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Study of Novel Rosin-Based Biomaterials for Pharmaceutical Coating

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ABSTRACT The film forming and coating properties of Glycerol ester of maleic rosin (GMR) and Pentaerythritol ester of maleic rosin (PMR) were investigated. The 2 rosin-based biomaterials were initially characterized in terms of their physicochemical properties, molecular weight (Mw), and glass transition temperature (Tg). Films were produced by solvent evaporation technique on a mercury substrate. Dibutyl sebacate plasticized and nonplasticized films were characterized by mechanical (tensile zzzz strength, percentage elongation, and Young's modulus), water vapor transmission (WVT), and moisture absorption parameters. Plasticization was found to increase film elongation and decrease the Young's modulus, making the films more flexible and thereby reducing the brittleness. Poor rates of WVT and percentage moisture absorption were demonstrated by various film formulations. Diclofenac sodium-layered pellets coated with GMR and PMR film formulations showed sustained drug release for up to 10 hours. The release rate was influenced by the extent of plasticization and coating level. The results obtained in the study demonstrate the utility of novel rosin-based biomaterials for pharmaceutical coating and sustained-release drug delivery systems.

KEYWORDS: rosin, film coating, biomaterials, pellets, mechanical properties.

INTRODUCTION

Rosin is a solid resinous mass obtained naturally in the oleoresin of pine trees. Principally it is composed of resin acids (abietic and pimaric) and a small amount of nonacidic components. Rosin and rosin derivatives are widely used in paints, varnishes, printing inks, chewing gums, and cosmetics. Pharmaceutically, rosin and its derivatives have been extensively studied. Rosin and rosin esters are reported as coating [1] and microencapsulating [2,3] agents for sustained and controlled drug release. Esters of rosin have been used as hydrophobic matrix material in tablet formulation [4]. Derivatives of abietic acid, the principal component of rosin, have been investigated for drug delivery applications [5,6]. Recently, a few rosin-based polymers have been evaluated for their film forming and coating properties [7,8]. Rosin-glycerol ester is biodegradable, both in vitro as well as in vivo [9]. This study investigates the drug delivery application of 2 new rosin-based biomaterials. The biomaterials are characterized and evaluated for their film forming and coating properties. Diclofenac sodium was selected as a model drug to evaluate the possible application of the 2 biomaterials to produce sustained-release coated forms.

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MATERIALS AND METHODS

Materials

Glycerol ester of maleic rosin (GMR) and Pentaerythritol ester of maleic rosin (PMR) were received as gift samples from Derives Resiniques Terpeniques Inc, Gambetta, France. Dibutyl sebacate (DBS) was obtained from Morflex Inc, Greensboro, NC. Diclofenac sodium was a gift sample from Zim Laboratories, Nagpur, India, and was used as received. Other reagents and chemicals were of analytical or Indian pharmacopoeial grade.

Material characterization

The biomaterials GMR and PMR were evaluated for the preliminary physicochemical properties such as color, acid value, softening point, and relative solubility using methods previously described [10]. 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 hours at 25°C. Two mL 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 5 times for each solvent/buffer solution. Buffers of different pH were prepared by the method described in Indian Pharmacopoeia [11].

The molecular weight was estimated using a gel permeation chromatography system (Perkin Elmer, series-10, Newton Center, Wellesley, MA) equipped with an Refractive index (RI) detector (La Chrom Detector L-7490) (Perkin Elmer). Samples were eluted through a PL gel 3 µ mixed column at a flow rate of 1 mL/min using tetrahydrofuran as a solvent. Polystyrene standards (Polysciences, Warrington, PA) were used for calibration. The glass transition temperature (Tg) of GMR and PMR was determined by differential scanning calorimetry (DSC-Shimadzu, METTLER, TA4000, London, England). Approximately 15 mg of GMR and 10 mg of PMR samples were placed in an aluminium pan and scanned over a temperature range of 25°C to 250°C at the rate of 10°C/min. Scanning was performed in triplicate.

Film preparation and characterization

Films were cast from a dichloromethane solution containing 30% (wt/vol) film forming agent, on a mercury substrate employing the principle of solvent evaporation. Plasticizer dibutyl sebacate (DBS) was added at concentrations of 0%, 10%, and 20% (wt/wt of the total solids) in the casting solution. Films were carefully cast on a 20-cm-diameter petri dish containing mercury (area of casting: 19.5 cm^2). After allowing the solvent to evaporate for 24 hours, the films were removed from the plate without difficulty and subsequently air dried for an additional 24 hours. The prepared films were carefully cut into strips (approximate dry film thickness: 0.4 mm; 12 mm width x 120 mm length), and the mechanical properties of the films were evaluated using Instron instrument (model 4467, Instron Corp, Canton, MA). The tests were conducted at 23 ± 1°C and 50% relative humidity employing a gauge length of 50 mm and cross head speed (CHS) of 5 mm/min. The stress-strain parameters including the tensile strength, percentage elongation at break, and Young's modulus were determined for each film specimen with at least 3 repetitions. The films were further characterized in terms of water vapor transmission rates (WVTR) and moisture absorption employing the methods described previously [8]. The studies were conducted by employing controlled relative humidities (RH) of 23%, 43%, 75%, and 93% achieved by using different saturated salt solutions containing excess solute.

Preparation of coated pellets

Drug model, diclofenac sodium, was initially layered onto 14/16-mesh nonpareil seeds (NPS) using a conventional coating pan (Retina India Company, Mumbai, India). For a 50-g batch size, 6 g of drug and 0.3 g povidone were dissolved in 50 mL of 95% ethanol to prepare the drug-binder solution, which was then sprayed over the cascading NPS by solution-layering technique [12]. After drying at 50°C, the drug-layered pellets were successively coated with F3 and F6 formulations of film coating solutions until different levels of coat consumption (percentage weight increase) were reached. The coating experiments were performed under conditions of inlet air temperature 70°C to 75°C, pellet bed temperature 40°C to 45°C, spray rate 1 mL/min, spray gun position 15 cm from pellet bed surface, and atomizing pressure 40 psi. The coated pellets were transferred and air dried at room temperature.

Intact pellets and cross-sectioned pellets were studied under a scanning electron microscope (Stereo Scan 250-MK-III, Cambridge, England). Samples were mounted on stubs and gold coated for 120 seconds using a sputter coater (Jeol JXA-840 A, London, England) under an argon atmosphere before examination under the scanning electron microscope.

Drug release analysis

Analysis of drug release from coated pellets was followed in 900 mL of 0.1 N HCl (pH 1.2) for first 2 hours followed by 900 mL of phosphate buffer solution (pH 6.8) up to 10 hours. The test was conducted using US Pharmacopeia XXIII dissolution apparatus 2 (Veego Scientific, Mumbai, India) at 37 ± 1°C at a speed of 100 rpm. Aliquots were withdrawn at specific predetermined time intervals and exchanged with new media of the same volume maintained at the same temperature. The amount of drug released was estimated spectrophotometrically at 276 nm with triplicate measurements.

RESULTS AND DISCUSSION

Preliminary characterization of GMR and PMR is shown in **Table 1**. Esterification of rosin acids is evident from the acid values of the biomaterials, which are significantly reduced compared with rosin (155 mg of KOH). Absence of a sharp melting point indicates the amorphous nature of the biomaterials. The molecular weights for GMR and PMR are 1860 and 2700, respectively, with polydispersity index close to 1. The Tg was determined using a differential scanning calorimeter with the pentaerythritol ester showing higher value compared with glycerol ester. The relative solubility showed low solubility of both the biomaterials in water (**Table 2**). They are freely soluble in almost all organic solvents. A pH-dependent solubility is observed with both the biomaterials showing increased solubility in alkaline medium.

Film characterization

Various film formulations given in **Table 3** were used for preparation of films. This study examines the effect of plasticizer on the mechanical, WVT, and moisture-absorption properties of GMR and PMR films. The plasticized and nonplasticized films were prepared by

Table 1. Characterization of Biomaterials*

Parameters	GMR	PMR
Color	Light brown	Light brown
Acid value (mg of KOH)	40.0	29.6
Softening point (°C)	85-90	110-115
Molecular weight (Mw)	1860	2700
Polydispersity (Mw/Mn)	1.12	1.03
Tg (°C)	72.8	91.4

*GMR indicates glycerol ester of maleic rosin; PMR, pentaerythritol ester of maleic rosin; Tg, glass transition temperature; Mw, weight average molecular weight; Mn, number average molecular weigh.

Table 2. Relative Solubility of Biomaterials

Solubility in Different Solvents*			Solubility in Different pH Solutions*		
Solvent	Solubility (g/mL)		pH	Solubility (g/mL) x 10^{-4}	
	GMR	PMR		GMR	PMR
Chloroform	0.53 ± 0.017	0.45 ± 0.016	1.6	5.0 ± 0.17	19.7 ± 0.24
Dichloro-methane	0.51 ± 0.024	0.40 ± 0.027	4.6	37.2 ± 0.64	52.5 ± 1.09
Acetone	0.50 ± 0.038	0.38 ± 0.032	6.8	74.9 ± 0.91	106.0 ± 0.74
Isopropyl al-cohol	0.15 ± 0.010	0.19 ± 0.014	8.0	113.2 ± 0.97	194.6 ± 2.13
Ethanol	0.09 ± 0.013	0.13 ± 0.021	10.4	189.3 ± 2.17	326.7 ± 2.01
Water	1.9 ± 0.13 x 10^{-4}	16.2 ± 0.97 x 10^{-4}			

*Each value is mean ± SD of 5 determinations.

Table 3. Formulations of Film Coating Solutions*

Ingredient	Composition (% wt/vol)					
	F1	F2	F3	F4	F5	F6
GMR	30.0	30.0	30.0	-	-	-
PMR	-	-	-	30.0	30.0	30.0
DBS	-	3.0	6.0	-	3.0	6.0
Dichloromethane q.s. to	100.0	100.0	100.0	100.0	100.0	100.0

*GMR indicates glycerol ester of maleic rosin; PMR, pentaerythritol ester of maleic rosin; DBS, dibutyl sebacate; q.s., Quantity sufficient.

Table 4. Mechanical Properties of Free Films*

Film formulation	F1	F2	F3	F4	F5	F6
Thickness (mm)	0.38	0.40	0.42	0.40	0.42	0.43
Tensile strength (MPa)	0.32	0.37	0.39	0.41	0.47	0.49
Elongation (%)	7.12	17.26	30.41	10.42	18.07	24.10
Young's modulus (MPa)	4.50	2.09	1.30	3.90	2.23	2.02

*Average of 4 determinations.

solvent evaporation/casting technique. Films produced from the plasticizer-free solutions were smooth and transparent but brittle. Improvement in the mechanical properties was attempted by addition of plasticizers. The addition of plasticizers plays a critical role in the performance of film coating [13], which results in decreased tensile strength, lowered Tg, and increased elongation and flexibility of the films [14]. In this study, the effect of plasticizer concentration was investigated by the addition of 10% and 20% wt/wt (based on polymer weight) of a hydrophobic plasticizer, dibutyl sebacate (DBS), to the film casting solutions. For both GMR and PMR, plasticizer level of 20% wt/wt was sufficient to obtain films that were flexible enough to be bent in the dried state without breaking. The mechanical properties of free films are generally defined by stress-strain data, which serve to characterize polymer properties [15]. The average results of the mechanical property measurements are shown in **Table 4**.

Incorporation of DBS up to 20% of polymer weight did not significantly affect the film thickness. Plasticized films show higher elongation (%), although the tensile strength is nearly constant. The low value for the tensile strength of all the films may be attributed to the low molecular weight of the biomaterials. Young's modulus is the constant of proportionality of stress to strain and is equal to the slope of the straight line portion of the stress-strain curve [16]. In the present study, the addition of DBS decreased the value of Young's modulus, which may contribute to an increase in the adhesion between the film and coating surface [17]. Although the tensile strength values suggest the risk of film cracking, no sign of cracking in either the free films or coated forms was observed, which may partly be attributed to the lower values of Young's modulus. Elongation is defined as the measure of the capacity of a film to deform prior to failure [18]. Lower elongation indicates a low deformation capacity of the film and a brittle film structure. DBS increased the percentage elongation of GMR and PMR films suggesting the suitability of adding DBS, which may increase the film flexibility and reduce the brittle state. These results can be attributed to an increase in the elasticity of the polymer and a lowering of the internal stresses within the film.

The results of the WVTR study are shown in **Table 5**. The low rates of water vapor transmission exhibited bythe film formulations are in accordance with the hydrophobic nature of the biomaterials as demonstrated by their extremely low solubility in water. The transmission-rates were further decreased by addition of plasticizer, which may be due to better film formation with the addition of dibutyl sebacate. A clear correlation was observed between the water vapor permeability and plasticizer concentration. The film formulations may therefore promise considerable utility in providing protection to the coated forms against moisture. This expectation is further supported by the results of the moisture absorption study shown in **Table 6**. Plasticized films of DMR and PMR show a drop in the percentage of moisture absorbed when compared with free films. Even at 93% RH, the films absorb only 1% to 2% moisture, which is indicative of their hydrophobic and moisture-resistant properties.

Pellet coating

Coating experiments performed using film solutions F1 and F4 posed a few problems such as sticking of coated forms with the pan surface being associated with film cracking and increased time required to obtain desirable level of coat build-up. Both these problems were effectively overcomed by using plasticizer-containing film coating solutions. The representative scanning electron micrographs of pellets coated with film formulation F3 and F6 is shown in **Figure 1** and **Figure 2**, respectively. The coated pellets are round shaped with a fairly smoothsurface. The cross-section shows distinct layers of core (NPS), drug layer, and coat. The core appears grained, while the coat displays a smooth surface with the drug layer compacted in between. No sign of cracking was observed on the surface as indicated by the smooth and uniform coat layer.

Table 5. WVTR Study of Free Films*

Film Formulations	Thickness (cm)	Area (cm^2)	WVTR† (g.cm/cm^2/24 h) x 10^{-5} at RH	
			43%	93%
F1	0.037	4.34	1.75 ± 0.06	4.68 ± 0.15
F2	0.040	4.32	1.29 ± 0.08	4.08 ± 0.12
F3	0.042	4.34	0.96 ± 0.07	3.60 ± 0.18
F4	0.039	4.32	4.25 ± 0.18	6.72 ± 0.20
F5	0.041	4.34	3.42 ± 0.10	5.77 ± 0.16
F6	0.044	4.34	2.87 ± 0.09	5.04 ± 0.14

*WVTR indicates water vapor transmission rates; RH, relative humidities.
†Each value is mean ± SD of 4 determinations.

Table 6. Moisture Absorption Study of Free Films*

Film Formulation	Percent Moisture Absorbed at RH†			
	23%	43%	75%	93%
F1	0.13	0.30	0.66	1.00
F2	0.10	0.20	0.59	0.92
F3	0.08	0.23	0.56	0.87
F4	0.21	0.41	0.66	1.20
F5	0.17	0.36	0.61	1.11
F6	0.13	0.34	0.57	1.07

*Average of 3 determinations.
†RH indicates relative humidities.

The release of DS from coated pellets depends on the percentage of the film-coat layer. The results from dissolution tests show that increasing the coating level decreased the drug release from coated pellets, which suggests that the film coat may be controlling the release process. The diffusion of the drug through a thicker membrane seems to govern the release profile. The results for film-coating solutions F3 and F6 are shown in **Figure 3** and **Figure 4**, respectively. Use of plasticizer was found to be imperative in performing coating experiments within reasonable time and process conditions. Nearly 20% of the drug was released for first 2 hours (pH 1.2), which may be due to poor solubility of drug in acidic medium [19] or the acid-resistant nature of biomaterials.

CONCLUSION

Two rosin-based biomaterials, GMR and PMR, investigated in this study showed good film-forming and -coating properties. Addition of plasticizer (DBS) improved the film characteristics by increasing the flexibility associated with increase in elongation and decrease in Young's modulus. All the film formulations show low rate of WVT and extremely low percentage of moisture

Figure 1. Representative scanning electron micrographs of pellets coated with formulation F3 (a) coated pellet (b) cross-section of coated pellet (c) surface of coated pellet.

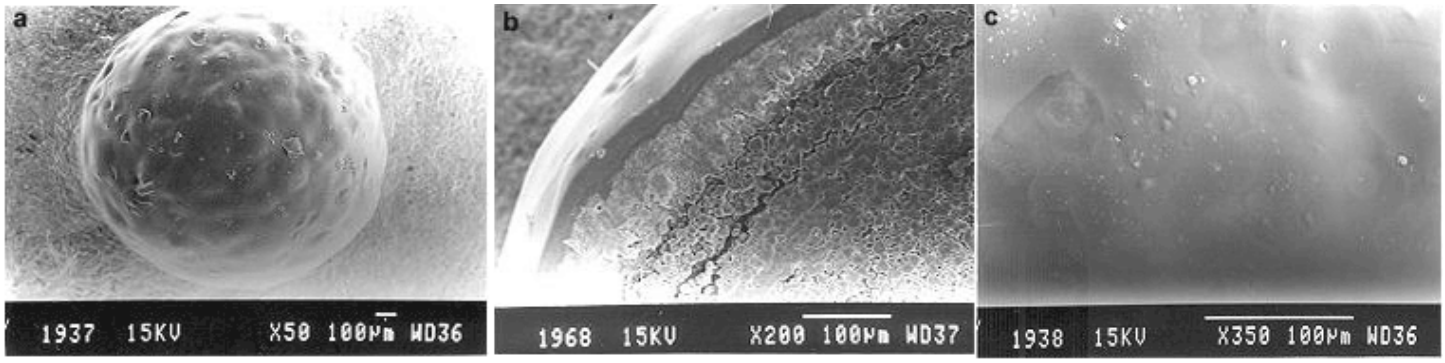
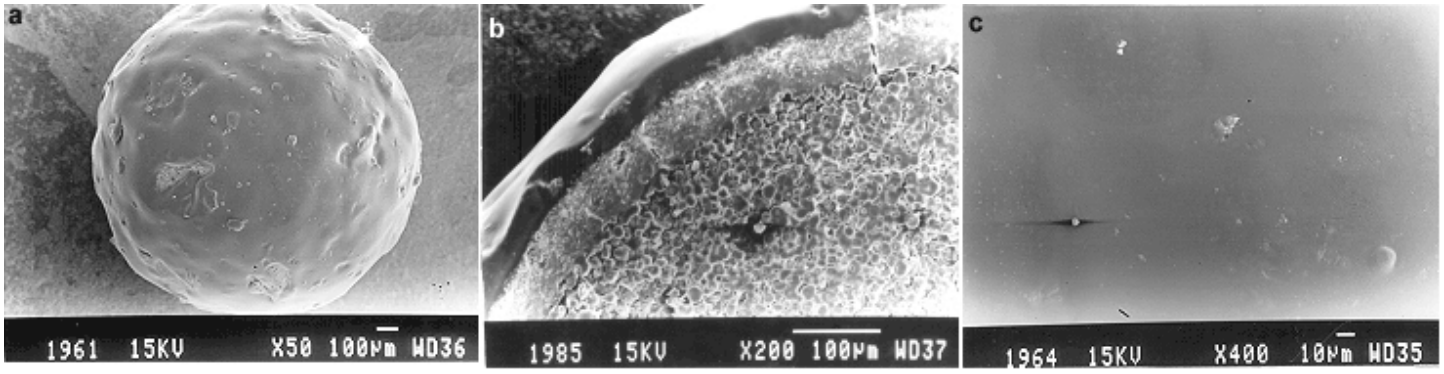


Figure 2. Representative scanning electron micrographs of pellets coated with formulation F6 (a) coated pellet (b) cross-section of coated pellet (c) surface of coated pellet.



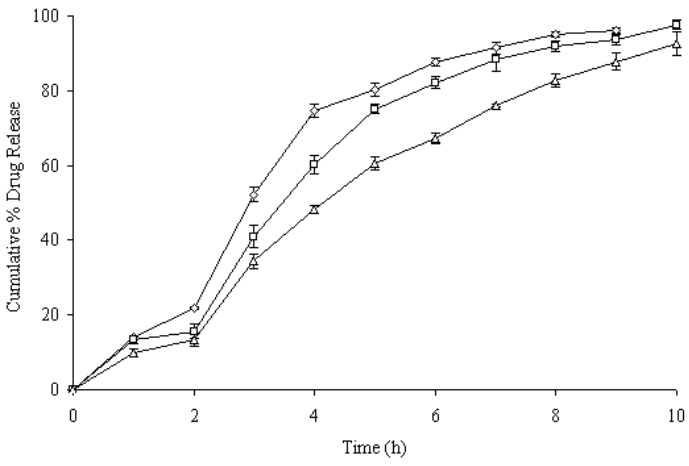


Figure 3. In vitro drug release from pellets coated with film formulation F3 at various percentage coating; ◇, 4% wt/wt; □, 6% wt/wt; △, 8% wt/wt.

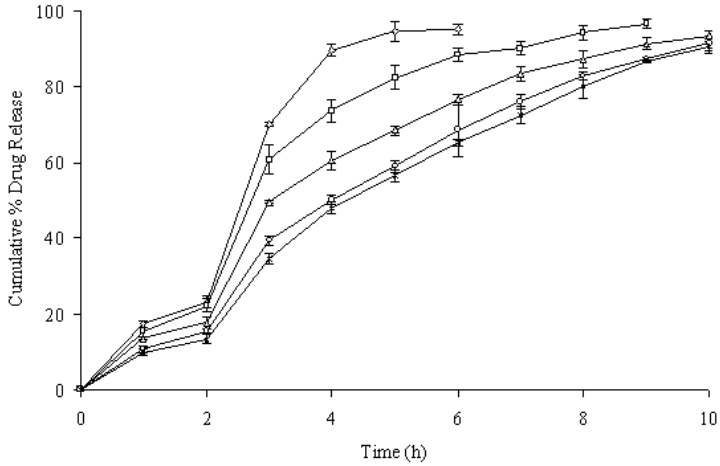


Figure 4. In vitro drug release from pellets coated with film formulation F6 at various percentage coating; ◇, 4% wt/wt; □, 6% wt/wt; △, 8% wt/wt; ○, 10% wt/wt; ✱, 12% wt/wt.

absorption, promising the utility of the biomaterials in moisture-resistant dosage forms. The film characterization studies showed DBS to be an effective and compatible plasticizer for both biomaterials. Coating experiments were conveniently performed using plasticizer-containing film formulations, with sustained drug release for up to 10 hours with increase in coat build-up.

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REFERENCES

1. Pathak YV, Nikore RL, Dorle AK. Study of rosin and rosin esters as coating materials. Int J Pharm. 1985;24:351-354.

2. Sheorey DS, Dorle AK. Release kinetics of drugs from rosin-glycerol ester microcapsules prepared by solvent evaporation technique. J Microencapsul. 1991;8:243-246.

3. Pathak YV, Dorle AK. Study of rosin-glycerol esters as microencapsulating materials. J Microencapsul. 1985;2:137-140.

4. Pathak YV, Dorle AK. Rosin and rosin derivatives as hydrophobic matrix materials for controlled release of drugs. Drug Des Deliv. 1990;6:223-227.

5. Ramani CC, Puranik PK, Dorle AK. Study of diabietic acid as matrix forming material. Int J Pharm. 1996;37:11-19.

6. Puranik PK, Dorle AK. Study of abietic acid-glycerol derivatives as microencapsulating materials. J Microencapsul. 1991;8:247-252.

7. Mandaogade PM, Satturwar PM, Fulzele SV, Gogte BB, Dorle AK. Rosin derivatives: novel film forming materials for controlled drug delivery. React Funct Polym. 2002;50:233-242.

8. Satturwar PM, Mandaogade PM, Fulzele SV, Darwhekar GN, Joshi SB, Dorle AK. Synthesis and evaluation of rosin based polymers as film coating materials. Drug Dev Ind Pharm. 2002;28:383-389 [PubMed lists pages 381-387].

9. Sahu NH, Mandaogade PM, Deshmukh AM, Meghre VS, Dorle AK. Biodegradation studies of rosin-glycerol ester derivative. J Bioact Comp Polym. 1999;14:344-360.

10. Ramani CC, Puranik PK, Dorle AK. Study of maleoabietic acid as matrix forming material. Int J Pharm Adv. 1996;1:344-352.

11. Ministry of Health and Family Welfare, Pharmacopoeia of India. Vol 2. New Delhi : Ministry of Health and Family Welfare, Govt of India; 1985. A-142.

12. Sarisuta N, Punpreuk K. In vitro properties of film coated diltiazem hydrochloride pellets compressed into tablets. J Control Rel. 1995;31:215-222.

13. Amighi K, Moes A. Influence of plasticizer concentration and storage conditions on the drug release rates from Eudragit RD30D film coated sustained-release theophylline pellets. Eur J Pharm Biopharm. 1996;42:29-35.

14. Felton LA, McGinity JW. Influence of plasticizers on the adhesive properties of an acrylic resin copolymer to hydrophilic and hydrophobic tablet compacts. Int J Pharm. 1997;154:167-178.

15. Lin SY, Lee CJ, Lin YY. The effect of plasticizers on compatibility, mechanical properties and adhesion strength of drug free Eudragit E films. Pharm Res. 1991;8:1137-1143.

16. Lehtola VM, Heinämäki JT, Nikupaavo P, Yliruusi JK. The mechanical and adhesion properties of aqueous based hydroxypropyl methyl cellulose coating systems containing polydextrose and titanium dioxide. Drug Dev Ind Pharm. 1995;21:675-685.

17. Okhamafe AO, York P. The adhesion characteristics of some pigmented and unpigmented aqueous based film coatings applied to aspirin tablets. J Pharm Pharmacol. 1985;37:849-853.

18. Lim LY, Wan LS. The effect of plasticizers on the properties of polyvinyl alcohol films. Drug Dev Ind Pharm. 1994;20:1007-1020.

19. Tehrani MR, Hatefi A. Characterization and evaluation of enteric-coated controlled release tablet formulations of diclofenac sodium. Acta Pharm. 1996;46:285-294.