Acta Pharmaceutica Sciencia
52: 31-38 (2010)

Evaluation of gum copal as rate controlling membrane for transdermal application: effect of plasticizers

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Abstract

The effect of plasticizers on the GC films casted using solvent evaporation method were evaluated in terms of uniformity of thickness, moisture absorption, water vapour transmission, tensile strength, percentage elongation, folding endurance and drug permeability characteristics. Tensile strength of films plasticized with DBP was more compared with other plasticized films. Drug diffusion through the free films followed zero order kinetics and Water vapour transmission decreased with increasing the film thickness. The films plasticized with PEG400 showed higher permeability for the drug as compared with other films. Diffusion of drug through the GC films containing 30 %w/w DBP was extended over a longer period of time at a controlled rate. Different type of plasticizers can be successfully used to modulate the drug release as desired from the GC films.

Key words: Permeability, gum copal, dibutyl phthalate, transdermal delivery.

Introduction

The usefulness of the film forming polymers in drug delivery system is well established. Polymers are the youngest members of the materials family and natural polymers have many advantages over the synthetic polymers generally because they are nontoxic, less expensive and globally available. The Current research on film forming polymeric systems holds considerable promise for the exploration of film formers of natural origin. GC occurs in large variety of hard, natural resins produced from a large number of different tree species from many parts of the world - Africa, Asia and South America. Today, most copal of commerce originates from *Agathis* species Family Araucariaceae of Southeast Asia1 (Riyanto 1980, Conelly 1985).

Agathis is the most tropical of all conifers. The copal yielding species are very tall trees, up to 60 m high, often with a near-cylindrical bole (Bowen and Whitmore 1980a, b). Copals are also obtained as fossil resins from Zaire and Zanzibar. Copal occurs in pieces of very varying size and of pale yellow to deep reddish brown or greenish red colour. It is usually transparent or semitransparent and consists of trachylolic acid (80%), associated with isotrachylolic acid (4%) and copal resene (6%) along with volatile oils and bitter principles etc. It is practically insoluble in water and soluble in almost all organic solvents. This property of GC propelled us to evaluate it as a rate controlling membrane for transdermal application. However GC films casted from its chloroform solution were very much brittle that the plasticizer has to be used. The plasticizer reduces the brittleness, improve flow, impart flexibility, and increase toughness, strength, tear resistance, and impact resistance of the polymer.

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As the permeability of drug through polymeric film depends upon the characteristics of the polymer, casting solvent and plasticizer used (Spitael and Kinget 1977, Crawford and Esmerin 1971), here in the present work we made an attempt to evaluate the effect of DBP and two hydrophilic plasticizers, PEG400 and Glycerol on the films physicomechanical properties as well as its drug permeation performance.

Materials and Methods

GC was purchased from Innovative marketing services, Mumbai, India, VH was obtained as a gift sample from Alembic Pharmaceuticals, Vadodara, India, Dibutyl Phthalate and was procured from Morflex Inc., Greensboro, NC., Polyethelene glycol 400 and Glycerol were purchased from Loba chemie, Mumbai, India and Chloroform was purchased from SRL, Mumbai, India. Other chemicals used were of AR grade.

Methods

Preparation of GC films: Free films of GC were prepared using 10% w/v solution in Chloroform on the mercury substrate using solvent evaporation method (Mundada and Shrikhande 2008). To evaluate the effect on the film characteristics, plasticizers like DBP, PEG400 and Glycerol were added at 30 %w/w, 15 %w/w and 40 %w/w (based on the total weight of dry polymer) concentration respectively in the polymer solution. Required quantity of GC was dissolved in the chloroform and sonicated using ultrasonicator to get uniform polymer solution. After the addition of the required quantity of plasticizer, the polymer solution was poured in the glass bangle of 6.2 cm diameter placed on the mercury surface in the petridish. Casted films were dried at a room temperature for 24 h. Controlled evaporation of the solvent was achieved by placing the inverted funnel over the petridish containing mercury. Free films of GC with different thicknesses were prepared by changing the casting volume of the polymer solution. 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 GC were then evaluated for thickness uniformity, mechanical properties, folding endurance, moisture absorption, and water vapor transmission rate and drug permeability characteristics.

Thickness uniformity: The thickness at three different points along the length of the film was determined using thickness gauge (Oswa scientific, Ambala, India). The test was carried out in triplicate.

Mechanical characterization of the GC films: The casted films after drying were carefully cut into film strips (length 40 mm x width 20 mm) and investigated for the mechanical properties like tensile strength, percent elongation and young's modulus 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 (ASTM Standards, 1995). Measurements were made at a crosshead speed of 10mm/min and gauge length of 50 mm at 50% relative humidity and 25°C temperature. For each film specimen all the parameters were determined in triplicate.

Folding endurance test: Folding endurance test was carried out by folding the films at the same point number of times till it breaks (Ubaidulla et al. 2007). The test was carried out to check the efficiency of the plasticizer and strength of the film prepared using varying concentration of the plasticizers. The test was carried out in triplicate.

Moisture absorption studies of GC films: GC films containing DBP, PEG400 and Glycerol showing maximum thickness were selected for moisture absorption studies. 25 x 10 mm^2 strips of films were used for percent moisture absorption studies. Strips in tared petri dishes were transferred to glass desiccators maintained at controlled relative humidities of 43 and 93 % respectively. Saturated solution of potassium carbonate and potassium nitrate were used respectively to get the required relative humidity in the

chamber (Patel et al. 1964). Accurately weighed film specimen were placed in various RH chambers and removed periodically and weighed until two consecutive readings were same. Percent Moisture absorption was calculated using the following formula:

$$\text{Percent Moisture absorption} = \frac{\text{Final Wt.- Initial Wt.}}{\text{Initial Wt.}} \times 100$$

Water vapor transmission rate studies: GC films containing DBP, PEG400 and Glycerol with minimum and maximum thickness were selected for water vapor transmission studies. The experiment was carried out using the permeation cell consisting of a glass body (2.25 cm internal diameter x 8.0 cm height) and a cup with opening of 23.4 mm diameter (test area 4.17 cm^2). The body and the cup of the cell were held in place with the help of three screw clamps. The polymeric films of the appropriate dimensions were cut and mounted on the permeation cell to determine the water vapor transmission rate (Sprocel et al. 1990). To provide effective surface area for water vapor transmission, the film under investigation was tightly clamped between cup and body of the permeation cell. The RH was maintained at 43% and 93%. The charged cells were weighed and transferred to the desiccators maintained at 0% RH. The cells were removed and weighed at regular time intervals 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 has been used to determine the water vapor transmission rate (Utsumi et al. 1961). Utsumi's equation taking Film thickness into consideration is given as,

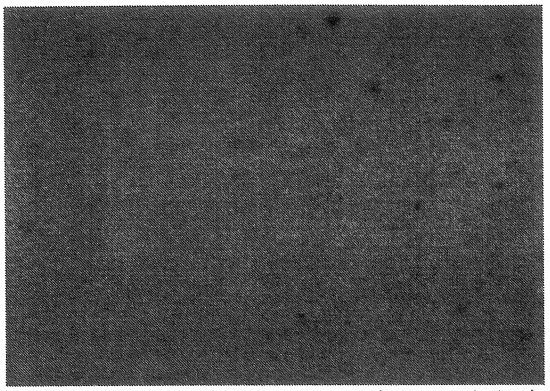
$$Q = \frac{W \times L}{S}$$

Where, W = gms of water transmitted per 24 h., L = Film thickness (cm), S = surface area (cm^2), Q = Water Vapor Transmission ($g.cm/cm^2$)/24 h.

Drug diffusion and permeability studies: Non jacketed bi-chambered donor receiver compartment model (Modified Franz diffusion cell) with the diffusional area of 4.90 cm^2 was used for these studies. Diffusion of verapamil hydrochloride was studied using GC films. The cell consists of two compartments, namely donor and receptor, with 20 mL capacity each. Double distilled water was used as the receptor fluid. The polymer film of appropriate dimensions was sandwiched between the two compartments. 10 mL of drug solution (2% w/v) was poured into the donor compartment. The receptor fluid was agitated using star head magnet and a temperature of 37 ± 1^0C was maintained by placing the cell on the magnetic stirrer with hot plate (Remis Equipments, Mumbai). Periodical samples (1 mL) were collected through the sampling port and drug content was assayed spectrophotometrically at 229 nm after suitable dilution of the withdrawn sample. After each sampling, an equal volume of double distilled water solution prewarmed to 37 ± 1^0C was added to maintain the constant volume of the receptor fluid.

Results and Discussion

Film forming polymers are the indispensable part of the transdermal drug delivery systems. GC is a pale yellow transparent crystalline material with softening point range of 79-82 ^0C. The glass transition temperature of GC was found to be 38.79 ^0C. Solubility studies of GC revealed that it is hydrophobic in nature and hence here we made an attempt to evaluate GC as a rate controlling polymer for transdermal application.



Photograph 1. GC free film surface bright field microscope photograph (Leitz Labor Lux S Microscope, Germany).

Photograph shows the surface of GC film taken using Bright field microscope with CCD camera (Leitz Laber Lux S Microscope). Verapamil hydrochloride owing to its low molecular weight (491.07) and low melting point (1440C) is suitable candidate for transdermal drug delivery and selected as model drug in the present study. Plasticizer addition to the polymeric solution was necessary as the GC films without plasticizer were very brittle and difficult to handle. The plasticizer will interpose itself between the polymer chains and interact with the forces held together by extending and softening the polymer matrix (Entwistle and Rowe 1979). These are incorporated into the films to improve the film properties. In the present study we tried DBP as hydrophobic plasticizers and polyethylene glycol 400 (PEG400) and glycerol as hydrophilic plasticizer. GC films prepared using DBP were transparent as that of unplasticized GC films whereas the films prepared with PEG400 and glycerol were hazy and opaque in the appearance. 10 %w/v GC films were prepared with DBP (30 %w/w), PEG400 (15 %w/w) and Glycerol (40 %w/w) (concentration based on the total weight of the dry polymer) were smooth and flexible. Films prepared with low and high concentration of the plasticizer were found to be tacky and brittle respectively. Thickness of the films prepared using solvent evaporation method on mercury substrate was found to be very much uniform as evident by the low value of standard deviation. This proves the efficiency of the method used for film casting. Films of the different thickness were obtained by changing the casting volume of the polymer solution. 5, 7.5 and 10 mL polymer solutions were used to get different thickness films of GC.

Mechanical properties of the GC films (Table 1) revealed that the films plasticized with DBP were tough compared to the other two plasticizers. The tensile strength and the % elongation was high for DBP plasticized films. The GC films plasticized with Glycerol showed moderate % elongation and lowest tensile strength when compared with others.

Table 1. Characterization of the GC free films

Batch code	Plasticizer	Plasticizer (%w/w)	Vol. of casting sol. (mL)	Thickness* (μm)	Folding endurance*	Tensile strength* x 10^8 (dyne/cm2)	% Elongation*
F1	DBP	30	5	52 ± 1.18	29 ± 0.06	2.89 ± 0.03	24 ± 0.04
F2			7.5	67 ± 0.09	27 ± 1.8	2.84 ± 1.16	22.3 ± 1.16
F3			10	81.2 ± 1.5	23 ± 1	2.87 ± 2.11	22.91 ± 0.3
F4	PEG400	15	5	51.1 ± 1.87	19 ± 1.11	2.14 ± 1.18	29.99 ± 1.18
F5			7.5	65 ± 0.04	19 ± 0.45	2.18 ± 0.04	27.76 ± 0.49
F6			10	82.7 ± 2.11	17 ± 0.03	2.19 ± 2.47	27.11 ± 2.22
F7	Glycerol	40	5	52.34 ± 2.4	19 ± 2.37	2.02 ± 0.88	34.33 ± 0.39
F8			7.5	64.44 ± 1.3	19 ± 0.87	2.03 ± 1.19	33.77 ± 2.56
F9			10	80.18 ± 1.9	18 ± 1.21	2.05 ± 0.07	31.97 ± 1.01

* Values are Mean ± SD (n = 3)

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

Table 2 a. Moisture absorption study of GC films

Batch Code	Thickness of the film* (μm)	% Moisture absorption*	
		RH 43%	RH 93%
F3	81.2 ± 1.5	0.88 ± 0.17	0.98 ± 1.17
F6	82.7 ± 2.11	4.37 ± 1.11	6.36 ± 0.91
F9	80.18 ± 1.9	5.93 ± 2.21	7.74 ± 0.03

*Values are Mean ± SD (n = 3)

Moisture absorption study results (Table 2a) revealed that GC films plasticized with DBP F1 showed less moisture absorption which could be due to their hydrophobic nature of polymer as well as the plasticizer. Glycerol plasticized films showed maximum moisture absorption and there was linear relationship between the moisture absorption and the relative humidity. Moisture absorption decreased in the following order Glycerol>PEG400>DBP.

Table 2 b. Water vapour transmission rate studies of GC films

Batch Code	Thickness of the film* (μm)	WVTR (g.cm/cm^2.24h)	
		RH 43%	RH 93%
F1	52 ± 1.18	2.32 ± 0.06 x10^{-3}	2.81 ± 1.17 x10^{-3}
F3	81.2 ± 1.5	2.03 ± 2.76 x10^{-3}	2.23 ± 0.97 x10^{-3}
F4	51.1 ± 1.87	3.38 ± 0.11 x10^{-1}	3.68 ± 0.14 x10^{-1}
F6	82.7 ± 2.11	3.07 ± 0.56 x10^{-1}	3.33 ± 1.66 x10^{-1}
F7	52.34 ± 2.4	4.42 ± 0.36 x10^{-1}	4.77 ± 0.89 x10^{-1}
F9	80.18 ± 1.9	3.89 ± 1.32 x10^{-1}	4.13 ± 1.36 x10^{-1}

Water vapor transmission rate (WVTR) study results (Table 2b) indicated that the hydrophilic plasticizers were responsible for the higher WVTR. The amount of water vapors permeated through the GC films plasticized with DBP was lowest when compared with the other plasticizers. The plasticizers in the order of their increased WVTR was as follows DBP<PEG400<PG. Thickness of the films also changes the rate of water vapor transmission. It was found that WVTR decreases as the thickness of the film increases. Further it was clear from the results that increase in the humidity leads to increase in the water vapor transmission as reported in the literature (Lachman and Drubulis 1964).

Diffusion studies of the films was carried out using verapamil hydrochloride as the model drug (Figure 1) and the data obtained indicated that films were permeable to drug and drug diffusion followed zero order kinetics.

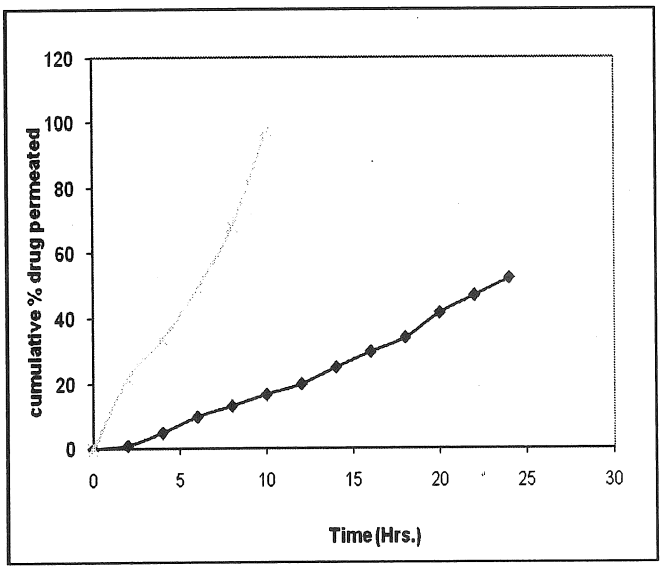


Figure 1. Diffusion profiles of verapamil hydrochloride through GC films
---x-- GC+15 %w/w PEG400, ---▲--- GC+ 40 %w/w Glycerol, ---♦--- GC+ 30 %w/w DBP

The diffusion rate of drugs increased with decreasing film thickness in all the cases. The permeability coefficient of the drug from plasticized films decreased in the following order Glycerol > PEG400 > DBP. The higher permeability coefficients of the drug in case of films plasticized with Glycerol and PEG400 might be due to hydrophilic nature of the plasticizer. Leaching out of glycerol and PEG400 fraction from the surface of the GC films might have lead to the formation of small pores and hence high permeability for the drug.

Conclusion

GC films casted in chloroform using solvent evaporation method were smooth and uniform. DBP at 30 %w/w, PEG400 at 15 %w/w and Glycerol at 40 %w/w concentration yielded tough films which were easy to handle compared to the unplasticized GC films. All the films were permeable to water vapour, and drug. WVTR was dependent on film thickness, relative humidity and plasticizer used. As the film thickness increased the WVTR was decreased, Films plasticized with glycerol showed the highest WVTR. Drug diffusion studies revealed that the rate of diffusion of drug through the GC films was dependent on the plasticizer used. The permeability coefficient for drug was high in case of films plasticized with hydrophilic plasticizer and low in case of films plasticized with hydrophobic plasticizer.

It can be concluded from this study that the plasticizers have a significant influence on the mechanical properties of the films as well as on the water vapor permeability and diffusion of the drug. The diffusion of the drug through these films followed zero order kinetics and 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.

Acknowledgement

The authors gratefully acknowledge V.N.I.T. Nagpur (India) for providing the Instron facility. We also thank Head, University Department of Pharmaceutical Sciences, Nagpur University, Nagpur (India) for providing the facilities. Auhtor (Atish Mundada) would like to thank Mr. Sharad C. Chandak, for the financial support during this work.

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Received: 03.12.2009
Accepted: 19.02.2010