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Research Article

Investigation of PEGylated Derivatives of Rosin as Sustained Release Film Formers

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Abstract. The purpose of the present study was to investigate the potential use of two PEGylated derivatives of rosin (PD) as sustained release film forming materials. The derivatives differed chemically by their acid numbers—PD-1 with 120.93 and PD-2 with 88.19. The derivative films were characterized for surface morphology, water uptake-weight loss, angle of contact, water vapor transmission rate, mechanical properties and permeability study. Dissolution of diclofenac sodium (DS) and propranolol hydrochloride (PHL) as model drugs was studied from coated pellets. The films of derivatives with and without plasticizers were smooth and continuous. PD-2 films developed greater numbers of pores when in contact with phosphate buffer pH 6.8. The low weight loss, low angles of contact and high water vapor transmission rate of PD-2 films were related to presence of higher concentration of PEG esters. Higher tensile strength and percent elongation of PD-2 films was due to greater degree of internal plasticization of the derivative. The permeability of films to model drugs propranolol hydrochloride and diclofenac sodium was inversely proportional to the film thickness and dibutyl phthalate concentration in them; the permeability being greatest in PD-2 films containing 10% PEG 200. Dissolution rate of propranolol hydrochloride was higher from the coated pellets. The dissolution data followed zero order, Baker–Lonsdale equation and Hixon–Crowell equation of release kinetics with high correlation coefficients. The mechanism of drug release from these coated systems however followed class II transport (n>1.0). The derivatives investigated could successfully retard release of the model drugs and offers an alternative to the conventionally used polymers.

KEY WORDS: angle of contact; PEGylated derivatives; permeability; release kinetics.

INTRODUCTION

Cellulose and acrylic acid based polymers are the most widely used polymers in pharmaceutical coatings (1–4). Despite their widespread use as film former for aesthetic purpose or for preventing the active medicament from exposure to gastric secretions or for sustaining drug release, careful monitoring of the formulation and experimental conditions are necessary to avoid problems during processing. Inherent nature of the polymers may result into undesirable tackiness (5) while incorrect coating composition may lead to film defects (6) or incompatibility with active medicament (7). Naturally occurring materials and their derivatives like starch acetate (8), binary mixtures chitosan and amylose cornstarch (9) and chitosan citrate (10) have shown to possess excellent film forming property.

Rosin or colophony is a clear, pale yellow to dark amber, thermoplastic solid resin obtained from the trees of Pinus species (Family *Pinaceae*). The major components of rosin include resin acids represented by general formula $C_{20}H_{30}O_2$ that are present as free acids or dimmers or as anhydrides (11, 12). Depending upon their composition, ester derivatives of resin acids provide sustained or controlled release of active medicaments from the coated substrates (13–16). Rosin was reacted sequentially with polyethylene glycol 200 (7.5, 15 and 25% *w*/*w*) and maleic anhydride (7.5% *w*/*w*) at elevated temperatures in presence of zinc dust to form ester-adduct derivatives PD-1, PD-2 and PD-3 respectively. These derivatives were characterized for their physico-chemical properties like molecular weight, acid number, solubility, glass transition temperature, film-forming property etc. (17).

The derivatives formed clear transparent amber colored homogenous films when cast on mercury substrate. The water vapor permeability of these films was very low for free films (<32 g cm/cm^2, 24 h$\times 10^{-5}$) and for films applied on a hygroscopic material- potassium nitrate (<11 g cm/cm^2, 24 h$\times 10^{-7}$). This property of the films to resist water vapor permission prompted us to investigate their usefulness as films for sustained drug release. PD-3 when applied to tablet surface as film former required very strict controlled temperature and humidity conditions and higher amount of talc was required as detackifier. However, presence of high concentration of talc as suspended particles in the film interferes with its properties (18). Also the lower Tg (~26 °C) of this derivative resulted in sticking of substrates to each other on standing and therefore was excluded from the present study.

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PD-1 and PD-2 with glass transitions temperatures (Tg) of 42.42 °C and 38.10 °C respectively were selected to investigate their sustained release film forming property.

The present study was undertaken to investigate the potential use of the partially PEGylated rosin derivatives as sustained release film formers. Free films of the derivatives were investigated for water uptake-weight loss study, water vapor transmission rate, mechanical properties and drug permeability study. Core pellets and tablets were prepared using conventional excipients taking diclofenac sodium and propranolol hydrochloride as model drugs. Derivatives were coated onto these substrates by spraying their solutions in acetone over the cascading bed. Drug release from these substrates was used as a measure of drug release retarding property of these derivatives.

MATERIALS AND METHODS

Materials

Polyethylene glycol derivatives PD-1 and PD-2 were synthesized and characterized in our laboratory. Propranolol hydrochloride (PHL) and diclofenac sodium (DS) were received as gift samples from Sun Pharmaceuticals Industries Limited, Vadodara, India and Zim laboratories, Nagpur, India. All the other chemicals and reagents were of analytical grade and were used as received.

Free Films of Derivatives

Solvent casting method on mercury substrate was used to prepare the free films of derivatives. Solutions of derivatives in acetone (30% *w*/*v*) were poured onto mercury placed in a Petri dish and allowed to dry in a closed glass cabinet having a small hole at the top. The films were cut using a sharp razor and placed in desiccators maintained below 10% RH (using concentrated sulfuric acid) till further study. Films containing plasticizers—polyethylene glycol 200 (PEG 200), dibutylphthalate (DBP), triethyl citrate (TEC), tributyl citrate (TBC), glycerol (GC) or propylene glycol (PG) were prepared by dissolving them in derivative solutions and casting on mercury.

Water Uptake and Weight Loss Study

Pre-weighed free films of the derivatives (~150 mg; W_i) were placed in separate boiling tubes containing 20 ml probe liquid phosphate buffer pH 6.8. These were placed in a mechanical shaker bath (set temperature 37±0.5 °C) and slowly agitated. Samples were withdrawn at predetermined time intervals and the excess surface water wiped by tissue paper and re-weighed (W_u). These samples were placed in desiccators maintained below 10% RH using concentrated sulfuric acid at 25 °C for 10 days and weighed again (W_l). The percent water uptake and percent weight loss by the films was calculated from their weight differences.

Angle of Contact

Wettability of derivative films was studied by measuring their contact angles with water drop. Glass slides were dipped in their solutions (with or without plasticizers) and dried at 40 °C for 24 h to form uniform films. These slides were mounted on a horizontal platform; drops of the probe liquid, phosphate buffer pH 6.8 (30 µl), were carefully placed onto them. The contact angles were measured at five different locations for five drops using a protractor and a magnifying glass at 10 min interval up to 30 min. The thermodynamics of wetting were computed from the equations mentioned in the literature (19).

Water Vapor Transmission Rate (WVTR)

Thickness of free films of derivatives was determined using a micrometer screw gauge. Films of predetermined thickness were fixed on mouth of the glass vials using silicon wax and aluminum seal. These vials were containing fused calcium chloride (approximately 800 mg in each vial) as desiccant. These vials were kept in desiccators maintained at relative humidity conditions of 43 and 75% at 25±0.5 °C for 24 h. The weight gains of vials indicated the amount of water vapor transmitted through the films (20).

Mechanical Properties of Films

The free films of derivatives were brittle and difficult to handle. Derivatives films with 5% *w*/*w* and 10% *w*/*w* DBP or PEG 200 were tested for tensile properties. Films of 120×20 mm were cut and kept at 25 °C 50% RH 24 h prior to experiment. The mechanical properties were evaluated using Instron (Model 4467, Instron Corp., Canton, MA). The measurements were made at a gauge length of 60 mm and crosshead speed (CHS) of 50 mm/min; samples were evaluated in triplicate.

Permeation Study

This study was carried out in a diffusion cell as shown in Fig. 1. The cell consisted of an 'L' shaped hollow glass tube, A, as the donor compartment. Films under investigation were fixed at one end of the tube, B, using a common adhesive. Saturated solutions of drugs 10 ml (in phosphate buffer pH 6.8) were introduced from the other open end; any entrapped air bubble was removed and sealed with an

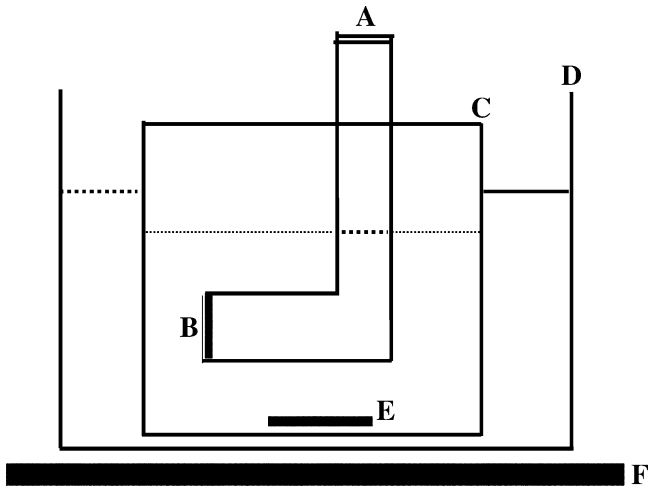

Fig. 1. Schematic diagram of diffusion cell. 'L' shaped hollow tube, *A*, containing drug solution; film fixed to the tube, *B*; closed receptor chamber, *C*, containing receptor liquid; water bath, *D*; Teflon coated bead for stirring, *E* and magnetic stirrer, *F*

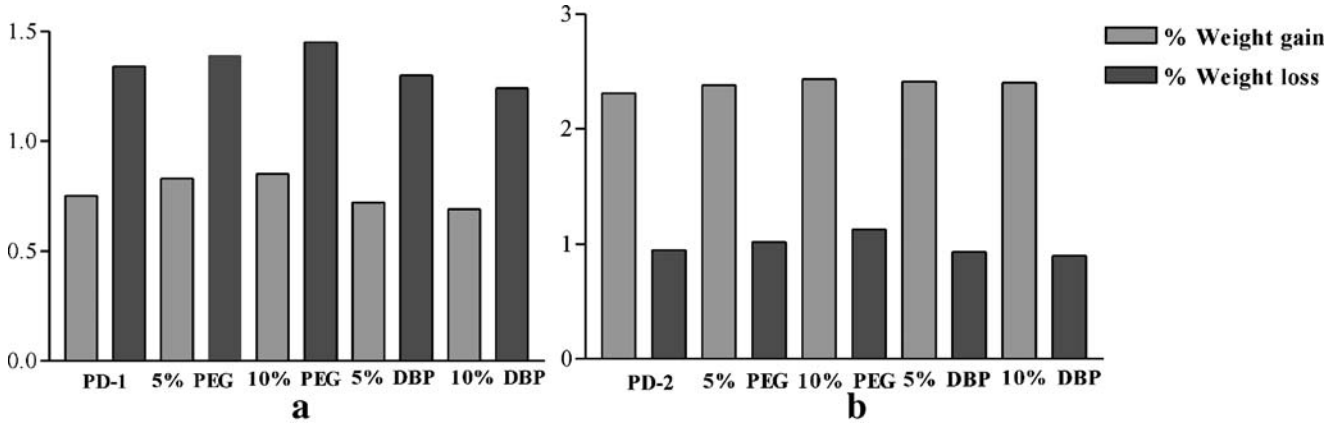

Fig. 2. **a** Water uptake and **b** weight loss of films in phosphate buffer pH 6.8 for 8 h

aluminum foil. The receiver compartment containing 100 ml phosphate buffer pH 6.8 consisted of a closed glass chamber, C, which had an opening at the top that fitted perfectly with the hollow tube of A and a port for sample withdrawal. The level of A into B was adjusted so that the levels of liquids in both the cells were equal. The temperature of the assembly was maintained at 37±0.5 °C using a water bath, D. The receiver compartment was mixed properly with a Teflon coated bead, E, and a magnetic stirrer, F. Samples were pippetted B at predetermined time intervals and replaced with fresh buffer. The rate of permeation of drug across the film was calculated (21).

Preparation of Core Pellets and Tablets

The composition of pellets and tablets was kept same to avoid variations in dissolution studies. The pellets prepared by extrusion-spheronization method composed of drug (10% *w*/*w*), lactose (15% *w*/*w*), microcrystalline cellulose (72% *w*/*w*) and polyvinyl pyrrolidone (PVP K-30; 3% *w*/*w*); the granulation end point was achieved using water as solvent. The wet mass was extruded through a 1.5 mm screen and spheronized using a 25 cm base plate with 2 mm groove width at 750 rpm for 4–5 min (Umang Pharmatech Pvt. Ltd., Thane, India). These pellets were dried in oven at 50 °C for 24 h. The dried pellets of 14–20# fraction were used coating with derivatives.

The core tablets had the composition same as that for core pellets; magnesium stearate (1% *w*/*w*) was compensated for microcrystalline cellulose. The lubricated granules were compressed into tablets at constant pressure using 8.5 mm circular standard concave punches (Manesty, Type-F3, Kilburn & Company, India).

Coating of Derivatives on Substrates

The coating operation was carried out in a conventional coating pan (5 in. diameter) rotating at 30 rpm. Derivative coating solution (30% *w*/*w*) in acetone was applied on the cascading substrate (pellets or tablets) using a 1.0 mm spray gun operating at a pressure of 1.0–1.5 kg/cm^2 from a distance of 10 cm from the bed. The solvent was allowed to evaporate at room temperature as any application of heat resulted in sticking and loss of material to the pan. Talc was sprinkled intermittently to avoid sticking. The coated samples, pellets or tablets, were cut into two halves using a sharp razor. The thickness of coat was measured by observing the cut halves under a microscope fitted with a micrometer eyepiece. Pellets and tablets were coated to get uniform coats of 12–15 and 25–30 μm. This coat thickness corresponded to 5 and 10% *w*/*w* weight gain for tablets and 10 and 15% *w*/*w* weight gain for pellets. Formulations with 5 and 10% plasticizers—PEG 200 or DBP—were coated to get coat thickness of 25–30 μm.

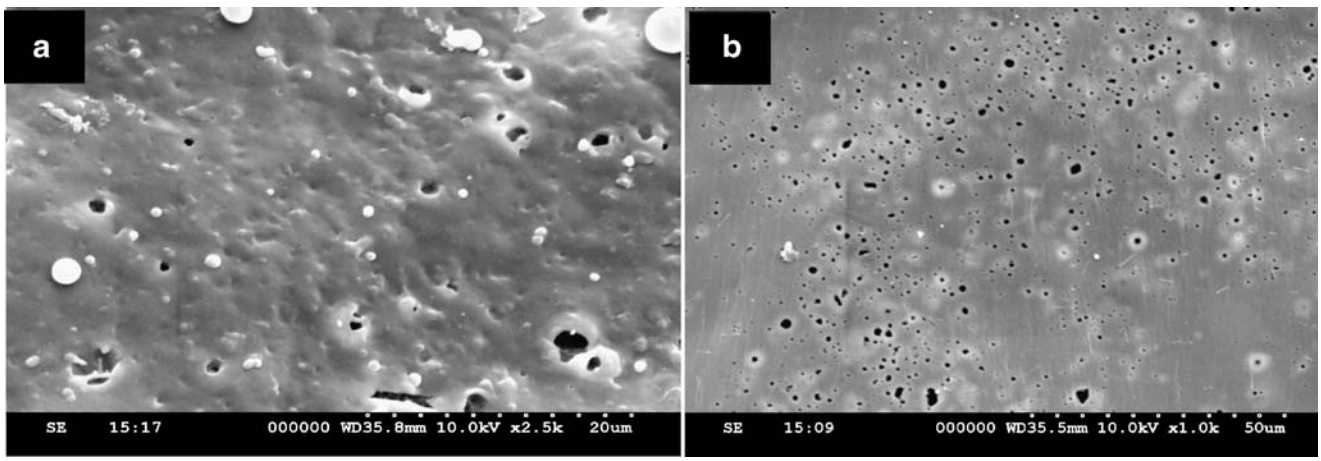

Fig. 3. Scanning electron photomicrographs of **a** PD-1 and **b** PD-2 film after 8 h in phosphate buffer pH 6.8

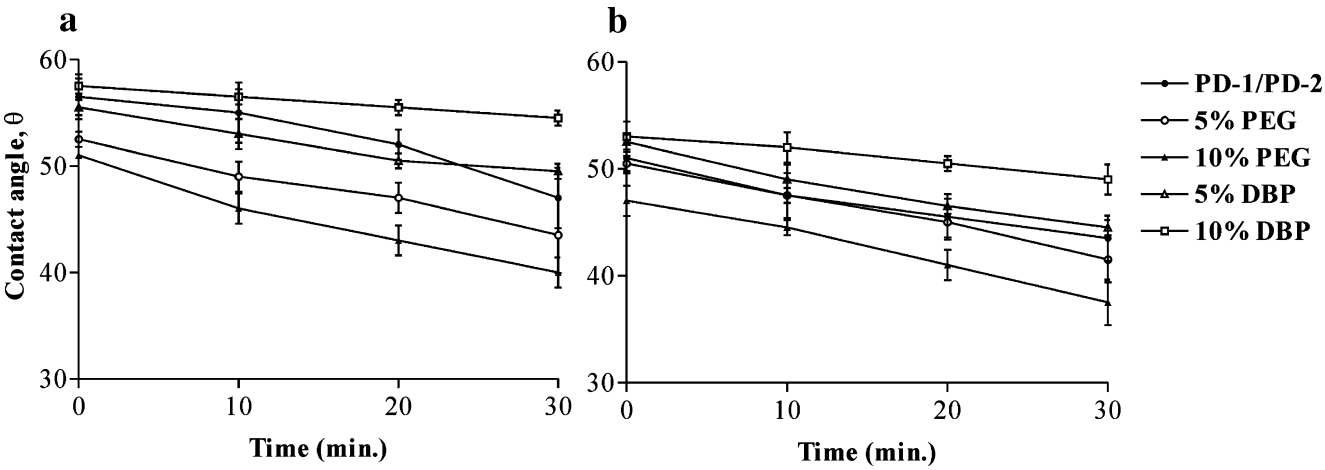

Fig. 4. Angles of contact of phosphate buffer pH 6.8 with films of **a** PD-1 and **b** PD-2 with or without plasticizers

Dissolution Study

For tablets the *in vitro* dissolution study was performed using USP 24 type II (paddle) dissolution test apparatus (Veego 6AD, India). Tablets were placed in the dissolution vessels containing 900 ml phosphate buffer pH 6.8 maintained at 37±0.5 °C and stirred at 75 rpm. Samples were withdrawn at regular time intervals and replaced with fresh buffer.

For pellets the dissolution study was carried out in USP 24 type I (basket) test apparatus.

Coated pellets equivalent to 20 mg drug were placed in baskets and the test run as in the case for tablets. The amount of drug released was determined spectrophotometrically at 276 and 289 nm for DS and PHL respectively.

Release Kinetics

The mechanism of drug release from the delivery devices was determined by using the release models described in literature (22,23).

RESULTS AND DISCUSSION

Derivative Free Films

The films were cast in small glass chambers that were closed after pouring the solution onto the mercury. Once cast, the chamber was saturated with vapors of acetone that escaped through a small orifice provided at the top. This arrangement prevented solvent or solute migration during drying. A change in solvent from acetone to chloroform or dichloromethane rendered the films with large pores and wrinkles on the surface. Chloroform being a relatively poor solvent for the derivatives rendered wrinkles on film surfaces. Dichloromethane cast films on the other hand developed large pores; the solvent evaporated so fast that the saturation step was bypassed. The time required for complete drying also varied with the solvents used. Films cast with acetone took 5–6 days for complete drying (as measured till constant weight) while those with chloroform or dichloromethane took 2–3 days or 10–12 h respectively. The plasticizers used namely PEG 200 and DBP were soluble in derivative solution and formed films of uniform appearance and thickness. The other plasticizers—TEC, TBC, GC and PG mixed well with the derivative solutions but upon casting formed films with large regions of segregations.

Water Uptake and Weight Loss

The results of water uptake-weight loss study of derivative films in phosphate buffer pH 6.8 are shown in Fig. 2. The differences in the behavior of PD-1 and PD-2 films in the probe media are related to their composition; PD-2 contain higher concentration of newly formed esters (17). Presence of more free acids in the derivative resulted in formation of soluble salts that dissolve in the probe media. PD-2 with higher PEG 200 concentration imbibed more water but the weight loss was less due to lower concentration of resin acids (acid number = 88.19 mg KOH). The scanning electron photomicrographs of films after 8 h in phosphate buffer pH 6.8 are shown in Fig. 3. The loss of material from film of PD-1 is reflected as pores on their surface. The surface of PD-2 film shows large number of pores (having small diameters)

Table I. Work of Adhesion (Wa), Adhesion Tension (AT) and Spreading Coefficient (SC) for Phosphate Buffer on Film Surfaces

Sample	W_a	AT	SC	Sample	W_a	AT	SC
PD-1	91.04	21.041	−48.95	PD-2	106.77	36.77	−33.22
5% PEG	39.74	−30.25	−100.25	5% PEG	108.85	38.85	−31.14
10% PEG	0.88	−69.11	−139.11	10% PEG	88.66	18.66	−51.33
5% DBP	137.54	67.54	−2.45	5% DBP	106.77	36.77	−33.22
10% DBP	71.54	1.55	−68.45	10% DBP	137.54	67.54	−2.45

All values in mN/m

Table II. Mechanical Property and Vapor Permeability of Selected Samples

Sample	Thickness (μm)	Tensile Strength σ (MPa)	Elastic Modulus (MPa)	Elongation (%)	WVTR (g cm/cm2, 24 h) × 10^{-5}
PD-1, 5% PEG	58 (0.9)	1.59 (0.9)	134.2 (10)	14.5 (3.2)	21.2 (1.2)
PD-1, 10% PEG	61(1.2)	1.23 (0.8)	115.7 (5)	21.2 (2.1)	24.1 (1.5)
PD-1, 5% DBP	60 (0.9)	1.65 (0.4)	146.4 (8)	18.4 (2.2)	20.8 (0.9)
PD-1, 10% DBP	63 (1.0)	1.42 (0.8)	121.1 (10)	26.6 (1.8)	18.4 (2.6)
PD-2, 5% PEG	56 (1.1)	2.34 (0.7)	186.3 (6)	19.4 (1.5)	29.6 (1.5)
PD-2, 10% PEG	59 (1.1)	2.10 (0.9)	164.1 (8)	26.4 (1.8)	33.4 (1.1)
PD-2, 5% DBP	58 (0.9)	2.41 (0.6)	193.7 (12)	23.8 (2.1)	28.7 (0.9)
PD-2, 10% DBP	60 (1.0)	2.16 (0.8)	177.9 (11)	29.1 (2.3)	26.7 (2.4)

SD in parenthesis; n=3–5

along with equal number of white spots formed by higher hydration of the derivative. The PD-1 and PD-2 films therefore undergo erosion in the alkaline media to create pores or channels. Drug release from substrates coated with these derivatives would occur by channel formation and drug diffusion through them (24). Incorporation of PEG 200 as external plasticizer expectedly increased the water uptake and weight loss of films; DBP had the opposite effect due to its hydrophobic property.

Angle of Contact

Wetting is one of the important parameters that govern drug release from a substrate (25,26). The lower angles of contact at all the time points reflects higher wetting of PD-2 surface (Fig. 4). For PD-1 films with plasticizers, W_a and AT varied between large extremes and no conclusion could be derived from these values as shown in Table I. In case of PD-2, though all these values were positive, no correlation could be made with the plasticizer type and their concentration. Complexity of chemical composition of derivatives together with the dynamics of wetting made it difficult to generalize the wetting behavior of these substrates. At the end of study a depression on substrate surface was observed where the drop was placed; the probe liquid favored penetration into the substrate over spreading. The high density of pores on the PD-2 film surface as observed in Fig. 3b could be directly correlated with the high AT values. PD-2 films therefore offer higher penetration of the probe liquid that renders pores on its surface. The SC values for both derivatives and their compositions remained negative suggesting less favored spreading.

Water Vapor Permeability and Mechanical Property

The water vapor permeability and mechanical properties of selected samples are as shown in Table II. The permeability of a polymer film for water vapor depends upon the number of polar or hydrophilic groups present in it (27). PD-2 with low acid value (and therefore higher ester value) contains higher concentration of PEG 200 as internal plasticizer. Presence of this molecule imparts hydrophilic character (as polar groups) to the derivative films, PD-2 being more hydrophilic than PD-1 as evidenced from contact angle study. PD-2 therefore form films that have higher permeability than those with PD-1. The higher WVTR for all film compositions of PD-2 than the corresponding compositions of PD-1 supports our predictions. The mechanical property of the derivatives studied as tensile strength, elastic modulus and percent elongation had higher values for all films of PD-2 over that of PD-1. These values were higher for films with DBP as plasticizer in either derivative than with PEG 200. The derivatives studied were basically hydrophobic in nature (water solubility< 3mg/ml). DBP being water insoluble gets uniformly distributed throughout the hydrophobic derivative films and interacts well with the derivative molecules. This greater interaction is reflected in the improved mechanical properties of films of their composition. PEG 200 on the other hand being water-soluble interacts

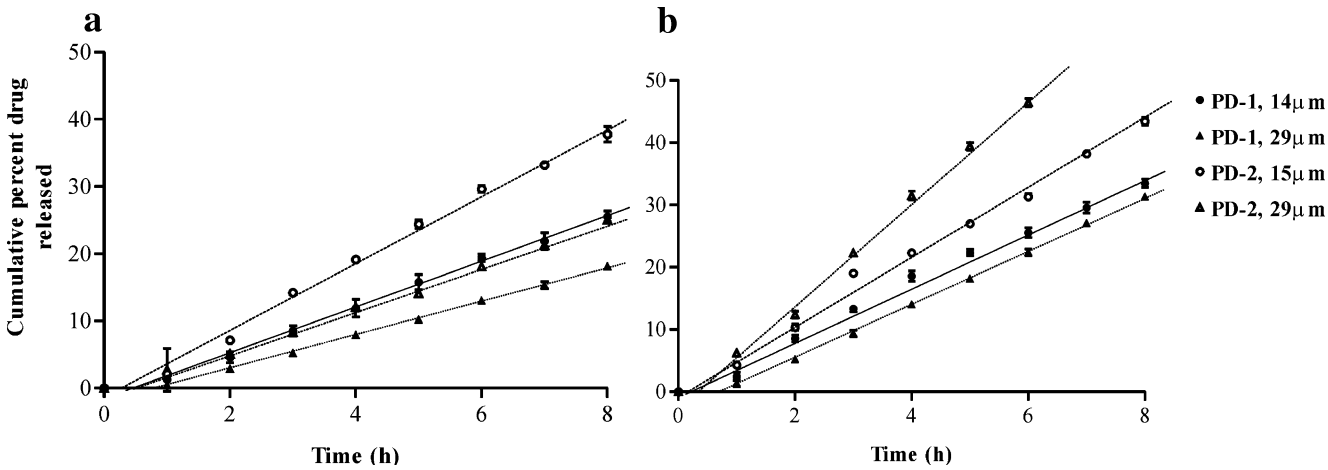

Fig. 5. Dissolution profile of **a** DS and **b** PHL from coated pellets

mainly with the polar regions of the film and therefore remains incompletely distributed in the film structure.

Permeation Study

The 'L' shape of the donor compartment together with lower liquid levels inside ensured that maximum pressure was beard by its horizontal arm as the weight of the liquid. Fluids in the donor and receptor compartments were adjusted to equal heights; this avoided any hydrostatic pressure on the film from either side. The horizontal arm also prevented influence of turbulent flow patterns formed by the magnetic stirrer on drug permeation. The amounts of DS or PHL permeated through selected films were analyzed statistically by linear regression with 95% confidence interval. For all the film compositions the amount of drug permeated increased with time after an initial lag period. The permeability data suggests that the diffusion of drugs across the films were affected by the drug type, derivative type, film thickness and water solubility of the plasticizer used. Any change in the film thickness or type of plasticizer added had similar effect on permeation through films of both the derivatives. Permeation through the plasticizer free derivative films exhibited extremely low permeation rate associated with extended lag period. The permeation rate for both the drugs investigated were higher in PD-2 films than with PD-1 films. Higher density of pores or channels as seen in water uptake-weight loss study together with higher AT (immersional wetting; angle of contact study) supports higher permeation rate through PD-2 films. The drugs permeate through the water filled channels across the films, the permeation rate being higher for the water-soluble drug PHL than DS (sparingly soluble). Increasing the thickness correspondingly increased the channel length and it takes longer time for drug to diffuse to the other side. The diffusion rate with the plasticizers was in reciprocal relationship; while PEG 200 improved the rate DBP tend to retard the same. The higher permeability through PD-2 films could be attributed to its lower glass transition temperature (Tg=38.10 °C) than PD-1 (Tg=42.42 °C); the PD-2 films were in rubbery state having higher permeability than in the glassy state (21,28).

Dissolution Study and Release Kinetics

The dissolution plots of the drugs from the coated pellets show linear curve with initial lag period for DS containing formulations (Fig. 5). A near perfect zero order release was observed with PHL pellets coated with PD-2 ($n \sim 1.0$). The dissolution data from coated pellets was applied to different equations for model fitting. High correlation coefficient values, r, together with least sum of squared residuals, SSQ, were the basis for best-fit model (data not shown for other models). The dissolution profiles of DS and PHL from pellets and tablets were almost similar; the standard deviation in tablets being more than with pellets. Henceforth the dissolution profile refers to the dissolution of drugs from coated pellets. The pellets were coated within the mentioned limits of coating thickness; 10 to 35 μm as below the limit the drug release could not be retarded while above it less than 20% of drug was released in 8 h. PHL having higher solubility (48 mg/ml) in the dissolution media dissolves to greater extent in the media and diffuses out faster than DS (solubility = 18 mg/ml). Increasing the film coat proportionately increases the diffusional path length across the film thereby resulting the decreased drug release. PHL pellets coated with PD-2 containing 10% w/w PEG 200 exhibited maximum drug release. The drug release in this case was a result of higher porosity of the coat coupled with high solubility of drug in the diffusing fluid. Higher interaction of DBP with the derivatives diminishes the number of pores on film surface through which the drug can diffuse out. The waterproofing effect of DBP renders the films less permeable to the dissolution media. The higher correlation coefficients for PHL suggest better compliance to the release kinetics equations. These high correlation coefficients along with lower SSQ values for all models indicate the drug release from the coated system followed more than one mechanism. The coating material comprises a mixture of acids and esters with different properties; the acids being soluble in the media (solubility = 28–30 mg/ml at 25 °C in 24 h) while the esters being more hydrophilic in nature. When placed in the media, the dissolution of the weak acids and added substances and hydration of esters present in the coat occurs simultaneously resulting in increased penetration of the media into the coat. The number of pores formed on the surface as a result of loss of material increases while the coat thickness diminishes with time. The drug release through the coated pellets therefore occurs via formation of pores and thinning of the coat thickness while retaining their shapes at the end of the study. The compliance of dissolution data to Baker and Lonsdale equation (drug release from spherical substrates) and Hixon–Crowell equation (drug release from surfaces undergoing change in their surface area and diameter) supports our theory of drug release through these coated substrates. Pore formation coupled with dissolution of components and low hydration of esters was the mechanism of drug release from PD-1 coated pellets. The drug release from the PD-2 coated pellets were a result of higher number of pores formed on the film surface together with dissolution of soluble components and relatively high hydration of esters.

CONCLUSIONS

The authors strongly recommend characterization of casted polymer films for their physical properties before investigating them for the end product. The investigated derivatives of rosin could be successfully used as sustained release film forming materials. The hydrophilic or hydrophobic nature of the derivative films also strongly influences their properties for sustaining the drug release from the core.

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