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A Comparative Study of Aqueous and Organic-Based Films and Coatings of PEGylated Rosin Derivative

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Rosin was partially esterified with polyethylene glycol 400 and reacted with maleic-anhydride to form an ester-adduct derivative. Derivative and native rosin were characterized for physicochemical properties. Aqueous coating system of derivative was developed by ammonia neutralization method. Organic-based films were produced using acetone. Aqueous and organic-based films were comparatively evaluated. Derivative exhibited an excellent coat-forming ability on spherical-units. Aqueous-based film exhibited very high water vapor transmission rate, wettability, water uptake, and leaching at pH 6.8. A 20% w/w aqueous-based coat could sustain diclofenac sodium release for 8 h, whereas, 20% w/w organic-based coat released 20.11% of drug in 8 h. In conclusion, aqueous coating system of synthesized rosin derivative can be developed; however, aqueous-coats are less efficient to retard the drug release rate. Instead, the organic-based coatings can efficiently be used for sustained drug delivery.

Keywords rosin; PEG 400; aqueous-coating; diclofenac sodium; pellets

INTRODUCTION

Rosin is a clear, pale-yellow to dark amber, thermoplastic solid resin occurs naturally in oleoresins of Pine trees (Family-*Pinaceae*). It is composed of 90% rosin acids and 10% non-acidic components. Acid value of rosin was found to be in the range of 169–172. The rosin acids are monocarboxylic acid and have a typical molecular formula $C_{20}H_{30}O_2$. Rosin is insoluble in water and soluble in most of the organic solvents. It is practically non-toxic and has fair biodegradation and biocompatibility characteristics (Satturwar, Fulzele, & Dorle, 2003; Stonecipher, 1976). The glass transition temperature (*Tg*) of rosin is less than 30°C and thus it is difficult to handle and use (Barabde, Fulzele, Satturwr, Dorle & Joshi, 2005). It has film-forming propensity but native rosin films are brittle and break easily upon handling (Nande, Barabde, Morkhade, Patil & Joshi, 2006). However, rosin can be modified into a worthy film former for pharmaceutical applications (Barabde et al., 2005). Modification of rosin also improves its safety and stability; maleic anhydride-pentaerythritol derivative of rosin was found to be four times safe than the parent material in guinea pigs (Enos, Harris & Hedrick, 1968; Stonecipher, 1976). For modification, rosin provides two reactive centers; carboxyl group and double bond (Barabde et al., 2005). Owing to these, rosin participates in esterification and Diels-Alder cycloaddition reactions. Consequently, researchers have synthesized numerous ester-adduct derivatives of rosin (Mandaogade, Satturwar, Fulzele, Gogte & Dorle, 2002; Pathak & Dorle, 1985; Pathak & Dorle, 1986; Pathak & Dorle 1987; Pathak, Nikore & Dorle, 1985; Satturwar, Fulzele, et al., 2004; Satturwar et al., 2002; Sheorey and Dorle, 1994). These derivatives exhibited an excellent film-forming ability and could be used as coating and microencapsulating material particularly for sustained drug delivery. However, only the polyhydric alcohols like glycerol, mannitol, sorbitol, and pentaerythrytol have been employed yet to prepare the ester derivatives of rosin. Also, most of these derivatives were having the complex composition (Barabde et al., 2005), which makes it difficult to propose a precise chemistry of the final product and understand the impact of component of derivative on its physicochemical and film properties. Moreover, all these derivatives were water insoluble and therefore the organic solvents were required to apply them as coatings to solid dosage forms. However, the problems associated with organic solvent-based film coatings have long been recognized (Dashevsky, Kolter & Bodmeier, 2004). In view of this, present study was undertaken with an objective to prepare a new rosin-derivative of simple composition using monohydric alcohol and to develop an aqueous coating system of this derivative. Among monohydric alcohols, PEG 400 was selected because of its excellent plasticizing activity and ester forming ability (Honary & Orafai, 2002; Mishra, Mishra, Namdeo, Jain & Jain, 2002). PEG 400 has

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also been used to develop the polymeric materials having high biological safety (Fujimori, Yomemochi, Fukuoka & Terada, 2002). Rosin and PEG 400 both are non-toxic, biodegradable, and biocompatible and thus the proposed derivative may also be expected to have the similar characteristics. Moreover, PEG 400 has been officially used in PEG ointments (Reilly, 1985), parental dosage forms and as a usual plasticizer in pharmaceutical film coatings (Seitz, Mehta & Yeager, 1990). Notably, polyethylene glycols (PEGs) are available in a wide range of MW; however, MW of PEG exhibits reciprocal relationship with its water solubility and plasticizing activity (Reilly, 1985). The low MW PEGs are hydrophilic, biocompatible, (Grosvenor & Staniforth, 1996) and their plasticizing activity is well accepted (Honary & Orafai, 2002). Moreover, in our pilot experiment, low MW PEGs have shown greater reactivity with rosin as compared to high ones. In previous study, an attempt was also made to PEGylate rosin with PEG 200 and the derivatives were investigated as matrixing agent in tablets for sustained drug delivery (Nande et al., 2006). In present study, PEG 400 was chosen to PEGylate rosin in view of its above-mentioned characteristics specifically in terms of biological safety and wide pharmaceutical use.

During the reaction between rosin and PEG 400, noteworthy decrease in acid value of rosin was observed. This was an indication of rosin esterification. But the final ester obtained (approximately at the end of 5 h) was soft and tacky, which was difficult to handle and investigate. It may be recalled that abietic acid of rosin isomerizes to levopimaric acid above 100°C and levopimaric acid by virtue of its conjugated double bond configuration reacts with maleic anhydride to form a Diels-Alder crystalline adduct (Berry, 1968). Such crystalline adduct usually exhibits the higher softening and melting temperature (Berry, 1968). In this context, when soft PEGylated rosin was treated with maleic anhydride at 160°C for 2 h, a final product with a good handling property could be obtained. Therefore, PEGylated rosin derivative comprised of rosin, PEG 400 and maleic anhydride was synthesized and investigated for the physicochemical and film forming properties. An attempt was also made to develop an aqueous-based coating system of this derivative by ammonia neutralization method. Diclofenac sodium in view of its low oral bioavailability (60%), short biological half life (1.1–4.0 h) and low therapeutic index (Morkhade, Fulzele, Satturwar, & Joshi, 2006) was selected as a drug candidate.

MATERIALS AND METHODS

Materials

Rosin N grade (Swastik Acids and Chemicals, Nagpur, India), maleic anhydride (Upper India Scientific, Nagpur, India), Non-pareil beads (H. V. Homoeopaths, Nagpur, India), PEG 400, potassium dihydrogen phosphate, sodium chloride, potassium nitrate, boric acid, glacial acetic acid, and mercury metal (S.D. Fine Chemicals, Mumbai, India), acetone, chloroform, isopropyl alcohol, hydrochloric acid, and dichloromethane (Qualigenes Fine Chemicals, Mumbai, India), were used. Diclofenac sodium was received as a gift sample from M/s. H-Joules and Co. Ltd., Nagpur, India.

Preparation of Derivative

Rosin (570 g) was placed in a glass reactor (1 L) provided with a stirrer and temperature-controlling device. Rosin was melted and temperature was set to 220°C. To this, PEG 400 (57 g) was added followed by 3 g zinc dust (Zn) with a constant stirring of 100 rpm. From this, an adequate sample was withdrawn hourly to determine the acid value. Reaction was continued at 220°C till the detection of a constant acid value. After getting a constant acid value, the above reaction mixture was allowed to cool to 160°C and maleic anhydride (31.35 g) was added. Reaction was carried at this temperature for 2 h for adduct formation. After adequate cooling, resultant reaction mixture was poured onto a still plate. After hardening, the solid mass was collected, crushed, washed with distilled water and dried. The reaction steps involved in synthesis of rosin derivative (using abietic acid as a model composite) are shown in Figure 1.

Fourier Transform Infrared Spectroscopy (FT-IR)

The IR spectra of rosin and derivative were obtained by FT-IR spectrophotometer (FT-IR-8101 A, Shimadzu, Japan) using KBr pellets. The spectra were obtained by averaging 40 scans at a resolution of 4.0 cm^{-1}.

Characterization of Rosin and Derivative

The color was observed visually and noted. An acid value of rosin and derivative was determined as per the method previously described (Morkhade et al., 2006). In brief, 10 g sample of each was dissolved in 50 mL mixture of equal volume of ethanol (95%) and ether previously neutralized with 0.1 M potassium hydroxide solution to phenolphthalein. After addition of phenolphthalein (0.5 mL), sample solution was titrated with 0.1 M potassium hydroxide until it remains faintly pink after shaking for 30 min. Acid value was determined by the formula, Acid Value = $5.61 \times n/W$, where, n = number of mL of 0.1 M potassium hydroxide required and W = weight in g of substance. Softening and melting temperature was observed by the Herculus drop technique using thistle tube. Solubility was determined at 25 ± 1°C as per the method described in literature (Nande et al., 2006). The molecular weight (MW) and polydispersity were determined by the Gel Permeation Chromatography system (Perkin-Elmer) equipped with refractive index detector (La Chrom Detector L-7490). The glass transition temperature (Tg) was determined by the Differential Scanning Calorimetry (DSC, Mettler-Toledo Star System).

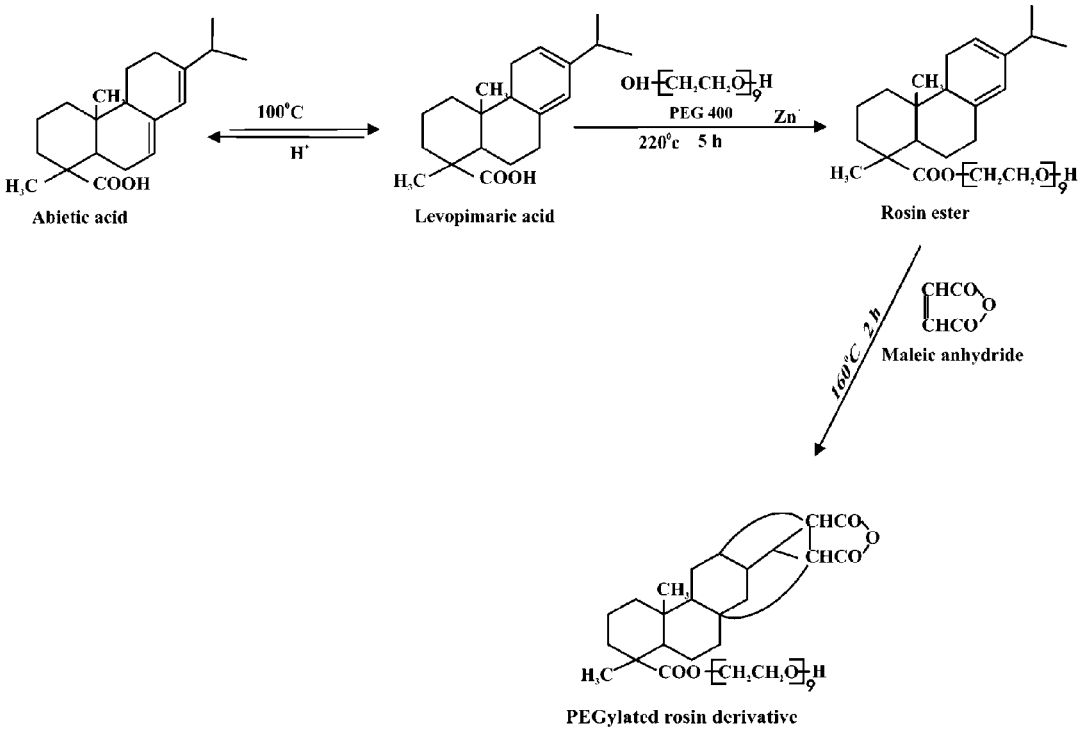

FIGURE 1. Scheme to produce PEGylated rosin derivative (on basis of abietic acid as a model composite).

Preparation of Organic and Aqueous-Based Films

Organic-based films were produced by the solvent casting technique. A derivative was readily soluble in acetone and therefore a 25% w/v solution of derivative in acetone was prepared and poured on mercury in a petri dish (area of film casting: approx. 19.64 cm^2). Films were allowed to dry at 29 ± 2°C for 48 h and stored in desiccators maintained at 0% relative humidity (RH) before use.

A 25% w/v aqueous solution of derivative was prepared by dissolving it in 1.0 N aqueous ammonia with continuous stirring for 2 h (this much time was required to achieve neutral pH of solution). After 2 h, solution was filtered through muslin cloth (mesh 500) and used for film casting. Aqueous-based films were dried at 45 ± 1°C and stored in desiccator at 0% RH before use.

Water Vapor Transmission Rate (WVTR) of Films

The WVTR of aqueous and organic-based derivative films was determined as per the method previously described (Morkhade & Joshi, 2005). In brief, weighed amount of dried calcium chloride (desiccant) was placed in a glass vial. Openings of these vials were then sealed with derivative films of known thickness using a silicon wax. These ready cells were weighed and placed in pre-equilibrated desiccators maintained at 75% and 93% RH. At the end of 24 h, the moisture from the film surface was gently removed with the help of tissue paper and cells were reweighed. The WVTR was calculated by the equation described by Utsumi, Ida, Takahashi and Sugimoto (1961). $Q = WL/S$, where, Q = WVT (g cm/cm^2/24 h), $W = g$ of water transmitted in 24 h, L = Film thickness (cm), S = Active surface area of the film (sq.cm).

Contact Angles on Films

To assess the wetting properties of organic and aqueous-based films, the solid-liquid contact angles of a probe liquid droplet on "air-side" of these films were examined. Phosphate buffer pH 6.8 (prepared as described in Indian Pharmacopoeia 1996, using 0.2 M potassium dihydrogen phosphate and 0.2 M sodium hydroxide solutions) was used as a probe liquid. A probe liquid droplet was carefully placed from a height of 5 mm on a dried film mounted on a glass slide. The contact angle was determined by the direct observations of liquid drop on horizontal film with the help of protractor and a magnifying glass (Morkhade & Joshi, 2005).

Water Uptake and Leaching of Films

The dried films (films dried to constant weight in desiccator maintained at 0% RH) with a weight (W_0) range of 80–100 mg were incubated separately for 1, 2, 3, and 4 h in individual weighing bottles containing 20 mL of phosphate buffer pH 6.8. After incubation, moisture from the film surface was gently

removed by the tissue paper and the weight of the wet film (W_W) was noted. The wet film was dried (to constant weight) at 28 ± 1°C before measuring the weight of the dried film (W_D). The fraction of water uptake (f_1) by the films and the fraction of weight loss (f_2) from the films during the incubation period were calculated by the following equations (Wu, Pan, Chen & Zhang, 2000),

$$f_1 = [(W_W - W_D) / W_D] \times 100\%$$
$$f_2 = [(W_0 - W_D) / W_0] \times 100\%$$

Stability of Ammonia in Aqueous-Film Network

Aqueous-based films were stored in ovens maintained at 30 and 40°C for three months. At the end of three months, IR spectra of film were recorded to determine the stability of ammonia in the film network. The IR spectra were obtained similarly as described earlier in the text.

Preparation of Pellets

Nonpareil beads of 8/14-mesh size were charged into coating pan and diclofenac sodium solution (15% w/v in isopropyl alcohol) containing polyvinyl pyrrolidone (PVP K-30) (1% w/v) was sprayed intermittently over the cascading beads using a spray gun (0.5 mm nozzle). Hot air was blown occasionally to evaporate the solvent. Drug layered pellets were dried at 28 ± 1°C for 24 h and coated with 15% w/v derivative solutions (organic and aqueous-based). The spray rate of the coating solution was 1 mL/min, with the spray gun position at 10–15 cm from pellet bed surface and automizing air pressure of 15–25 psi. The rotational speed of coating pan was set to 40 rpm throughout the study. Sufficient coating material to achieve 10 and 20% weight gain was applied to the drug layered pellets. Talc (0.4% w/w) was sprinkled intermittently as an anti-tackiness agent during coating process.

Morphology of Derivative Coated Pellets

Surface morphology of derivative coated pellets was observed by the scanning electron microscopy (LEO 435 VP, LEO Electron Microscopy Ltd., England).

In Vitro Drug Release

The USP 25 basket type dissolution test apparatus was used to study the drug release profile of pellets. Pellets equivalent to 25 mg of diclofenac sodium were placed in a baskets rotating at a speed of 100 rpm. 0.1 N HCl (pH 1.2) for initial two h and phosphate buffer pH 6.8 for the remaining period was used as a dissolution medium. The volume of medium was 900 mL and the temperature was maintained at 37 ± 0.5°C throughout the study. Hourly, 5 mL of sample was withdrawn and analyzed at 276 nm for drug content by UV-Spectrophotometer (UV-1601, Shimadzu, Japan).

RESULTS AND DISCUSSION

Owing to the steric hindrance of large hydrophenanthrene moiety, the reactions of rosin in which the carboxyl groups are involved take place at either high temperatures (above 200°C) or drastic conditions, usually in presence of the catalysts (Berry, 1968; Finar, 1975). A PEG 400 was therefore treated with rosin at an elevated temperature (220°C) in the presence of Zn (Figure 1). During the reaction between rosin and PEG 400, it was observed that the acid value of rosin decreases proportionally with time until a limiting value due to ester formation. Two successive constant acid values indicate that all added PEG 400 molecules have reacted to form an ester with rosin. This PEG-ester of rosin was then reacted with maleic anhydride at 160°C for 2 h for adduct formation. The degree of esterification and adduct formation in final product was found to be in the range of 29–33 and 11–13%, respectively. To verify the esterification and adduct formation, derivative was characterized by FT-IR spectroscopy. The FT-IR spectra of rosin and derivative are shown in Figure 2. The FT-IR spectra of rosin and derivative depicted the characteristic absorption bands at 1693.7, 2868.5, and 3568.7 cm^{-1} for C = O, –CH and –OH stretching, respectively. This indicates the presence of free carboxyl groups both in rosin and derivative. The absorption band at 1724.6 cm^{-1} for C = O stretching of ester was seen only in derivative and not in rosin, which verifies the presence of ester in derivative. The absorption bands at 1780.5 and 1850 cm^{-1} due to the symmetrical and asymmetrical stretching of C = O of acid anhydrides were present in derivative. As compared to rosin, the prominent absorption band at around 3568.7 cm^{-1} for –OH stretching indicates the presence of –OH groups of PEG 400 in derivative.

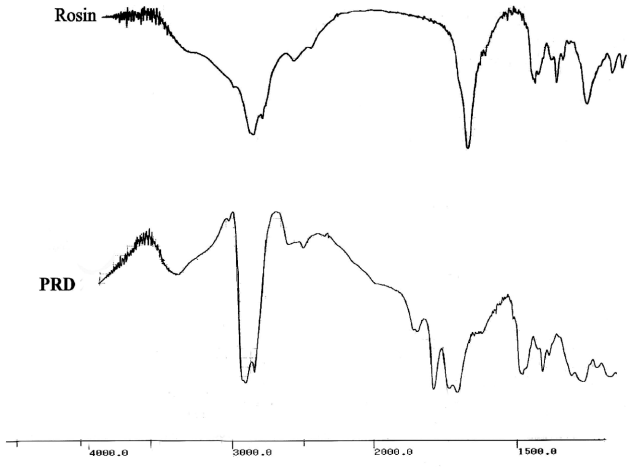

FIGURE 2. FT-IR spectra of rosin and pegylated rosin derivative (PRD).

The physicochemical properties of rosin and derivative are summarized in Table 1. Color of rosin was yellow and that of derivative was brown. Acid value of rosin and derivative was 169.0 and 116.87, respectively. The softening and melting temperature of derivative was 52–54°C and 78–80°C, respectively, which was greater than that of native rosin (Table 1). The higher softening and melting temperature of derivative can be ascribed to the presence of maleic anhydride, which forms a crystalline adduct with rosin. Rosin and derivative both were readily soluble in most of the organic solvents (Table 2). Derivative showed highest solubility in acetone (Table 2). As regards the effect of pH, rosin, and derivative showed greater solubility at alkaline compared to acidic pH (Table 3). This may be attributed to the ionization of free carboxyl groups of rosin as well as derivative at alkaline pH. The result was in agreement with Limmatvapirat et al. (2004), who have stated that shellac exhibits greater solubility at alkaline pH due to the ionization of free carboxyl groups. The MW of derivative was found to be 585, which was slightly greater than that of rosin (380) (Table 1). The higher MW of derivative was due to the presence of PEG 400 and maleic anhydride in its network. Low polydispersity index values of 1.1 and 1.4 for rosin and derivative, respectively, indicate narrow range of molecular weight distribution in both materials. Rosin has T_g less than 30°C and therefore it is difficult to handle and use (Barabde et al., 2005).

TABLE 1
Physicochemical Properties of Rosin and Derivative

Characteristics	Rosin	Derivative
Color	Yellow	Brown
Mw	380	585
P.I.* (Mw/Mn)	1.2	1.4
Tg (°C)	< 30	37.46
Acid value (mg of KOH)	169.0	116.87
Softening point (°C)	48–50	52–54
Melting point (°C)	72–74	79–81

*Polydispersity index.

TABLE 2
Solubility of Rosin and Derivative in Different Solvent

	Solubility (g/mL)	
Solvents	Rosin	Derivative
Acetone	0.48 ± 0.05	1.16 ± 0.06
Dichloromethane	0.71 ± 0.08	0.86 ± 0.05
Chloroform	0.83 ± 0.04	1.12 ± 0.07
Isopropyl alcohol	0.41 ± 0.07	0.66 ± 0.09
Water	Insoluble	Insoluble

Each value is a mean of 4 determinations ± *SD*.

TABLE 3
Solubility of Rosin and Derivative at Different pH

	Solubility (g/mL)	
pH	Rosin	Derivative
1.2	0.002 ± 0.0005	0.002 ± 0.0004
5.0	0.013 ± 0.004	0.018 ± 0.003
6.8	0.019 ± 0.005	0.020 ± 0.002
7.4	0.020 ± 0.008	0.021 ± 0.004
10	0.021 ± 0.003	0.021 ± 0.005

Each value is a mean of 4 determinations ± *SD*.

However, the T_g of derivative was found to be 37.46°C, which indicates its good handling property and the film forming ability at low temperature range.

Preparation of Films

The organic-based films and coatings of derivative were produced using acetone. Previously, the ammonia neutralization method has been used successfully to develop an aqueous coating system of cellulose polymers (Wu, Wyatt & Adams, 1997). Also, Limmatvapirat et al. (2004) have developed an aqueous coating system of shellac by ammonia neutralization method. They initially treated shellac with sodium hydroxide solution to generate more free carboxyl groups, which were then neutralized with ammonium hydroxide to form the water soluble ammonium salts. Acid value of derivative was found to be 116.87, which indicates presence of substantial amount of free carboxyl groups in derivative. An attempt was thus made to neutralize the free carboxyl groups of derivative with ammonia. To produce aqueous solution, 1.0 N ammonium hydroxide solution was prepared in distilled water. The derivative was slowly added to this with constant stirring and 25% w/v solution of derivative was prepared. This solution was poured on mercury in petri dishes. Initially the aqueous film casting was attempted in bangles, however, with time, noteworthy increase in viscosity of aqueous solution was observed. Due to high viscosity, it was difficult to cast aqueous-based films in bangles on mercury substrate. Therefore, aqueous and organic solutions of derivative were poured directly on mercury in petri dish. Area of film casting (approx. 19.64 cm^2) and concentration of derivative were kept constant during film fabrication process throughout the study.

The presence of ammonia in aqueous film was verified by FT-IR spectroscopy. The FT-IR spectra of organic and aqueous-based film are shown in Figure 3. Unlike the organic-based film, the additional peaks at 1560 and 3250 cm^{-1} for N-H bending and stretching in aqueous films verifies the presence of ammonia in its network.

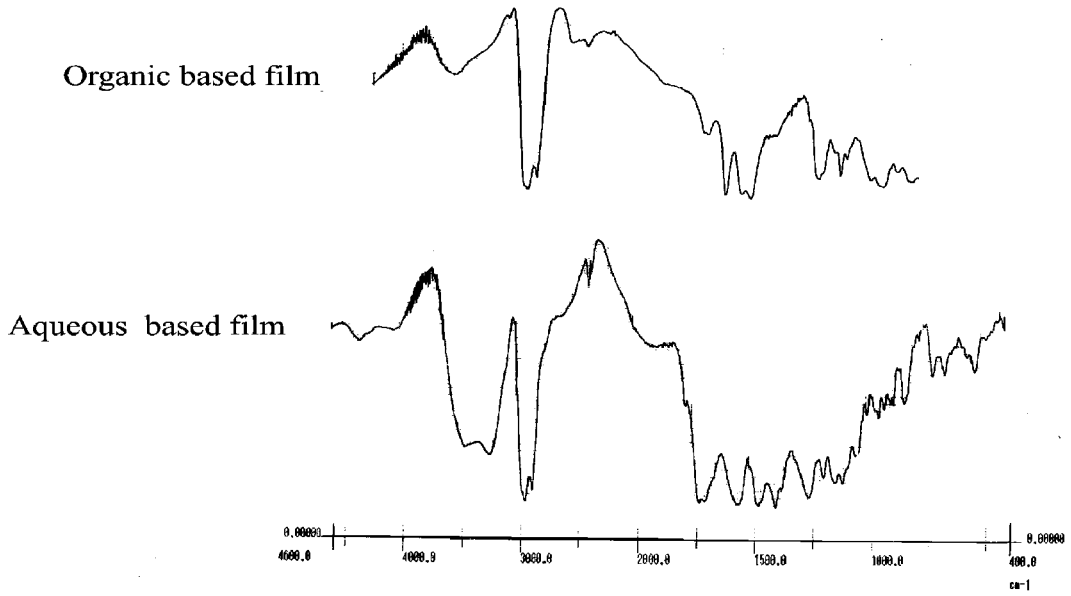

FIGURE 3. FT-IR spectra of organic and aqueous-based films of derivative.

Film Properties

The WVTR data of organic and aqueous-based films is given in Table 4. Aqueous film compared to organic one exhibited very high WVTR at 93% RH in 24 h, which may be attributed to its high hydrophilicity. Also, WVTR of aqueous as well as organic-based film was increased proportionally with RH. This may be due to the high vapor pressure gradient across the film at high RH.

Contact angles of a probe liquid droplet on both films as a function of time are shown in Figure 4. A substantial decrease in contact angle of a probe liquid droplet on aqueous film as compared to organic one was observed. Organic-based film contains few hydrophilic segments (of PEG 400 and maleic anhydride), whereas, aqueous-based film due to the presence of PEG 400, maleic anhydride and ammonium salts of carboxylic acid contains more hydrophilic domains and thus showed higher wettability.

TABLE 4
Water Vapor Transmission Rates of Organic and Aqueous Based Derivative Films

Films	Film Thickness (cm)	WVTR (g.cm/cm^2/24 h) at RH	
		75%	93%
Organic-based	0.042 ± 0.004	15.46×10^{-5}	23.20×10^{-5}
Aqueous-based	0.044 ± 0.003	178.61×10^{-5}	219.06×10^{-5}

Each value is a mean of 3 determinations ± *SD*. Area of film (1.13 ± 0.02 cm^2) was constant in both cases.

At the end of 4 h, the water uptake of organic and aqueous-based film was 8.08 and 319% w/w, respectively (Table 5). An aqueous-based film contains water soluble ammonium salts and thus exhibited very high water affinity. Organic-based films exhibited insignificant leaching in probe liquid in 4 h. On the other hand, aqueous-based films have shown 24.4% w/w leaching in 4 h at pH 6.8 (Table 5). This may be attributed to the loss of ammonium ions from aqueous-based films.

Since ammonia could be lost from carboxylic binding sites as observed in ammoniated films of cellulose acetate phthalate and shellac (Bechard and Leavy, 1995; Limmatvapirat et al., 2004), preliminary study employing FT-IR measurement was conducted to ensure the presence of ammonia in aqueous films over a period of three months. The relative peak intensities of N-H bending and stretching at 1560 cm^{-1}

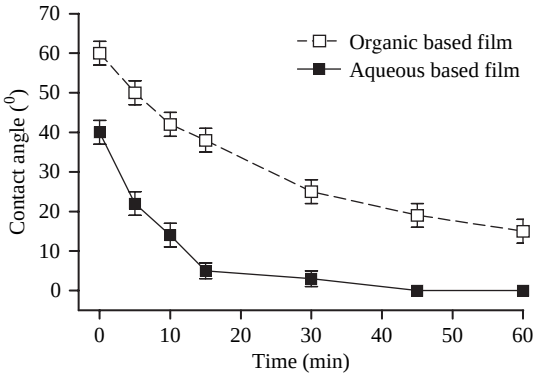

FIGURE 4. Contact angles on derivative-films as a function of time (probe liquid; phosphate buffer pH 6.8).

TABLE 5
Water Uptake and Leaching of Films

	Water Uptake (%)				Leaching (%)			
Films*	1 h	2 h	3 h	4 h	1 h	2 h	3 h	4 h
Org. based	1.66 ± 0.47	3.11 ± 0.71	5.27 ± 0.66	8.08 ± 0.89	0	1.43 ± 0.86	2.61 ± 0.69	3.97 ± 0.97
Aq. based	132 ± 6.5	184 ± 8.2	261 ± 7.3	319 ± 9.6	3.14 ± 0.72	9.20 ± 0.55	15.08 ± 1.64	24.4 ± 2.88

Each value is a mean of 3 determinations ± *SD*. Probe liquid was phosphate buffer pH 6.8.
*The average film thickness was 0.040 ± 0.003 mm.

and 3250 cm^{-1} due to ammonium ion were not altered when these films were dried at 30 and 40°C for 24 h. Also, no significant decrease in peak intensities was noticed when the films were stored at 30°C for 3 months (Figures 3, 5). However, the peak intensity of both peaks was substantially decreased when the films were stored at 40°C for 3 months (Figure 5). Thus, it may be stated that ammonium fairly bounds to carboxyl group in derivative and the high temperature should be avoided during drying process. These results were in accordance with the findings of Bechard and Leavy (1995), Wu et al. (1997), and Limmatvapirat et al. (2004).

Morphology of Pellets

The cross sections of pellets are shown in Figure 6. The organic solvent-based system could produce smooth derivative-coats on spherical units. The surface of aqueous-coat was slightly rough with few cracks; however, both the coatings were continuous, smooth and exhibited the non-pores bulk (cross section), which indicates an excellent coat-forming ability of derivative. At low MW, polymer did not have sufficient entanglement network to form an elastic films. At higher MW, dense packing of polymer chains results in higher interchain attraction to produce adequate entanglement network during film formation, which develops the continuous and flexible

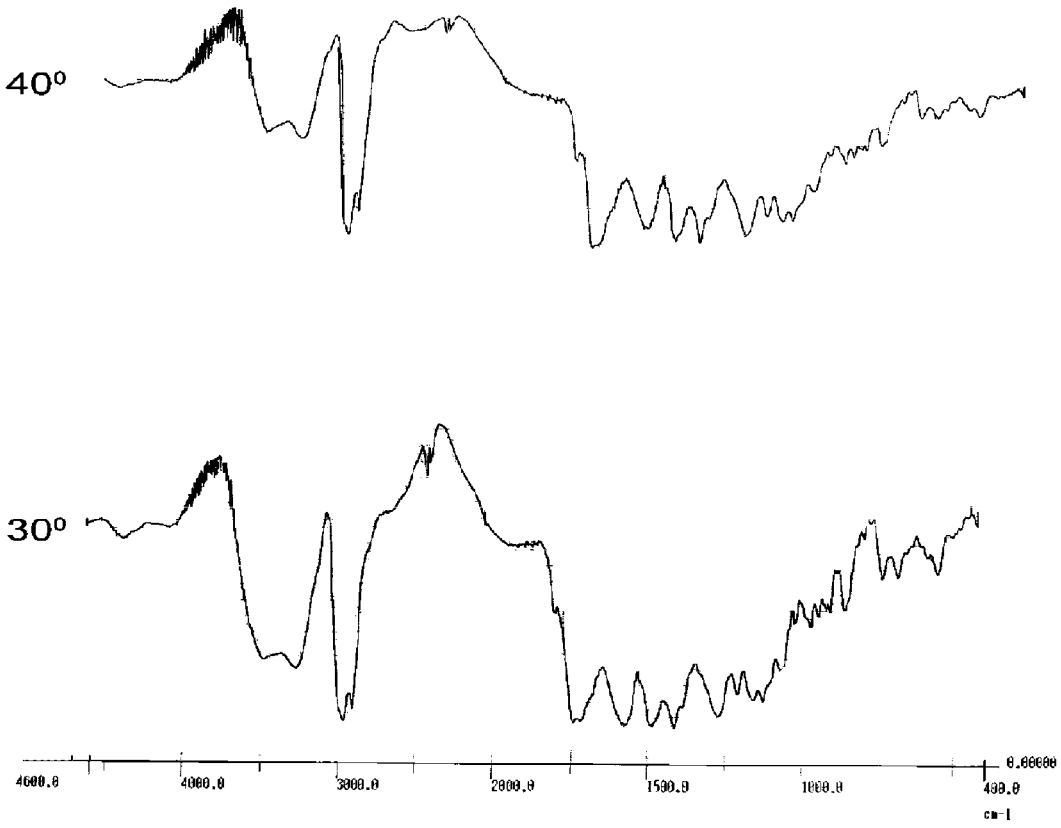

FIGURE 5. FT-IR spectra of aqueous-based films after three months aging at 30 and 40°C.

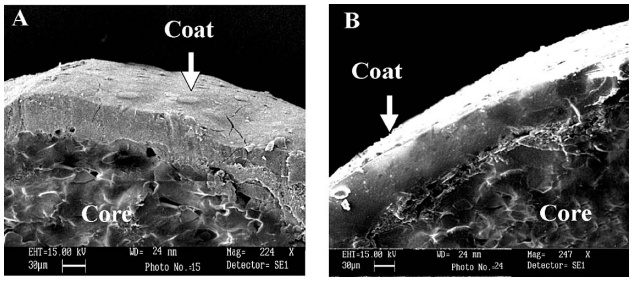

FIGURE 6. SEM of cross-section of pellets coated with (A) aqueous-based film and (B) organic based derivative film.

films. Rosin itself is a low MW (MW –380) polymer having brittle film forming propensity. And thus, flexible film forming property of derivative can be attributed to the plasticizing potential of PEG 400 and the higher MW of derivative as compared to native rosin.

In Vitro Drug Release

The diclofenac sodium release profile of the aqueous and organic-based film coated pellets is shown in Figure 7. The drug release study was executed at pH 1.2 for initial 2 h. The amount of drug released through 20% w/w aqueous- and organic-based derivative coat was about 14 and 3%, respectively. Aqueous-coat contains water soluble ammonium salts that perhaps leached out of film to form channels or pores for drug release even at low pH, whereas, organic-based coatings due to the low solubility of derivative (2.4 mg/mL at pH 1.2 in 24 h) could not favor the drug escape at low pH. A 10 and 20% w/w organic-based coat released 83.50 and 53.94% drug in 12 h, whereas, 10 and 20% w/w aqueous-based coat could sustain diclofenac sodium release for 6 and 8 h, respectively. In both cases, increase in coating load decreased the drug release rate. This can be ascribed to the increased diffusional path length of drug as the thickness of 10 and 20% w/w derivative-coat was about 45–55 μm and 100–115 μm, respectively. Also, during the film application, pellets are continuously layered with an additional coating material; the film formed is therefore composed of overlapping segments. As more layers are applied, the holes from overlapping films are gradually blocked and thus thick coat retards the drug release rates.

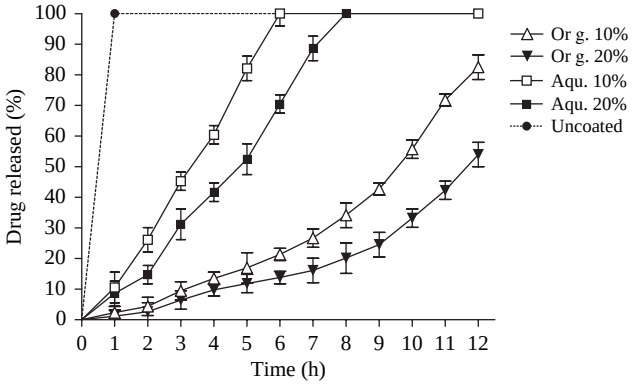

FIGURE 7. Drug release profile of diclofenac sodium pellets coated with organic and aqueous-based derivative-films.

Notably, the organic-based film coatings released diclofenac sodium slowly for initial 2 h (Figure 7). As stated earlier this can be attributed to low solubility of derivative at pH 1.2. However, as per Cheng et al. (2004), PEG 400 is a channeling agent. This when added to coating material, forms micro-channels in coat and enhances the drug release rate. In this study, PEG 400 molecules have formed ester-linkage with carboxyl groups in derivative. Thus, although the hydrophilic segments of PEG 400 and maleic anhydride were present in organic-based coat also, these probably took time to hydrate and facilitate the drug release. On the other hand, aqueous-based coats exhibited fast drug delivery right from the first hour. Uncoated diclofenac sodium pellets showed complete drug release in 1 h.

To compare the properties of organic-based rosin and synthesized derivative coats, attempts were made to coat the pellets with native rosin but such attempts failed. Coating with native rosin posed number of problems such as agglomeration, cracking of dried coat, sticking and long processing time; it was observed that the dried rosin coat breaks into numerous fine chips during coating process and the removal of chips or fragments from coat renders coating non-uniform. Therefore, native rosin coatings could not be used for comparative study. Notably, the researchers also have developed the aqueous coating system of ethyl cellulose (Surelease®); one of the widely used sustained release coat forming materials. It was found that surelease® coatings release 87 diclofenac sodium in 7 h at 20% w/w coating load (Sadeghi, Ford, Rubinstein, & Rajabi-siahboom, 2001). 20% w/w PEGylated rosin derivative coat (aqueous coating system) released about 86 ± 4% drug in 7 h. Thus, aqueous coating system of derivative seems comparable with that of surelease® to retard the drug release rate. Most of the earlier rosin derivatives synthesized with glycerol, mannitol, sorbitol, and pentaerythritol showed about 75–80% diclofenac sodium release at the end of 10 h with 10% w/w coating load (Barabde et al., 2005; Fulzele, Satturwar & Dorle, 2002; Satturwar, Mandaogade, et al., 2002; Satturwar, Fulzele, et al., 2004). The proposed derivative showed about 60% drug release at the end of 10 h at 10% w/w coating load. Thus, the PEGylated rosin derivative seems more effective to retard the drug release from the coated pellets. This may be ascribed to the different physicochemical properties of rosin derivatives containing different alcohols.

To evaluate the stability of derivative coats, the stability test of pellets coated with PEGylated rosin was conducted as per the ICH guidelines. At the end of three months, F2 values for all formulations were found to be in the range of 75–85, which indicates that the organic-based coated dosage forms were

stable. Aqueous-based coats showed substantial faster drug release when stored at 40°C for 3 months. This can be ascribed to the loss of ammonium ions from aqueous-coats.

CONCLUSION

Rosin successfully could react with PEG 400 and maleic anhydride to form a PEGylated rosin derivative. The derivative could form a clear aqueous solution having neutral pH by ammonia neutralization method. Aqueous film-coatings of derivative were highly permeable and thus showed faster drug release profile. In conclusion, synthesized rosin derivative has an excellent film-forming ability. Its aqueous coating system can be developed, however, it is less efficient to retard the drug release rate. On the other hand, organic-based coatings at 10% w/w coating load can be used effectively for sustained drug delivery of diclofenac sodium.

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