.02	3.18±0.016
C 2	22.8±2.1	0.625±0.56	5.8±0.05	0.132±0.0014	3.24±0.01	0.84±0.11
C 3	24.2±2.3	0.550±0.29	5.8±0.11	0.122±0. 0028	3.26±0.02	0.87±0.17
C 4	26.1±2.8	0.569±0.21	5.7±0.15	0.141±0.0061	3.25±0.03	1.01±0.12
C 5	24.1±2.5	0.532±0.21	5.2±0.12	0.146±0.0041	3.22±0.06	1.08±0.17
C 6	25.1±2.4	0.587±0.21	5.4±0.12	0.139±0.0018	3.26±0.01	0.95±0.011
C 7	27.1±2.7	0.625±0.21	5.3±0.13	0.129±0.0011	3.25±0.01	1.16±0.018
C 8	26.5±2.6	0.578±0.21	5.7±0.21	0.131±0.0032	3.24±0.01	1.03±0.012
C 9	22.3±2.7	0.579±0.21	5.5±0.18	0.136±0.0023	3.26±0.04	2.18±0.014

(C1, Tables 2 and 3). HPMC E5 containing with TEC and Tween 80 (C6) film has showed excellent tensile strength, folding endurance. Films require certain amount of hardness, to with stand the mechanical shocks in handling, packaging and at the time of application. The hardness of films varied from 281 to 335 g. The formulation C5 and C3 had low amount of hardness and C6, C8 had good hardness. Therefore the tensile strength related to hardness of formulations. This was concluding that these mechanical properties of films were basically depending on the properties of the polymers and plasticizers. Surface pH of different formulations varied between 5.2 to 5.8, indicating that no irritation will be occur on the skin at films apply on skin of animal during skin irritation experimental study (Table 3). Water vapour transmission study was carried out for a period of 24 h. Vapor transmission was between 0.122 to 0.172 mg/cm^2/h. Obviously, the rate of water vapor permeation reduced with increasing thickness and hardness of films. *In-vitro* permeation study showed that release kinetic of drug containing prepared formulations followed zero order kinetics. The polymers used in the preparation of films were found to be appreciably permeable water vapor due to its hygroscopicity provided by different plasticizers used for reservoir and polymers used for rate controlling membrane. HPMC E5 as reservoir polymer and ERL 100 as rate controlling polymer containing film (C3) had greater thickness than chitosan containing formulation (C5). So water vapour permeation was lesser in ERL 100 film as compared with the other polymeric films. Swelling was varied between 34.12±2.01 to 41.32±2.13%. Film containing HPMC E5 (C1) as a polymer had more swellability than HPMC E5 with TEC (C7), because film prepared without plasticizer came to direct contact with distilled water with more hardness. Plasticizer containing films enhance plasticity of film and could not be penetrable by water molecule easily. The polymers with hydrophilic in nature showed more swellability than hydrophobic polymer(s). All polymeric films showed satisfactory physical properties and significantly with each other. In vitro permeation study showed that formulation containing HPMC E5 (C1) was not retard the drug release from polymer matrix while rest of all formulations were retard the permeation of drug. The nonionic surfactants such as Tween 80 and Span 80 were introduced in the films to enhance the drug permeation rate through skin of guinea pig (Table 1). The in-vitro drug permeation studies of films with permeation enhancers permeates drug 78.82, 55.59, 59.61 and 89.78% at the end of 24 h from C6, C7, C8 and C9 respectively. The result showed improvement of drug permeability through guinea pig skin from the prepared formulations containing permeation enhancers. The affectivity of films with permeation enhancers was determined by comparing drug retardation between formulations has presence and absence of each enhancer with combination of polymer matrix as rate controlling

membrane. The films with Tween 80 also enhanced the permeation rate but to a lesser extent in combination with eudragit (C6) than chitosan (C8). Span 80 permeate more permeation rate in combination with chitosan (C9) than Tween 80 with chitosan (C8). Permeation rate through guinea pig skin of carvediolol from film containing HPMC E5 with eudragit and Span 80 as permeation enhancer (C7) was retarded permeation rate 55.59% due to highly complexing polymeric matrix than film containing HPMC E5 with chitosan and Tween 80 (C8). Span 80 is more hydrophobic surfactant, which enhanced the carvediolol skin permeation rate probably due to changes the barrier properties of the skin and partition coefficient between vehicle and drug. Results conclude that Span 80 was best permeation enhancer in combination with chitosan (C9) but also showed good retarding property with eudragit combination (C7). Results indicated that the cutaneous barrier of skin influences by the nature of enhancers head group. The zero-order plots of C2, C3, C5, C7, C8 and C9 were found to be fairly linear, as indicated by their high regression value. This was indicated that the drug permeation rate from these films follow either near zero or zero-order kinetics. For the confirmation of exact mechanism for drug permeation through these films, the data were again fitted in Korsmeyer-Peppas model. The result of skin irritation test showed that no erythma is produced with the prepared transdermal films. There was no signs of erythema, oedema or ulceration were observed on the skin of guinea pig after 7 days.

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