RESEARCH ARTICLE

Exploring Film Forming Ability of Newly Synthesized Rosin Esters

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ABSTRACT

The present investigation was planned to confirm the film-forming potential of synthesized rosin esters. The free films of rosin esters were prepared by solvent evaporation and characterized for the physicochemical and mechanical attributes. Suitable concentrations of rosin esters were used for coating tablets, and coated tablets were evaluated for official and unofficial quality control tests. The free films had low tensile strength, higher percent elongation value, and smooth surfaces. Therefore, the plasticizer was used to provide tensile strength to the films. The tablets were coated rapidly without agglomeration, confirming the suitability of rosin esters as a coating agent. The drug release from tablets was delayed up to 6 to 8 hours because of 10% w/w coating of rosin ester, and regioselectivity was achieved by coating with hydroxypropyl methylcellulose with sodium bicarbonate. The pH-dependent solubility of rosin esters produces chrono-triggered drug release from coated tablets. The present investigation confirms the suitability of newly synthesized rosin esters in in designing a region selective chrono-triggered drug delivery system.

Keywords: Captopril, Chrono-triggered, Film former, Solvent evaporation, Regioselective, Rosin esters.

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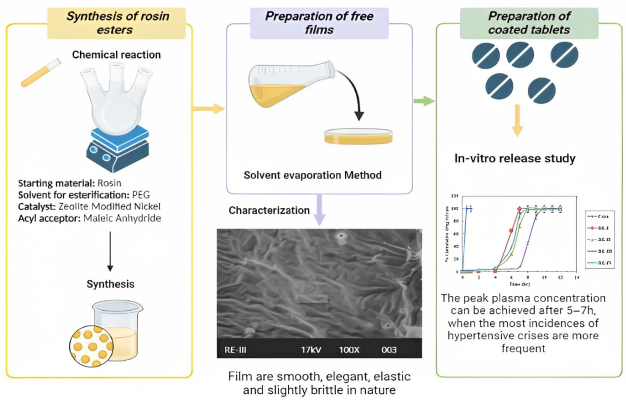
Graphical Abstract



INTRODUCTION

Rosin is a solid polymer composed of 90% monocarboxylic acids (abietic and pimaric acids) with the chemical formula $C_{20}H_{30}O_2$ and 10% non-acidic mass, and it is obtained from several *Pinus* species such as *Pinus longifolium*, *P. soxburghui*, and *P. toeda*.[1] One of the rosin's most abundant conjugated double-bond acids is abietic acid. Pimaric acid is a rosin acid with a double bond but no conjugation.[2] Carboxylic acid (–COOH) group and double bond are the reactive centers present in rosin. The rosin and its esters are used in inks, varnishes, paints, paper, and wood painting manufacture.[3] They are deployed as cosmetics, dental products, and chewing gum additives.[4] The rosin esters are used as tablet coating agents and excipients in microencapsulation.[5-9] The abietic acid esters have been used in extended-release drug delivery systems. They are safe, biodegradable, and biocompatible. The *in-vivo* study confirmed the biodegradable nature of glyceryl ester of rosin.[10] They are used as binders, matrix former, and film former in delayed-release products.[11-14] In the present synthetic polymer era, natural polymers are conducive to pharmaceutical research. They remain the matter choice because of their cost-effectiveness, easy availability, safety, and suitability for chemical modifications.[15]

Captopril is prescribed in combination therapy for essential hypertension & congestive cardiac failure.[16] The half-life of captopril is 2 to 4 hours, with negligible protein binding and better bioavailability during fasting. It is stable in acidic pH

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and unstable in alkaline pH.[17] Hence, it is the ideal candidate for designing regioselective drug delivery systems.[18] Generally, most hypertensive crises occur in the early morning. If we can maintain drug levels steady in the therapeutic window during this period, the incidences of hypertensive crises may reduce.[19]

The dosage form coating has numerous objectives like masking unpalatable organoleptic properties, improving stability, protecting the drug from the gastrointestinal tract (GIT) environment, protecting mucosal linings of GIT from the drug, modifying the drug release, improving the elegance, averting incompatibility, lubrication, etc.[20]A regioselective chrono-triggered system of captopril was developed using a rosin ester, and its film-forming potential was tested in the present study.

MATERIALS AND METHODS

Materials

Nicholas Piramal of India provided a sample of the drug captopril as a gift. Our N-grade rosin came from the Indian company Modern Chemicals. Our supplies of polyethylene glycol 200 (PEG 200), polyethylene glycol 400 (PEG 400), and maleic anhydride (MA) came from Qualigens and SD Fine Chemicals, respectively. All compounds used were of a high enough purity for analytical use.

Methods

Synthesis and Evaluation of Rosin Esters (RE)

Synthesis of rosin esters

The three-necked glass reactors were filled with various molar ratios of PEG 200: rosin (9:1, 11:1, 13:1, and 15:1), heated to 240 to 260°C and stirred at 500 rpm for three hours. The zeolite-modified nickel at 2% of rosin was used as a catalyst. The melts were cooled to 140 to 160°C, and maleic anhydride was added to melt slowly. The melts were poured on tar plates for drying. The rosin esters were powdered, washed, and dried.[21-23] They were evaluated for physiochemical properties.[24, 25]

Preparation and Evaluation of Free Films

Preparation of free films

After dispensing 10% (w/v) RE in absolute ethanol into a plate with a surface area of around 19.36 cm^2, we used solvent evaporation to create the free films of rosin esters. The films were dried in a desiccator at 25°C for 24 hours before being characterized.[25]

Mechanical Characteristics

[Sterling Manufacturing Company, India] A screw gauge was used to determine the film's thickness. Texture analyzer [Brookfield AMTECK-CT3-1000] measurements of elongation at break, tensile strength, and Young's modulus were taken from the films. We characterized the 50 mm films at 25 mm/min crosshead speed, 25°C, and 50% RH.[26]

Surface Morphology

Scanning electron microscopy (SEM; JEOL-JSM-6360; Jeol Datum Ltd., Japan) was used to examine the surface morphology of free films. For this, we used double-sided adhesive dried carbon tape [NEM Tape, Nisshin Em. Co. Ltd., Japan] to attach small segments of the free films to the ends of the stubs. Secondary electron imaging (SEI) was used to capture the SEM images.[27]

Table 1: Operating conditions for tablet coating

Sr. No.	*Parameter*	*Operating condition*
1	Pan type	Conventional coating pan
2	Speed	45 rpm
3	Coating solution	10% w/v rosin & 2% w/v $NaHCO_3$ in HPMC
4	Target weight gain	10% of core weight
5	Tablet charged	100 g
6	Spray gun	Master-art
7	Gun distance from tablet bed	18 cm
8	Diameter of spray gun	1.2 mm
9	Rate of spraying	2 mL/min
10	Spraying pressure	40 psig
11	Air inlet temperature	70–75°C
12	Temperature of tablet bed	35–40°C
13	Total Coating time	3 hours

Preparation of Coated Tablets

Dry granules with captopril (50 mg), lactose monohydrate (50 mg), sodium starch glycolate (2 mg), 2% solution of polyvinyl pyrrolidone K-30 and lubricated with magnesium stearate (1 mg) were prepared. The granules were compressed into 105 mg tablets using 5 mm punches [Karnavati Engineering Pvt. Ltd., India] and coated in pan coater. The 10% w/v rosin ester in absolute ethanol followed by 2% w/v sodium bicarbonate ($NaHCO_3$) in hydroxypropyl methylcellulose (HPMCK15M) solution was used for coating tablets. The coating was continued until the weight gained by 10 and 5%, respectively.[28,29] The operating conditions for tablet coating (Table 1).

Evaluation of Tablets

Both official and unauthorized tests were conducted on tablets with and without coatings.[30,31]

In-vitro release study

The in-vitro dissolution test was conducted at 37 ± 0.5°C with a basket speed of 50 rpm in a United States Pharmacopoeia (USP) dissolution test apparatus I [Veego Scientific, India]. At regular intervals, 5 mL samples were taken from each vessel, filtered, and diluted appropriately. The absorbance of samples was determined using a UV spectrophotometer [UV-3300, Shimadzu, Japan]. The medication release percentage over time was graphed.[32,33]

Stability Studies

Aluminum foil was used to seal the coated tablets inside the vials. The vials were kept for three months at 25 ± 2°C/60 5% RH and 40 ± 2°C/75 ± 5% RH, respectively, in accordance with ICH recommendations. Drug levels in the samples were checked on a monthly basis.[34]

Table 2: Physicochemical properties of rosin derivative

Parameter	*Rosin*	*RE-I*	*RE-II*	*RE-III*	*RE-IV*
State	Solid	Solid	Solid	Solid	Solid
Color	Faint yellow	Pale yellow	Yellowish-orange	Yellowish-red	Light yellow
Softening point (°C)	85–90	65–70	55–60	50–55	80–85
Melting point (°C)	115–120	90–95	70–75	65–70	105–109
Molecular weight (Mw)	388	557	675	785	578
Polydispersity (Mw/Mn)	--	1.65	1.45	1.55	1.60
Glass transition temperature (°C)	88.14	72.23	75.79	82.06	70.68
Acid value (mg of KOH)	165.4	121.3	90.9	55.7	115.2
pH (1% w/v solution)	5.7	5.8	5.8	6.1	5.1
Loss on drying (%)	2.06	2.35	2.95	3.51	2.15

Table 3: Solubilities of rosin and rosin esters at different pH

pH	*Solubility (g/mL)*				
	Rosin	*RE-I*	*RE-II*	*RE-III*	*RE-IV*
1.2	$6.5 \pm 0.1 \times 10^{-3}$	$7.2 \pm 0.2 \times 10^{-3}$	$7.5 \pm 0.9 \times 10^{-3}$	$8.2 \pm 0.9 \times 10^{-3}$	$6.8 \pm 0.1 \times 10^{-3}$
4.0	$7.2 \pm 0.1 \times 10^{-3}$	$8.3 \pm 0.2 \times 10^{-3}$	$8.2 \pm 0.4 \times 10^{-3}$	$9.1 \pm 0.0 \times 10^{-3}$	$6.9 \pm 0.1 \times 10^{-3}$
6.8	$7.9 \pm 0.2 \times 10^{-3}$	$10.2 \pm 0.1 \times 10^{-3}$	$11.5 \pm 0.0 \times 10^{-3}$	$10.2 \pm 0.8 \times 10^{-3}$	$7.4 \pm 0.2 \times 10^{-3}$
8.0	$8.4 \pm 0.1 \times 10^{-3}$	$14.1 \pm 0.1 \times 10^{-3}$	$13.1 \pm 0.6 \times 10^{-3}$	$11.4 \pm 0.5 \times 10^{-3}$	$8.1 \pm 0.1 \times 10^{-3}$

Each value represents mean ± SD, where samples were analyzed for triplicate determination.

Table 4: Mechanical properties of free films

Property	*RE-I*	*RE-II*	*RE-III*	*RE-IV*
Thickness (mm)	0.157 ± 0.006	0.153 ± 0.006	0.173 ± 0.006	0.167 ± 0.006
Tensile strength (kg/mm^2)	2.52 ± 0.524	1.26 ± 0.233	1.95 ± 0.512	1.22 ± 0.281
Elongation (%)	5.33 ± 1.155	7.66 ± 0.577	8.33 ± 2.517	3.66 ± 0.577
Modulus of elasticity (mN/m^2)	0.42 ± 0.03	0.44 ± 0.02	0.34 ± 0.03	0.48 ± 0.03

Each value represents mean ± SD, where samples were analyzed for triplicate determination.

Table 5: Evaluation of tablet core and coated tablets

Formulation	*Weight variation† (mg)*	*Diameter‡ (mm)*	*Thickness‡ (mm)*	*Drug content‡ (%)*	*DT* (s)*	*Hardness* (kg/cm^2)*	*Friability† (%)*
Core	105.35 ± 0.35	5.01 ± 0.02	2.56 ± 0.02	99.06 ± 0.15	45.6 ± 0.6	3.78 ± 0.06	0.53 ± 0.03
RE-I	116.51 ± 0.67	5.25 ± 0.01	2.66 ± 0.02	98.93 ± 2.08	--	4.53 ± 0.08	0.35 ± 0.02
RE-II	115.40 ± 1.04	5.26 ± 0.02	2.68 ± 0.01	99.67 ± 1.23	--	4.65 ± 0.10	0.26 ± 0.01
RE-III	117.74 ± 1.28	5.26 ± 0.01	2.69 ± 0.03	98.47 ± 1.31	--	4.63 ± 0.08	0.39 ± 0.02
RE-IV	114.64 ± 1.89	5.24 ± 0.02	2.67 ± 0.02	98.06 ± 2.46	--	4.61 ± 0.06	0.25 ± 0.01

Each value represents mean ± SD, where †, ‡&* indicate the number of samples used for evaluation (n =20, 3, and 6, respectively).

RESULTS AND DISCUSSION

Synthesis and Evaluation of Rosin Esters

Four rosin esters were synthesized using varying the molar ratio of PEG 200: rosin under controlled conditions. The temperature, time, catalyst concentration, and PEG: rosin ratio were optimized to get the maximum yield of rosin esters. Reaction rate was confirmed by timely determining acid value of the reaction mixture. The constant acid value was considered the end point of esterification.

Physicochemical Characterization of Rosin Esters

The physicochemical characterization of rosin and its esters was done (Table 2). The intensity of the color of rosin esters was the function of molecular weight. The maleic anhydride provides physical uniqueness to rosin esters. The polydispersity index represented the narrow molecular weight distribution of rosin esters.

Glass transition temperature (Tg) by differential scanning calorimeter displays the order of Tg as RE-III > RE-II > RE-I> RE-IV. The rosin esters show higher water solubility than rosin

due to higher hydrogen bonding ability. The rosin esters are more permeable in a glassy state than in a rubbery state where the Tg are closer to 37°C. The pH (1% solution) of rosin esters has lower acid values than rosin due to esterification of -COOH.

Solubility Studies of Rosin Esters

The pH-dependent solubility was observed in the case of rosin esters (Table 3).

Preparation of Free Films

The optimization of the concentration of rosin esters for the fabrication of films was necessary. The 10% w/v solution in absolute ethanol was to be optimized based on trial to form free films with ideal flexibility and %elongation.

Evaluation of Free Films

Mechanical characteristics

The film-forming ability and suitability in the pharmaceutical coating were confirmed by evaluating mechanical properties (Table 4).

Surface morphology

The SEM photographs of free films show their smooth, elegant, elastic, and slightly brittle nature. Hence, PEG 400 in 0.5% concentration was added to enhance the mechanical strength of the free film (Figure 1).

Preparation of Tablets

Captopril tablets were prepared and coated in a conventional coating pan with baffles. Parametric and nonparametric tests were performed on the tablets.

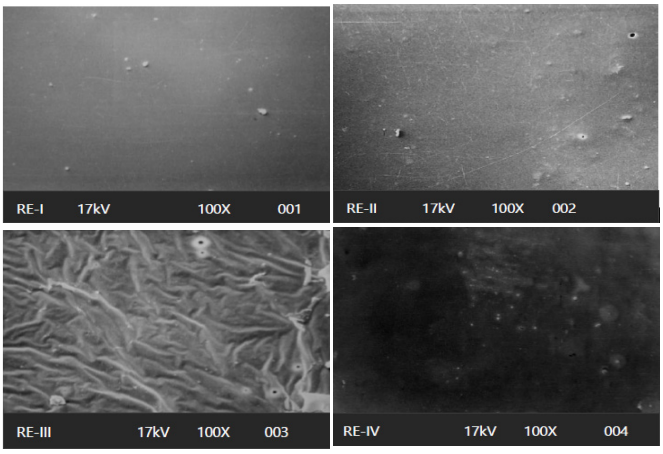

Figure 1: SEM of free films of rosin esters.

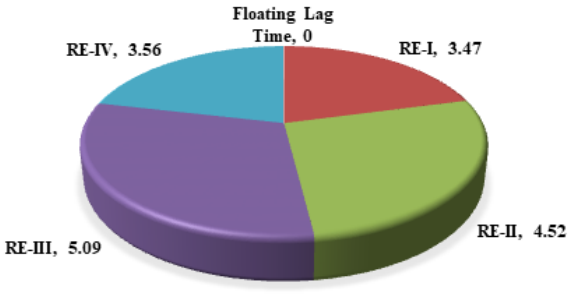

Figure 2: Floating lag time (min) for RE-coated tablets.

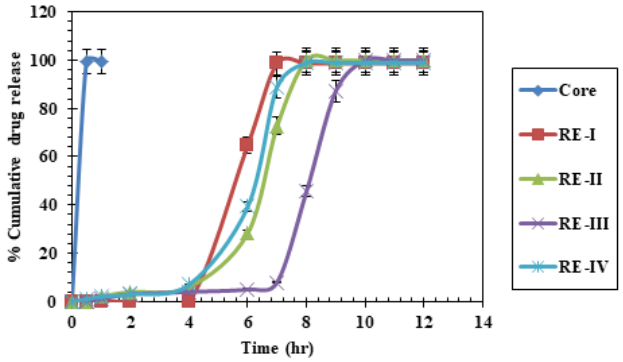

Figure 3: *In-vitro* dissolution study of coated tablets.

Evaluation of Tablets

As per USP, the results of core and coated tablets comply with the standards of tests (Table 5).

Floating study

The tablets show 100% floating ability and a floating time of more than 6 hours. The average floating lag time is shown in (Figure 2).

In-vitro release study

In-vitro release profile of all four rosin esters coated tablets shows the sigmoid curve indicates the suitability for pulsatile release of the drug (Figure 3). The concentration of rosin ester, molecular weight of rosin esters, coating composition & thickness of coating film affects the drug release from tablets. Lower standard deviation values indicate that the tablets prepared by the present method were reproducible. Conventional tablets can achieve peak plasma concentration in 1.2 hours for captopril. In case captoprilcoated tablets with RE-III are administered at 8 pm, the peak plasma concentration can be achieved after 5 to 7 hours, when most incidences of hypertensive crises are more frequent.

Stability Studies

The coated tablets stored per ICH guidelines were smooth, uniform, and had no signs of cracks after three months. The drug content after 1, 2, and 3 months were 98.02, 97.93, and 96.71%, respectively, at normal conditions. The drug content at accelerated conditions after 1, 2, and 3 months were 97.87, 97.74, and 96.71%, respectively. Therefore, the coated tablets were stable as per ICH guidelines.

CONCLUSION

The four novel rosin esters were synthesized and evaluated for film-forming ability successfully. All four rosin esters at 10% w/vwere employed in fabricating free films using plasticizers to provide mechanical strength and flexibility. No agglomeration of tablets was observed, confirming the suitability of the coating ability of rosin ester and the method used. The effervescent layer provides gastro-retention to the system. Hence, this confirms the suitability of novel rosin esters as a potential film former in region-selective chrono-triggered drug delivery systems. In the future, there is a need to perform preclinical and clinical studies of these formulations before commercialization.

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AUTHOR CONTRIBUTIONS

Conceptualization: PB, SS; Table Work: PB, MB; Supervision: SS; Revisions: HT, RK; Writing and Editing: HT, RK; Proofreading: MB, SS.

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