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SCIENTIFIC PAPER

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PERMEABILITY STUDIES OF DAMAR BATU FREE FILMS FOR TRANSDERMAL APPLICATION

Damar Batu (DB) looks like stone with black or dark brown color inside. Due to its film forming ability it is used in the manufacture of paper, wood, varnishes, lacquers, polishes and additives for beverages. In the present study the permeability of free films of DB casted from chloroform solution containing different plasticizers was studied with a view to developing a suitable rate controlling membrane for transdermal use. The free films of DB were prepared by a mercury substrate technique and dibutyl sebacate (DBS), dibutyl phthalate (DBP), polyethylene glycol 400 (PEG400) and propylene glycol (PG) were tried as plasticizers. DB films were then evaluated for uniformity of thickness, moisture absorption, water vapour transmission, tensile strength, percentage elongation and folding endurance. Permeability characteristics of free films of DB were studied using diltiazem hydrochloride (DH) as a model drug. Little variation in film thickness ensured the uniformity of the films. DBS produces tough DB films with more tensile strength. Drug diffusion through the free films followed zero order kinetics. The films plasticized with PEG400 showed higher permeability for DH compared with other films. The order of decrease of permeability of plasticized films with plasticizers was PEG400 > PG > DBP > DBS. Diffusion of drugs through the free films of DB was extended over a longer period of time at a controlled rate. DB seems to be a promising rate controlling membrane for the transdermal application.

Key words: permeability; Damar Batu; diltiazem hydrochloride; plasticizer, transdermal delivery.

The usefulness of the polymers in a drug delivery system is well established. Damar Batu is the gum which comes out from the hard wood tree and falls into the ground. Batu ("stone") refers to the opaque stone or pebble-shaped damar collected from the ground. It is much harder than other resins, yellowish to brown in colour, obtained from *Shorea* species like *S. lamellata* Foxw., *S. virescens* Parijs, *S. retinodes* Sloot., *S. guiso* and *S. robusta,* Family *Dipterocarpaceae.* The polymer of DB was identified as polycadinene and is said to contain about 40% α-resin (alcohol soluble part), 22% β-resin (alcohol insoluble part), 23% dammarol acid and 2.5% water, in addition it also contains a small sesquiterpenoid fraction [1]. DB is mainly used as an emulsifier and stabilizer for the production of color, paints, inks and aromatic emulsions in food and cosmetic industries [2]. These uses of DB suggested its film forming property and prompted us to evaluate it for application in transdermal drug delivery. Free films of DB were brittle and hence the addition of plasticizer was needed. The plasticizer interposes itself between the polymer chains and interacts with the forces held together by extending and softening the polymer matrix [3]. These are incurporated into the films for various reasons such as to reduce brittleness, impart flexibility, increase strength and also to improve adhesiveness of the film with other surfaces or membranes. The selection of a suitable plasticizer and its concentration has a profound influence on the mechanical properties of the film, as well as on the permeability of drugs through it. In the present study, we have made an attempt to explore DB, due to its excellent film forming property and hydrophobic nature, as a rate controlling membrane for application in transdermal drug delivery and to study the effect of plasticizers on its film properties. Plasticizers we used include dibutyl sebacate (DBS), dibutyl phthalate (DBP), polyethylene glycol 400 (PEG400)

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and propylene glycol (PG). Plasticized free films of DB were prepared and evaluated for parameters like uniformity of thickness, tensile strength, percentage elongation and water vapour transmission. Further, plasticized films were subjected to permeability studies, using diltiazem hydrochloride (DH) to determine the effect of plasticizers on the DB films permeability characteristics. DH (Fig. 1) was used as model drug as it is a potential candidate for transdermal administration owing to its pharmacokinetic properties, and is investigated for transdermal applications by various researchers [4-6].

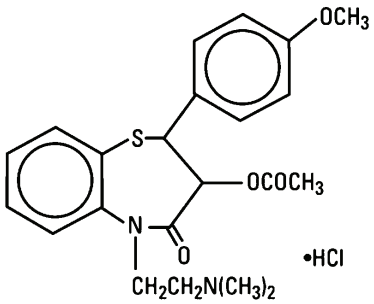

Fig. 1. Structural formula of diltiazem hydrochloride.

MATERIALS AND METHODS

Materials

DB was purchased from R. R. Enterprises, Mumbai, India; DH was obtained as a gift sample from Torrent pharmaceuticals, Ahmadabad, India; dibutyl sebacate and dibutyl phthalate were procured from Morflex Inc., Greensboro, NC; polyethylene glycol 400 and propylene glycol were purchased from Loba Chemie, Mumbai, India and chloroform was purchased from SRL, Mumbai, India. Other chemicals used were of analytical grade.

Methods

Preparation of DB films

Free films of DB were prepared on the mercury substrate by a solvent casting method [7] using a 10% w/v solution in chloroform. To evaluate the effect on the film characteristics, plasticizers like DBS, DBP, PEG400 and PG were added in the polymer solution at different concentrations (based on the total weight of dry polymer). The required quantity of DB was dissolved in the chloroform using ultra sonicator to get a clear solution. The polymer solution after the addition of the respective plasticizer was poured into a glass bangle placed on a mercury surface in the Petri dish. Free films of DB with different thicknesses were prepared by changing the casting volume of the polymer solution. Casted films were dried at room temperature for 24 h. The controlled evaporation of the solvent was achieved by placing an inverted funnel over the Petri dish containing mercury [6]. The dried films were then carefully removed from the mercury surface, cut into appropriate dimensions and stored in the desiccators until further use.

Free films of DB were then evaluated for thickness uniformity, moisture absorption, water vapor transmission rate, mechanical properties, folding endurance and permeability characteristics.

Thickness uniformity

The thickness was determined at three different points on one film using a thickness gauge (Oswa Scientific, Ambala, India) recording the mean along with the standard deviation for each specimen.

Mechanical characterization of DB films

The casted films after drying were carefully cut into film strips (42.4 mm×19.8 mm) and investigated for mechanical properties like the tensile strength and percent elongation using Instron Instrument (model 4467, Instron Corp., Canton, MA). The method used for evaluating the mechanical properties was based on guidelines of the American Society for Testing Materials, method D 882-95a [8]. The measurements were made at the crosshead speed of 10mm/min and the gauge length of 50 mm at 50% relative humidity and temperature 25 °C. For each film specimen all the parameters were determined in triplicate.

Folding endurance test

A folding endurance test was carried out by folding the films at the same point number of times till it breaks [9]. The test was carried out in order to check the efficiency of the plasticizer and the strength of the film prepared using a varying concentration of the plasticizers. The test was carried out in triplicate.

Moisture absorption studies of DB films

DB films, prepared using the optimum concentration of each plasticizer and having maximum thickness, were selected for moisture absorption studies. Accurately weighed film strips (25×10 mm^2) were placed in glass desiccators maintained at controlled relative humidities (RH) of 43 and 93% and removed periodically and weighed until two consecutive readings were the same. Saturated solutions of potassium carbonate and potassium nitrate were used respecttively to get the required relative humidity in the chamber [10]. The percent moisture absorption was calculated using the following formula: Moisture absorption (%) = 100(final weight – initial weight)/initial weight.

Water vapor transmission rate studies

DB films prepared using the optimum concentration of plasticizer of each type with minimum and maximum thicknesses were selected for water vapor transmission studies. Patches with different thickness were selected to study the effect of thickness on the water vapor transmission rate (WVTR). The experiment was carried out using the permeation cell consisting of a glass body (2.25 cm internal diameter; 8.0 cm height) and a cup with the opening of 23.4 mm diameter (test area 4.17 cm^2). To determine the water vapor transmission rate, polymeric films of the appropriate dimensions were cut and mounted between the body and the cup of the cell to provide the effective surface area for a water vapor transmission. The body and cup of the cell were then held in place with the help of three screw clamps and the RH was maintained at 43 and 93% within the permeation cell [11]. These cells were then weighed and transferred to the desiccators maintained at 0% RH. The cells were removed at regular time intervals and reweighed for a period of 72 h. The amount of water vapor transmitted though the film was given in terms of the weight loss of the assembled cell. The Utsumi's equation is used to determine the water vapor transmission rate, Q [12]:

$$Q = wL/S$$

where w is mass of water (g) transmitted per 24 h, L is film thickness (cm) and S is surface area (cm^2).

Drug diffusion and permeability studies

Non-jacketed bi-chambered donor receiver compartment model (modified Franz diffusion cell) with the diffusion area of 4.906 cm^2 was used for these studies. Diffusion of DH was studied using DB films. The cell consists of two compartments, namely donor and receptor, with 20 mL capacity each. Phosphate buffer, pH 7.4, was used as a receptor fluid. The polymer film of appropriate dimensions was sandwiched between the two compartments. Ten mL of drug solution in water (2% w/v) was poured into the donor compartment. The receptor fluid was agitated using a star head magnet and the temperature of 37±1 °C was maintained by placing the cell on the magnetic stirrer with a hot plate (Remis Equipments, Mumbai). The samples (1 mL) were collected at periodic intervals through the sampling port and after each sampling equal volume of drug free phosphate buffer solution pre-warmed to 37±1 °C was added to maintain the constant volume of the receptor fluid. The drug content was assayed spectrophotometrically at 236 nm after a suitable dilution of the withdrawn sample and the amount of the drug diffused was determined with the help of the standard calibration curve of DH prepared in phosphate buffer, pH 7.4, taking a dilution factor into account in the calculations. Flux was determined directly as the slope of the curve between the steady state values of the amount of drug permeated (mg/cm^2) *vs.* time [13] and permeability coefficients were deduced by dividing the flux by the initial drug load (mg/cm^2) [14]. The drug diffusion data was analyzed using zero order, first order and Higuchi kinetics in order to investigate the mechanism of permeation of the drug through DB films. The most appropriate model was selected on the basis of a goodness of the fit test [15].

RESULTS AND DISCUSSION

The usefulness of the polymers in a drug delivery system is well established. In the present study, an attempt has been made to evaluate Damar Batu, a novel film forming biomaterial for its application in a transdermal drug delivery. DB is a yellowish brown colored (stone Fig. 2) like gum with the softening point range of 90–93 °C and the glass transition temperature of 38.79 °C. Its application in the manufacture of varnishes, lacquers and polishes explains its film forming property along with its hydrophobic nature and this prompted us to evaluate DB as a rate controlling membrane for transdermal application. Free films of DB were very brittle and the addition of plasticizer was necessary to improve the film properties. The plasticizer shifts the glass transition temperature to lower the temperature and is an important formulation factor [16]. We used two hydrophobic plasticizers and two hydrophilic plasticizers to study their effect on the film characteristics. Figure 3 shows the surface of the plasticized DB film taken using a Bright field microscope with CCD camera (Leitz Labor Lux S Microscope, Germany) and it was found to be wrinkle free and there were no defects on the surface.

Fig. 2. Damar Batu.

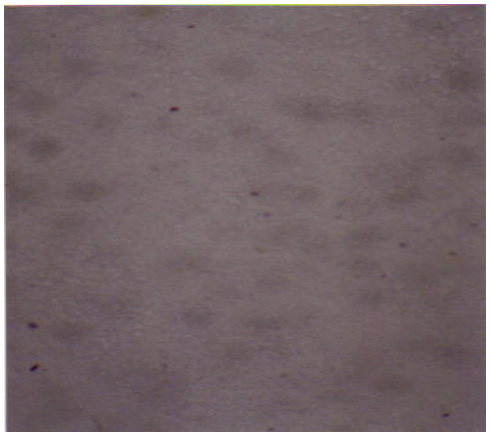

Fig. 3. Damar Batu free film surface.

Table 1 shows the concentrations at which all four plasticizers were added. DBS below 10 %w/w concentration could not improve the film property and beyond 30 %w/w concentration led to the formation of tacky films. Similarly, DBP below 20 %w/w concentration failed to improve the film property and beyond 40 %w/w concentration gave rise to soft and sticky films which could not be handled. A trial and error method shows that PEG400 should be incorporated in 5 to 15 %w/w concentration in the film formulation whereas PG in 10 to 30 %w/w improved the film properties. The DB films plasticized with PEG400 and PG were slightly opaque as compared to the films plasticized with DBS and DBP which were transparent and brown colored.

Plasticized films were smooth, uniform, free from wrinkles and defects and were easy to handle compared to the non plasticized films. The method of

Table 1. Characterization of Damar Batu free films casted from 10 %w/v DB

Batch code	Content of plasticizer, %w/w	Vol. of casting solution, mL	Thickness* µm	Folding endurance*	Tensile strength* N/mm^2	Elongation* %
Films plasticized with dibutyl sebacate						
F1	10	5.0	130.30 ± 1.35	2.33 ± 0.50	Brittle films	Brittle films
F2		7.5	173.20 ± 1.11			
F3		10.0	265.00 ± 0.10			
F4	20	5.0	129.00 ± 1.17	11.00 ± 1.00	0.10 ± 0.31	21.94 ± 0.13
F5		7.5	178.60 ± 0.03			
F6		10.0	270.60 ± 0.005			
F7	30	5.0	131.30 ± 1.23	13.66 ± 1.10	0.21 ± 0.65	25.45 ± 0.17
F8		7.5	174.80 ± 0.89			
F9		10.0	275.30 ± 0.001			
Films plasticized with dibutyl phthalate						
F10	20	5.0	125.70 ± 1.87	2.00	Brittle films	Brittle films
F11		7.5	169.00 ± 1.09			
F12		10.0	263.10 ± 2.11			
F13	30	5.0	128.10 ± 2.21	9.66 ± 0.50	0.08 ± 1.10	19.90 ± 2.10
F14		7.5	172.20 ± 0.99			
F15		10.0	270.70 ± 1.17			
F16	40	5.0	127.40 ± 0.45	12.33 ± 1.50	0.09 ± 2.37	21.40 ± 1.70
F17		7.5	168.90 ± 1.12			
F18		10.0	271.10 ± 0.44			
Films plasticized with polyethylene glycol 400						
F19	5	5.0	129.30 ± 0.89	1.33 ± 1.50	Brittle films	Brittle films
F20		7.5	165.30 ± 1.76			
F21		10.0	265.70 ± 1.43			
F22	10	5.0	130.00 ± 2.20	8.33 ± 0.50	0.08 ± 0.06	19.80 ± 1.17
F23		7.5	171.20 ± 0.07			
F24		10.0	266.00 ± 1.19			
F25	15	5.0	129.60 ± 1.76	9.66 ± 0.50	0.08 ± 1.41	20.90 ± 2.13
F26		7.5	175.30 ± 1.17			
F27		10.0	269.80 ± 0.03			

Table 1. Continued

Batch code	Content of plasticizer, %w/w	Vol. of casting solution, mL	Thickness* µm	Folding endurance*	Tensile strength* N/mm^2	Elongation* %
Films plasticized with propylene glycol						
F28	10	5.0	128.89 ± 1.80	3.00 ± 1.10	Brittle films	Brittle films
F29		7.5	172.40 ± 2.11			
F30		10.0	270.20 ± 0.89			
F31	20	5.0	129.10 ± 1.42	7.00	0.07 ± 0.06	18.60 ± 0.01
F32		7.5	169.50 ± 1.07			
F33		10.0	268.00 ± 0.45			
F34	30	5.0	130.40 ± 0.67	9.66 ± 0.50	0.08 ± 0.06	20.70 ± 1.11
F35		7.5	171.40 ± 2.23			
F36		10.0	270.60 ± 1.53			

*Values are mean ± *SD* (*n* = 3)

the film casting used in the study was found to be useful and satisfactory as the thickness of the film was uniform when it was measured at three different points along the length of the film. The thickness of the film varied with changing of the volume of the casting solvent. Volumes of 5.0, 7.5 and 10 mL of the polymer solvent were casted in the glass bangle of the equal diameter to get the films of different thickness. Mechanical properties of the DB films (Table 1) revealed that the films plasticized with DBS were tough compared to other plasticizers. Mechanical properties studied showed that the tensile strength and the % elongation was high for DBS plasticized films whereas for PG plasticized films it was low.

A folding endurance test was carried out to check the strength and the flexibility of the film and the effectiveness of the plasticizer. The folding endurance test results (Table 1) indicated that the patches would maintain their integrity with general skin folding when applied. The films plasticized with DBS showed higher folding endurance and the results were found to be in agreement with the results of mechanical studies. The films having higher tensile strength showed a higher folding endurance.

The moisture absorption study results (Table 2) showed that DB films plasticized with DBS and DBP (F9 and F18) showed less moisture absorption which could be due to their hydrophobic nature. PG plasticized films showed the maximum moisture absorption compared to the films plasticized with others. Moisture absorption decreased in the following order PG > > PEG400 > DBP > DBS. WVTR study results (Table 3) indicated that the hydrophilic plasticizers were responsible for the higher WVTR. The amount of water vapors permeated through the DB films plasticized with DBS was lowest when compared with other plasticizers and it was expected due to their lowest moisture absorption results. The plasticizers in the order of their increased WVTR were as follows DBS < DBP < < PEG400 < PG. The thickness of the films also changes the rate of the water vapor transmission. It can be said that as the thickness of the film increases the WVTR decreases. Further, it is clear from the results that the increase in humidity leads to the increase in the water vapor transmission which is in accordance with what is reported in the literature [7,17].

Table 2. Moisture absorption study of DB films

Batch code	Moisture absorption* (%)	
	RH 43%	RH 93%
F9	0.66 ± 0.11	0.89 ± 1.12
F18	0.69 ± 1.14	0.93 ± 0.09
F27	4.60 ± 0.11	5.93 ± 1.43
F36	6.32 ± 0.20	9.52 ± 2.23

*Values are mean ± *SD* (*n* = 3)

Table 3. Water vapour transmission rate studies of DB films

Batch code	Thickness of the film* (µm)	WVTR* (g cm/cm² 24h)	
		RH 43%	RH 93%
F7	131.30 ± 1.23	$4.91 \pm 0.07\times10^{-3}$	$6.12 \pm 3.12\times10^{-3}$
F9	275.30 ± 0.001	$3.21 \pm 1.13\times10^{-3}$	$5.23 \pm 1.11\times10^{-3}$
F16	127.40 ± 0.45	$5.01 \pm 2.21\times10^{-3}$	$7.35 \pm 0.09\times10^{-3}$
F18	271.10 ± 0.44	$3.93 \pm 0.09\times10^{-3}$	$5.98 \pm 1.11\times10^{-3}$
F25	129.60 ± 1.76	$2.04 \pm 1.17\times10^{-2}$	$2.56 \pm 2.67\times10^{-2}$
F27	269.80 ± 0.03	$1.97 \pm 1.76\times10^{-2}$	$2.03 \pm 2.22\times10^{-2}$
F34	130.40 ± 0.67	$1.67 \pm 0.05\times10^{-1}$	$1.95 \pm 2.37\times10^{-1}$
F36	270.60 ± 1.53	$1.21 \pm 1.11\times10^{-1}$	$1.43 \pm 1.99\times10^{-1}$

*Values are mean ± *SD* (*n* = 3)

Diffusion studies of the films when carried out with diltiazem hydrochloride as the model drug indicated that films were permeable to drug and the drug diffusion followed zero order kinetics (Figure 4). The

permeability coefficient of the drug from plasticized films decreased in the following order PEG400 > PG > > DBP > DBS. The higher permeability coefficients of the drug in case of films plasticized with PG and PEG400 might be due to leaching out of the plasticizer fraction from the films, which might have lead to the formation of small pores and hence high permeability. DB films plasticized with PEG400 showed more permeability to the drug compared to the films plasticized with PG which might be due to the higher water solubility of PEG400 than PG.

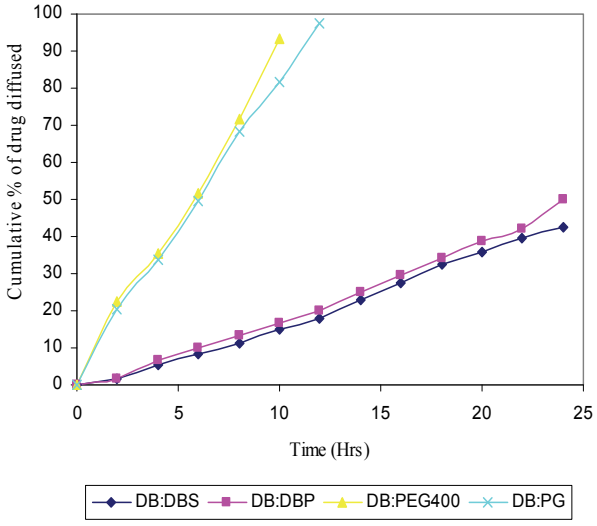

Fig. 4. Diffusion profiles of diltiazem hydrochloride through Damar Batu films.

CONCLUSION

DB films obtained by using the mercury substrate method were smooth, wrinkle free and uniform. All the films were permeable to water vapor and DH. WVTR was observed to be dependent on the film thickness, relative humidity and plasticizer used. WVTR found to decrease as the thickness of the film increased and films plasticized with PG showed highest WVTR. Drug diffusion studies revealed that the rate of the diffusion of the drug through DB films was dependent on the plasticizer used. The permeability coefficient for DH was high in case of films plasticized with PEG400 and low in case of films plasticized with DBS.

It can be concluded from the outcome of the present study that plasticizers have a significant influence on the mechanical properties of the DB films and also on the water vapor transmission and diffusion of the drug through it. DB films plasticized with 30 %w/w DBS yielded tough films with excellent mechanical properties and permeability compared to the films plasticized with other plasticizers. The diffusion of the drug through these films followed zero order kinetics and the drug diffusion was extended over a longer period of time at a controlled rate. Hence, these films may be used as rate controlling membranes for the development of transdermal drug delivery systems. The study is in progress with respect to the skin permeation studies *in vitro* and *in vivo* in animal models.

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