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Evaluation of new rosin derivatives for pharmaceutical coating

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Abstract

Rosin and Rosin-based polymers have diversified drug delivery applications achieving sustained/controlled release profiles. In this manuscript, two new Rosin derivatives were synthesized and evaluated for physicochemical properties, molecular weight, polydispersity and glass transition temperature. Plasticizer-free films prepared by solvent evaporation were tested for surface morphology, water vapour transmission and mechanical properties (tensile strength, percent elongation and modulus of elasticity). The films showed low tensile strength and high percent elongation values achieving smooth and uniform surface. The derivatives were further characterized for film coating by evaluating the release of a model drug (diclofenac sodium) from pellets coated with the rosin derivatives as retarding membrane. Drug release was sustained up to 10 h due to 10% (w/w) coat built up with the new rosin derivatives. Increase in coat-built-up further facilitated sustained release from coated forms. Film coating could be achieved without agglomeration of the pellets within a reasonable operating time. The present study proposes novel film forming materials with potential use in sustained drug delivery.

Keywords: Rosin derivatives; Film coating; Pellets; Drug delivery

1. Introduction

The use of natural polymers and their semi-synthetic derivatives in drug delivery continues to be an area of active research despite the advent of synthetic polymers. Natural polymers remain attractive primarily because they are inexpensive, readily available, capable of multitude of chemical modifications and potentially degradable and compatible due to their origin. One such biopolymer, rosin, and also its derivatives have been pharmaceutically evaluated as microencapsulating materials (Sheorey and Dorle, 1990, 1991) and as anhydrous binding agents in tablets (Pathak and Dorle, 1990; Ramani et al., 1996a). They are also used in chewing gum bases and cosmetics. Rosin is a widespread natural product obtained from pine trees. It is composed of approximately 90% rosin acids. The rosin acids are monocarboxylic and have a typical molecular formula $C_{20}H_{30}O_2$. The prominent ones include abietic with conjugated double bonds and pimaric with non-conjugated double bonds. The rosin acid molecules possess two chemically reactive

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centres: the double bonds and the carboxyl group. Being of natural origin, rosin and its derivatives are expected to be biodegradable and biocompatible. Rosin–glycerol ester is biodegradable in vivo (Sahu et al., 1999). They are also widely used for their film forming properties in paints and varnishes and have been found to be useful for enteric and delayed release coating of drugs (Pathak et al., 1985; Pathak and Dorle, 1985). Rosin, itself however does not have very good film forming property. Rosin films break with pressure and are comparatively difficult to handle when compared to known film forming polymers like hydroxypropyl methylcellulose (HPMC). Keeping this in view the present study aims to synthesize and report the film forming and coating properties of two new rosin derivatives synthesized in our laboratory.

2. Experimental

2.1. Materials

Rosin N grade was purchased from Swastik Acids & Chemicals, Nagpur, India. Diclofenac sodium was received as a gift sample from Zim Laboratories, Nagpur, India and used as received. All the other chemicals were of analytical grade and purchased locally.

2.2. Synthesis of rosin derivatives

Rosin derivatives were synthesized in a four-neck glass reactor (2 l) fitted with a condensor, stirrer and temperature control arrangement. Five percent xylene was added as solvent. Rosin derivative-I (RD-I) was synthesized by reacting the ingredients [Rosin: 60%; maleic anhydride: 5%; fumaric acid: 5%; glycerol: 10% and castor oil: 20%] in the glass reactor at 225 °C [1 h], 210 °C [2 h], 200 °C [2 h] and 190 °C [2 h] consecutively. Rosin Derivative-II (RD-II) was synthesized by reacting the ingredients [Rosin: 60%; maleic anhydride: 7.5%; fumaric acid: 2.5%; glycerol: 10% and castor oil: 20%] in the glass reactor at 225 °C [1 h], 210 °C [2 h], 200 °C [2 h] and 190 °C [2 h] consecutively. Synthesis was carried out at different temperatures with a constant stirring of 60 rpm. At the end of the reaction, the product was strained through a fine metal strainer. Xylene was stripped off from final product by heating it under vacuum.

2.3. Characterization of rosin derivatives

The synthesized derivatives were characterized for physiochemical properties like colour, acid value, softening point and relative solubility (Ramani et al., 1996b). Colour was determined visually, while for determination of the solubility, 2 g of material with 50 ml of solvent was placed in an airtight screw-capped tube and agitated for 24 h at 25 °C. Two millilitres of supernatant was withdrawn in a tared dish. Solvent was evaporated by a mild heat and the tared dish was weighed again. The difference in weight gives the amount of material dissolved in the solvent. Different solvents and pH solutions were used for this purpose, and the experiment was repeated five times for each solvent/buffer solution. Buffers of different pH were prepared by the method described in Indian Pharmacopoeia (Pharmacopoeia of India).

Rosin derivatives were evaluated for molecular weight (Mw) and polydispersity (Mw/Mn) by Size Exclusion Chromatography using two consecutive Ultrastyragel® columns (10^4 Å, 3.8 mm × 100 mm, Waters, Milford, MA) coupled to a laser light scattering detector (DAWN-DSP®, Wyatt Technology, Santa Barbara, CA). An interferomeric refractometer (Optilab®, Wyatt Technology) was used as the auxiliary detector. All measurements were done using K-5 type cell with a laser of wavelength 633 nm. Methylene chloride was used as mobile phase with a flow rate of 1 ml/min. Mw and Mw/Mn were computed by ASTRA 7.70.07 software (Wyatt technology).

The glass transition temperature (T_g) was determined by a differential scanning calorimetry (DSC-Shimadzu 50). Approximately 10 mg of the sample was placed in an aluminium pan and scanned over a temperature range of 25–200 °C at the rate of 10 °C/min. Samples were scanned in triplicates. The moisture content was expressed as the percent of weight loss and was determined by thermogravimetric analysis (TGA-Shimadzu-50).

2.4. Free film preparation and characterization

Free films of RD-I and -II were prepared by solvent evaporation technique on a mercury substrate. A 30% (w/v) solution of RD-I and -II was prepared in chloroform and poured in a petridish containing mercury (area of casting: 19.64 cm^2) allowing the solvent

to evaporate for 24 h. Films were stored in desiccators at ambient temperature for 24 h before studied. Film thickness was measured by a thickness gauge (Oswa Scientific, Ambala, India) and recorded as mean of three determinations. Free films [Approx. dry film thickness: 0.2 mm; 12 mm width × 130 mm length] were evaluated for the mechanical properties by a plastic tensile test, performed on Instron Instrument (Model 4467, Instron Corp., Canton, MA) based on ASTM D-412 test (Lin and Lee, 1991). The measurements were made at a gauge length of 50 mm, cross head speed (CHS) of 25 mm/min at 50% RH and 25 °C. The tensile strength, percent elongation and modulus of elasticity were computed with at least three repetitions.

Surface morphology was studied under scanning electron microscope (Stereo Scan 250-MK-III Cambridge, England). Samples were mounted on studs and gold coated for 120 s using sputter coater (Jeol JXA-840A, London, UK).

2.5. Water vapour transmission rate (WVTR) studies

Films were cut into appropriate dimensions and mounted on a permeation cell containing saturated salt solution (excess salt) of potassium acetate, potassium carbonate, sodium chloride and potassium nitrate to provide relative humidity (RH) conditions of 23, 43, 75 and 93%, respectively (Patel et al., 1964). The charged cells were weighed and placed in pre-equilibrated desiccators maintained at 0% RH. The cells were reweighed at the end of 24 h. The amount of water transmitted (W) through the film was given by the weight loss of assembled cell. The WVTR was computed using Utsumi's equation (Utsumi et al., 1961) taking the film thickness into consideration as shown below.

$$Q = \frac{WL}{S}$$

where, W: gram of water transmitted/24 h, L: film thickness (cm), S: surface area (cm^2), Q: water vapour transmission ($g\,cm/cm^2/24\,h$).

2.6. Moisture absorption by free films

Films were cut into 25 mm × 10 mm strips. The strips were transferred to a tarred petridish and transferred to glass desiccators maintained at controlled relative humidities of 23, 43, 75 and 93%, respectively. The relative humidity in the chamber was controlled by the use of different saturated solutions containing excess solute. The film specimens were accurately weighed, placed in relative humidity chambers, removed and weighed again at the end of 14 days. Increase or decrease in weight and changes in physical appearance were than observed. Percent moisture absorption was calculated by using the formula: $a - b/a$; where a: weight of conditioned film; b: initial weight of film.

2.7. Preparation of pellets

Non-pareils were initially coated with a layer of drug and thereafter with membrane of either RD-I or -II. A solution of 6.0 g diclofenac sodium and 0.3 g povidone in 50 ml 95% alcohol (12%, w/v of diclofenac in alcohol) was sprayed onto 1.3 mm non-pareils charged into a Conventional Coating Pan (Retina Ind. Co., Mumbai, India, 50 g charge) using a spray gun to obtain a drug-layered beads. After drying at 50 °C, the drug layered beads were coated with the solution of rosin derivatives until the coat consumption reached 2, 4, 6, 8 and 10% based on weight increase of core pellets (drug layered). 0.25% magnesium stearate as anti-tackiness agent and 5% dibutyl phthalate as plasticizer were added in 10% (w/v) coating solution of rosin derivatives prepared using dichloro methane solvent. With 30 g charge, 70–75 °C supply air temperature, 40–45 °C pellet bed temperature a spray rate of 1.0 ml/min and spray gun position 15 cm from pellet bed surface was used for coating experiments. The coated pellets were transferred and air dried at room temperature.

Whole intact pellets and cross-sectioned pellets obtained by splitting them with a sharp sterile scalpel blade were fixed on a spherical brass stub using adhesive tape. The mounted samples were gold coated for 120 s using a sputter coater under an argon atmosphere before examination under the scanning electron microscope (Stereo-scan 250-MK-III).

In vitro dissolution of coated pellets (equivalent to 50 mg drug) was studied using USP XXIII dissolution apparatus 2 (Veego scientific, Mumbai, India) at 37 °C at a speed of 100 rpm. The test was conducted in 900 ml of simulated gastric fluid (without pepsin,

pH 1.2) for first 2 h followed by 900 ml of simulated intestinal fluid (without pancreatine pH 6.8) upto 10 h. Aliquots were withdrawn at predetermined time intervals and the amount of drug released was monitored by measuring the UV absorbance of filtered solution at 276 nm.

3. Results and discussion

The application of a film coat is commonly used in the preparation of controlled release dosage forms (Knaig and Goodman, 1962; Rosilio et al., 1988; Phuapradit et al., 1995). In vitro characterization of the coating material is essential for optimization of the formulation. Two new rosin derivatives, RD-I and -II, were synthesized and characterized in the present study for film forming and coating properties. The synthesized derivatives were glossy, brownish yellow in colour and soft in nature. The physicochemical properties of RD-I and -II are shown in Table 1. Both RD-I and -II have lower acid values as compared to rosin (155 mg of KOH for rosin) probably due to esterification of rosin acids with glycerol. Rosin acids, abietic and pimaric, react with maleic anhydride and furnaric acid forming adducts viz. maleic rosin and rosin fumarate. Absence of a sharp melting point is indicative of their amorphous nature. A study of relative solubility was carried out in different solvents and under different pH conditions. RD-I and -II are insoluble in water and soluble in all organic solvents tested as shown in Table 2. The solubility increases with increase in the pH of the solution.

Weight average molecular weights (Mw) of RD-I and -II were found to be 1937 and 1456, respectively (Table 3). Both derivatives had a narrow range of molecular weight distribution as indicated by polydispersity index (Mw/Mn) of 1.65 and 1.45 for RD-I and -II, respectively. The glass transition temperature (T_g) is slightly higher for RD-II as compared to RD-I. The low T_g values and the softening point range of the two derivatives indicate their soft nature.

Table 1
Physicochemical properties of rosin derivatives

Parameter	Rosin derivatives	
	RD-I	RD-II
Colour	Dark yellow	Light brown
Acid value (mg of KOH)	94.07	106.27
Softening point (°C)	73–79	83–86

Table 3
Characterization of rosin derivatives

Parameter	RD-I	RD-II
Molecular weight (Mw)	1937	1456
Polydispersity (Mw/Mn)	1.65	1.45
T_g (°C)	72	75
Percent weight loss	2.35	2.95

Table 4
Mechanical properties of free films

Mechanical property	RD-I	RD-II
Thickness (mm)	0.16 ± 0.02	0.15 ± 0.02
Tensile strength (MNm^{-2})	2.52 ± 0.52	1.26 ± 0.23
Percent elongation	561.50 ± 112.21	308.60 ± 79.15
Modulus of elasticity (MNm^{-2})	0.42 ± 0.03	0.44 ± 0.02

Each value is mean ± S.D. of four determinations.

Table 2
Relative solubility of rosin derivatives

Solubility in different solvents			Solubility in different pH solutions		
Solvent	Solubility (g/ml)		pH	Solubility (g/ml)	
	RD-I	RD-II		RD-I	RD-II
Chloroform	0.38 ± 0.032	0.41 ± 0.029	1.6	$7.0 \pm 0.9 \times 10^{-3}$	$6.0 \pm 0.4 \times 10^{-3}$
Dichloro methane	0.30 ± 0.012	0.34 ± 0.042	4.0	$9.3 \pm 1.0 \times 10^{-3}$	$9.0 \pm 0.8 \times 10^{-3}$
Acetone	0.25 ± 0.036	0.29 ± 0.017	6.8	$11.2 \pm 1.4 \times 10^{-3}$	$10.7 \pm 0.4 \times 10^{-3}$
Isopropyl alcohol	0.16 ± 0.027	0.18 ± 0.024	8.0	$15.0 \pm 1.6 \times 10^{-3}$	$11.7 \pm 0.6 \times 10^{-3}$
Ethanol	0.12 ± 0.021	0.13 ± 0.032			
Water	Insoluble	Insoluble			

Each value is mean ± S.D. of four determinations.

Table 5
Water vapour transmission rate of free films of Rosin derivatives

Product	Free film thickness (cm)	Area (cm^2)	Q (g cm/cm^2/24 h) at RH			
			23%	43%	75%	93%
RD-I	0.0166	4.34	6.70×10^{-5}	7.90×10^{-5}	9.20×10^{-5}	10.43×10^{-5}
RD-II	0.0164	4.30	8.40×10^{-5}	8.98×10^{-5}	9.60×10^{-5}	10.45×10^{-5}

Q: water vapour transmission; RH: relative humidity.

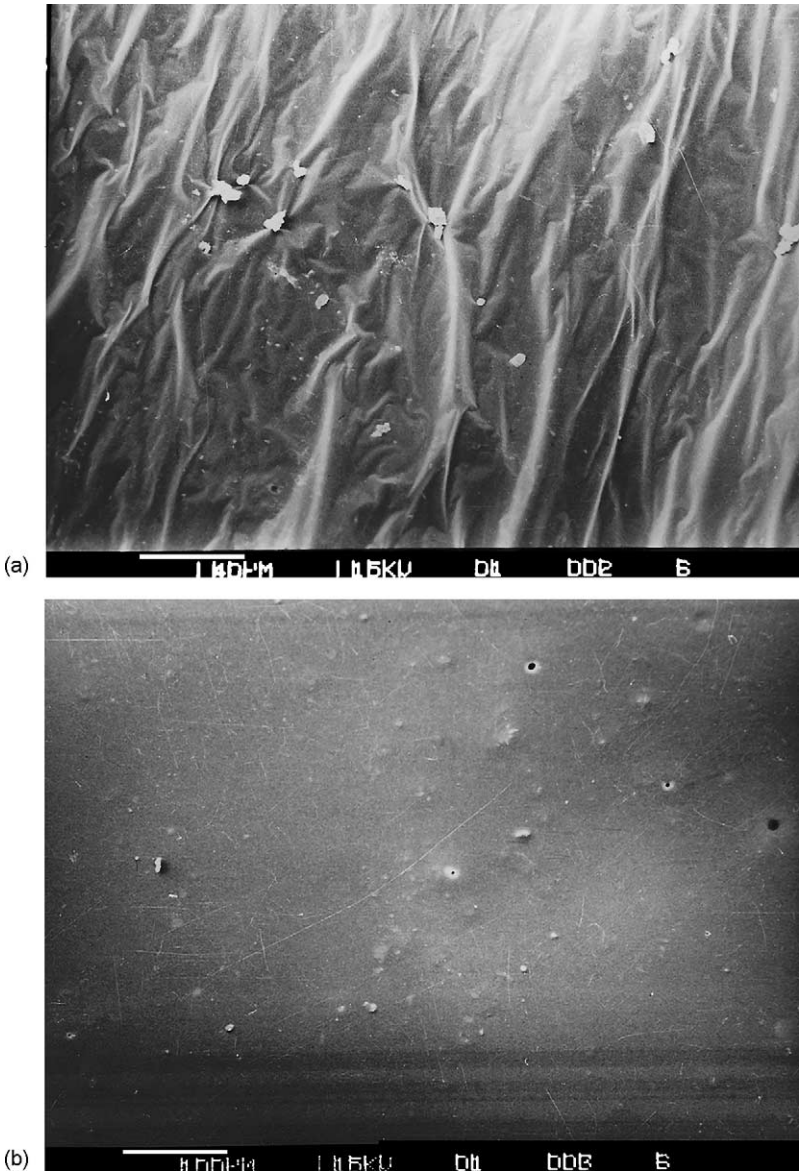

Fig. 1. Scanning electron micrographs of free film: (a) RD-I, (b) RD-II.

3.1. Free film characterization

Mechanical properties of free films are useful to assess the basic film forming property of new materials thereby predicting their usefulness for pharmaceutical coating (Lopez and Bodmeir, 1996). Chloroform was used as solvent for preparation of free films of RD-I and -II as it showed maximum solubility. A 30% (w/v) solution was used for preparation of free films. Results of the mechanical properties are shown in Table 4. Tensile strength is the maximum stress applied to a point at which the film breaks. The risk of cracking of a film increases with low tensile strength as shown with RD-I and -II. Elongation is defined as a measure of the capacity of a film to deform prior to failure (Munden et al., 1963). Thus, low elongation indicates a low deformation capacity of the film and a brittle film structure. The elongation is however very high for the free films of RD-I and -II. Young's modulus is the constant of proportionality of stress to strain and increases with increasing internal stress. The tensile strength results obtained with free films indicate the risk of film cracking. However no sign of cracking in the plasticizer free films of RD-I and -II or coated particles was observed. This may be due to high value for elongation and low value for Young's modulus exhibited by the test films (Lehtola et al., 1995).

SEM pictures of the free films of the Rosin derivatives are shown in Fig. 1. Relatively smooth surface is observed with RD-II while the surface is rough and irregular with RD-I.

As the film thickness is likely to affect the WVT rate, Utsumi's equation has been employed for determination of WVT rate taking the film thickness

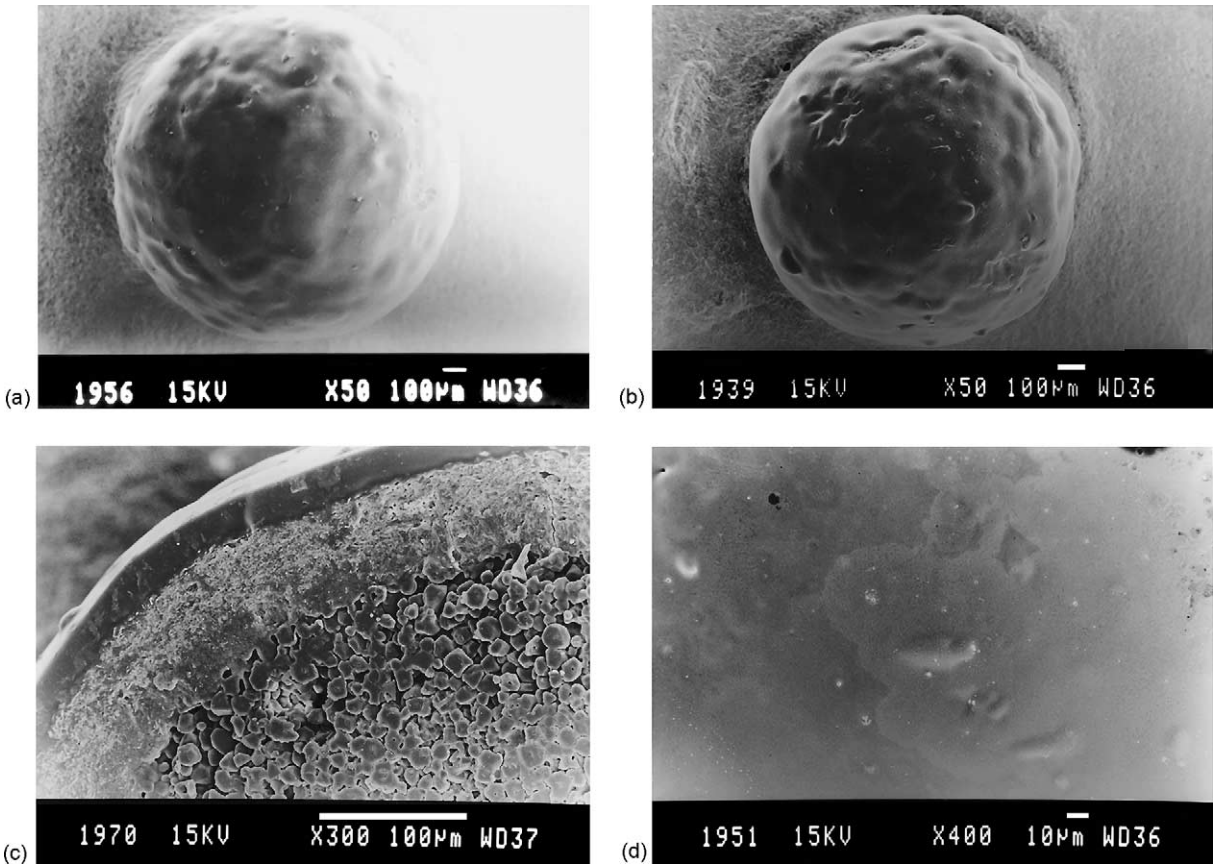

Fig. 2. Scanning electron micrographs of RD-I coated pellets: (a) uncoated pellet, (b) coated pellet, (c) cross-section of coated pellet, (d) surface of coated pellet (10%, w/w, coat built-up).

Table 6
Moisture absorption study of free films

Product	Percent moisture absorbed at RH			
	23	43	75	93
RD-I	0.476 ± 0.11	1.172 ± 0.15	2.680 ± 0.67	4.270 ± 0.83
RD-II	0.910 ± 0.19	1.342 ± 0.28	3.145 ± 0.63	5.188 ± 0.14

Each value is mean ± S.D. of four determinations.

into consideration. The results of WVT rate, which varies inversely with the thickness of film, are shown in Table 5. The rate of WVT was low even at high humidity, viz., 10.43×10^{-5} g cm/cm^2 and 10.45×10^{-5} g cm/cm^2 at 93% RH for RD-I and -II, respectively, which is indicative of strong moisture protecting ability of the film (Utsumi et al., 1961).

Results of the moisture absorption study by free films conducted at different RH conditions are shown in Table 6. Increase in RH increased the moisture absorption. Even at high RH of 75 and 93%, the free films showed nearly 4–5% moisture absorption with slight change in their physical appearance, the films becoming slightly sticky and soft in 14 days.

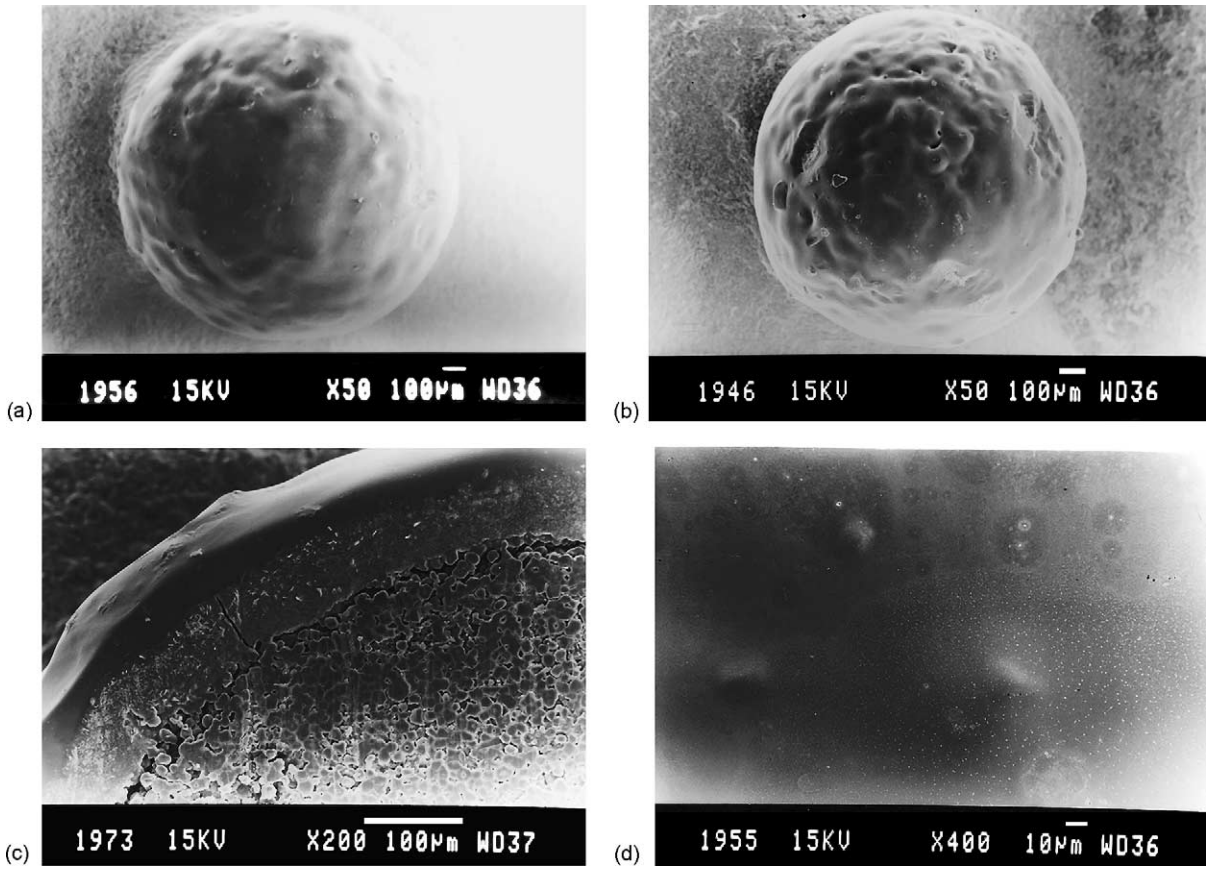

Fig. 3. Scanning electron micrographs of RD-II coated pellets: (a) uncoated pellet, (b) coated pellet, (c) cross-section of coated pellet, (d) surface of coated pellet (10%, w/w, coat built-up).

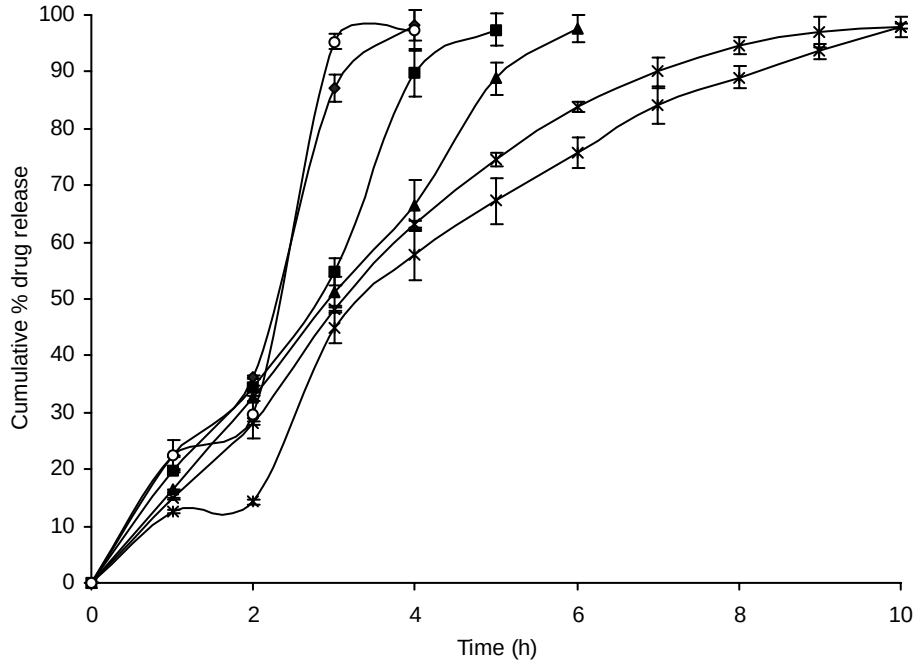

Fig. 4. Cumulative percent drug release ± S.D. from RD-I coated pellets: (◆) 2% (w/w); (■) 4% (w/w); (▲) 6% (w/w); (×) 8% (w/w); (*) 10% (w/w); (○) uncoated pellets.

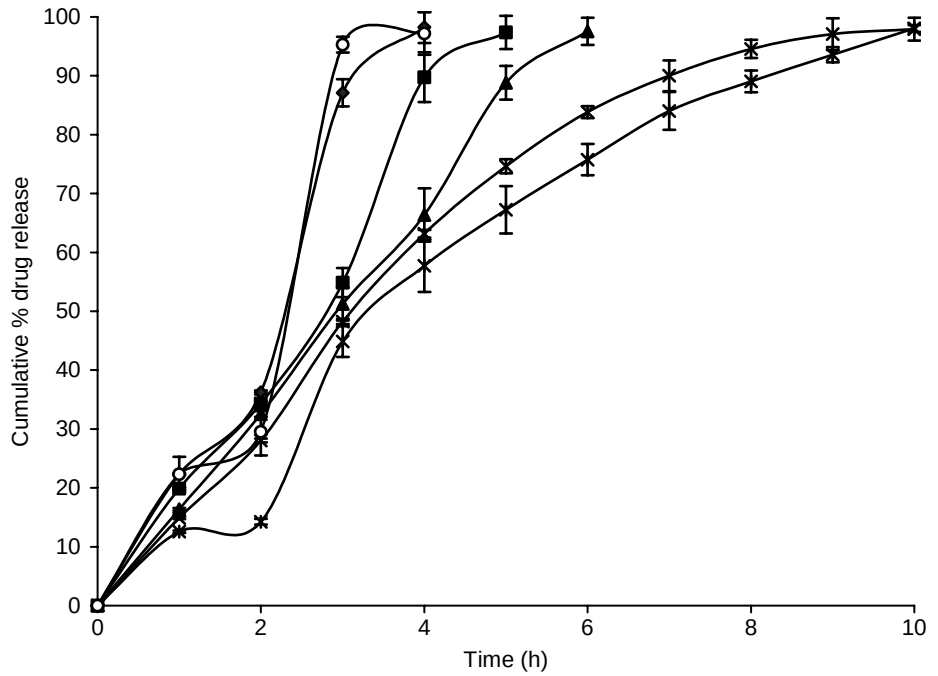

Fig. 5. Cumulative percent drug release ± S.D. from RD-II coated pellets: (◆) 2% (w/w); (■) 4% (w/w); (▲) 6% (w/w); (×) 8% (w/w); (*) 10% (w/w); (○) uncoated pellets.

3.2. Pellet coating

Drug loaded non-pareil seeds (NPS) were coated with RD-I and -II as retarding membranes with different coat build-ups. Scanning electron micrographic views of the uncoated pellet, coated pellet, the cross-section showing distinct core-coat regions and the surface of coated pellet for RD-I and -II are show in Figs. 2 and 3, respectively. Coated pellets (50×) appear as spherical units with smooth and uniform surface. At a higher magnification, the cross-section of coated pellets show distinct uniform layers of coating material (RD-I and -II), drug and NPS. The film coat displays smooth and uniform features, drug layer appears compact and grained separating NPS and film coat, while the NPS is porous granular material. At still higher magnification (400×), the surface of coated pellets appears smooth and homogenous. No sign of cracking or agglomeration was observed in coated pellets, which may be due to low values for Young's modulus due to increased adhesion between film and coating surface (Lehtola et al., 1995). The drug release profile for coated particles is shown in Figs. 4 and 5 for RD-I and -II, respectively. Drug release was sustained up to 10 h with more than 8% (w/w) coat built ups. Nearly 30% of drug was released for first 2 h (pH 1.2) with all the coat built ups except 10% (w/w).

4. Conclusions

Novel natural product based biomaterials are proposed in the present study with potential application in drug delivery. The present study has examined the film forming and coating property of two new rosin derivatives, RD-I and -II. Both the derivatives have shown good film forming property with potential for sustaining the drug release from coated dosage forms. Addition of suitable plasticizers may be attempted to modify/improve the film forming property. Coating of drug layered non-pareil seeds resulted in sustaining the drug release up to 10 h with 8 and 10% (w/w) coat built up without any agglomeration of pellets during coating. These biomaterials may provide economically viable and potentially biodegradable alternatives to the existing range of matrices used in drug delivery systems. The synthesized derivatives therefore merits further study in the design of film-coated sustained drug delivery devices.

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