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Polymerized rosin: novel film forming polymer for drug delivery

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Abstract

Polymerized rosin (PR) a novel film forming polymer is characterized and investigated in the present study for its application in drug delivery. Films were produced by a casting/solvent evaporation method from plasticizer free and plasticizer containing solutions. Films prepared from different formulations were studied for their mechanical (tensile strength, percent elongation and Young's modulus), water vapour transmission and moisture absorption characteristics. Neat PR films were slightly brittle and posed the problem of breaking during handling. Hydrophobic plasticizers, dibutyl sebacate and tributyl citrate, improved the mechanical properties of free films with both the plasticizers showing significant effects on film elongation. Release of diclofenac sodium (model drug) from coated pellets was sustained with high coating levels. Concentration of plasticizer was found to affect the release profile. PR films plasticized with hydrophobic plasticizers could therefore be used in coating processes for the design of oral sustained delivery dosage forms.

Keywords: Polymerized rosin; Hydrophobic plasticizers; Films; Mechanical properties; Pellet coating; Sustained release

1. Introduction

The potential utilization of films as specialized coatings on medications, as vehicles for medicaments or as packaging agents has prompted several studies which evaluated various film forming materials for these applications (Knaig and Goodman, 1962). The application of a polymer film coat is a common practice in the preparation of sustained and controlled release dosage forms (Phuapradit et al., 1995). The release of a drug from a coated particle has been investigated by various investigators for different conditions (Benita et al., 1986; Rosilio et al., 1988; Kokubo et al., 1998). The utility of film forming materials has often been characterized in terms of their mechanical properties (Rowe et al., 1984; Nagarsenkar and Hegde, 1999), permeability (Sun et al., 1987) and water vapour transmission (Shogren, 1997). The properties of the free film are evaluated without being influenced by the nature of dosage form or the coating technique (Sprockel et al., 1990).

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Rosin and rosin derivatives are polymeric biomaterials and have been pharmaceutically evaluated as microencapsulating materials (Pathak et al., 1987; Sheorey and Dorle, 1991) and as anhydrous binding agents in tablets (Pathak and Dorle, 1990; Ramani et al., 1996a). Rosin derivatives and its glycerol, sorbitol and mannitol esters are reported to have excellent film forming properties and can be used for enteric coating and delayed release of drug (Pathak et al., 1985; Pathak and Dorle, 1987a,b). Being of natural origin, rosin and its derivatives are expected to be biodegradable in vivo (Sahu et al., 1999). In this study, Polymerized rosin (PR) is evaluated for its film forming and coating properties. Free and plasticized films of PR are evaluated for their mechanical, water vapour transmission and moisture absorption properties. Further, the pellets coated with PR film formulations are investigated for drug release characteristics.

2. Materials and methods

2.1. Materials

PR was received as Gift sample from Derives Resiniques and Terpeniques Inc., Gambetta, France. Dibutyl sebacate (DBS) and tributyl citrate (TBC) were received from Morflex Inc., Greensboro, NC. Diclofenac sodium was a gift from Zim Laboratories, Nagpur, India and used as received. All other chemicals were of analytical grade and purchased locally.

2.2. Characterization

PR was initially characterized for physicochemical properties like color, acid value, softening point and relative solubility (Ramani et al., 1996b). The molecular weight of the polymer was estimated using a Gel Permeation Chromatography System (Perkin Elmer) equipped with a differential refractometer (La Chrom Detector L-7490). Samples were eluted through a PL gel 3 μ mixed column at a flow rate of 1.0 ml/min using tetrahydrofuran as solvent. Polystyrene standards (Polysciences) were used for calibration. The glass transition temperature (T_g) was determined by a differential scanning calorimeter (DSC-Schimadzu 50). Approximately 6 mg of the sample was placed in an aluminium pan and scanned over a temperature range of 25–250 °C at the rate of 10 °C/min. Samples were scanned in triplicates.

2.3. Free film preparation and characterization

Free films of PR were prepared by solvent evaporation technique on a mercury substrate. A 30% w/v solution of PR was prepared in dichloromethane and films were carefully cast on a 20 cm diameter petridish containing mercury (area of casting: 19.4 cm^2) and dried at room temperature for 24 h. Films were further stored in dessiccators at ambient temperature for 24 h before analysis. Various formulations of PR film casting solutions given in Table 1 were used in the preparation of free films. In order to investigate the plasticizer effect, free film formulations containing either DBS or TBC as plasticizers at 0, 10 and 20% w/w were prepared. The prepared cast films were carefully cut into film strips (≈ dry film thickness: 0.4 mm; 12 mm width × 120 mm length) and were evaluated for the stress–strain parameters using Instron Instrument (Model 4467, Instron. Corp., Canton, MA) by ASTM standard test principle. The measurements were made at a gauge length of 50 mm, cross-head speed of 5 mm/min at 50% relative humidity (RH) and 23 °C. Stress–strain parameters including the ultimate tensile strength, percent elongation at break and Young's modulus were determined for each film specimen with at least three repetitions. Film thickness was measured using a thickness gauge (Oswa Scientific, Ambala, India) and recorded as mean of four measurements.

2.4. Water vapour transmission rate studies

To measure the water vapour transmission, polymer films were cut into appropriate dimensions and mounted on a permeation cell (Sprockel et al., 1990). The cell consisted of a glass body (2.25 cm internal diameter × 8.0 cm height) and a cap with a opening of 23.4 mm diameter (test area: 4.3 cm^2), the two held in place by means of three

Table 1
Formulations of film coating solutions

Ingredient	Composition (% w/v)				
	F1	F2	F3	F4	F5
PR	30.0	30.0	30.0	30.0	30.0
DBS	–	3.0	6.0	–	–
TBC	–	–	–	3.0	6.0
Dichloromethane q.s. to	100.0	100.0	100.0	100.0	100.0

screw clamps. A disk of the film under investigation was clamped tightly between the two to provide an effective surface area of 4.3 cm^2 for water vapour transmission. The RH was maintained with saturated salt solutions in contact with the undissolved salt: potassium carbonate (43% RH) and potassium nitrate (93% RH) (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 through the film was given by the weight loss of assembled cell. The water vapour transmission rate (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, g of water transmitted per 24 h; L, film thickness (cm); S, surface area (cm^2); Q, WVT (g cm/cm^2)/24 h.

2.5. Moisture absorption by free films

Films were cut into 25×10 mm^2 strips. The strips were transferred to a tarred petridish and then to glass desiccators maintained at controlled relative humidities of 23, 43, 75 and 93%, respectively. The RH in the chamber was controlled by the use of different saturated solutions containing excess solute. The film specimens were accurately weighed, placed in RH chambers, removed and weighed again at the end of 14 days. Changes in weight and physical appearance were noted. Percent moisture absorption was calculated in terms of the increase in the weight of the film (if any) over the initial weight of film specimen. Increase in the weight is indicative of moisture absorption.

2.6. Preparation of film coated pellets

The uncoated diclofenac sodium (model drug) pellets were prepared by means of layering the drug onto the 1.3 mm (14/16-mesh) non-pareil seeds (NPS). For a 50 g batch size, 6.0 g of drug and 0.3 g povidone were dissolved in 50 ml of 95% ethanol to prepare the drug-binder solution, which was sprayed using a spray gun (0.5 mm nozzle) (MEIJI, MP-2, Osaka, Japan) onto the NPS charged in a 150 g batch size, 10 cm diameter, pear-shaped, baffled conventional coating pan (Retina Ind. Co., Mumbai, India). The drug layered pellets were prepared under conditions of inlet air temperature 70–75 °C, pellet bed temperature 40–45 °C, spray rate 1.0 ml/min, spray gun position 15 cm from pellet bed surface and atomizing pressure 2.8 kg/cm^2. The drug layered pellets were successively coated with F1, F3 and F5 formulations of film coating solutions until the coat consumption reached 4, 6 and 8% weight increase.

Whole intact pellets and cross-sectioned pellets obtained by splitting them with a sharp sterile 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 argon atmosphere before examination under the scanning electron microscope (Stereo scan 250-MK-III).

2.7. Drug release analysis

Drug release from coated pellets was tested using USP XXIII dissolution apparatus 2 (Veego Scientific, Mumbai, India) at 37 °C at a speed of 100 rpm. The release profile was followed in 900 ml of 0.1 N HCl (pH 1.2) for first 2 h followed by 900 ml of phosphate buffer solution (pH 6.8) upto 10 h. At predetermined time intervals, aliquots of solution were withdrawn and exchanged with new media of same volume maintained at same temperature. The amount of diclofenac sodium released was determined spectrophotometrically at 276 nm. The experiments were carried out in triplicate.

3. Results and discussion

Natural polymers and their semisynthetic derivatives were widely investigated in drug delivery systems despite the advent of synthetic polymers. PR is one such biopolymer investigated in the present communication for its film forming property and drug release from coated forms. PR is light yellow in color with softening point range of 75–80 °C. Absence of a sharp melting point indicates its amorphous nature. The physicochemical properties of PR are shown in Table 2. The weight average molecular weight (M_w) of the polymer was found to be 680 with a narrow range of molecular weight distribution as indicated by the value of polydispersity index (M_w/M_n) which is close to 1.0. The glass transition temperature (T_g) of PR is 65 °C which is above the normal body temperature. The T_g value and the softening point range are indicative of soft nature of the polymer. Relative solubility study of PR was conducted in different solvents and under different pH conditions. It is totally insoluble in water and soluble in almost all the organic solvents as shown in Table 3. A pH dependent solubility was observed with increased solubility in alkaline pH conditions.

Table 2
Characterization of PR

Parameters	PR
Color	Light yellow
Acid value (mg of KOH)	151.0
Softening point (°C)	75–80
Molecular weight (M_w)	680
Polydispersity (M_w/M_n)	1.01
T_g (°C)	65.0

3.1. Characterization of films

Films produced from the plasticizer free solutions were smooth and transparent but slightly brittle. Therefore, plasticizers were added with the aim of improving their mechanical properties. Film formulations containing either DBS or TBC as plasticizer at 10 and 20% w/w were prepared. Plasticizer is an important formulation factor affecting mechanical properties of films. It shifts the glass transition temperature to lower temperatures (Lopez and Bodmeier, 1996). Since PR is hydrophobic in nature, in this study two hydrophobic plasticizers, DBS and TBC, were employed to study the plasticizer effects. Although variations in film thickness may emerge for different lots prepared (F1–F5), it was found from one-way ANOVA test at 95% confidence level that film thickness was independent of formulation composition. Mechanical properties of the free films of various formulations are shown in Table 4. The results revealed that both the plasticizers did not significantly affect the tensile strength of films at 95% confidence level. However, addition of plasticizers did affect the film elongation. The tensile strength results (Table 4) obtained with all films indicate the risk of film cracking. But, no sign of cracking in the plasticized films of PR or coated particles was observed. This may be attributed to the increase in the elongation due to addition of plasticizers (Lehtola et al., 1995). Films containing 20% of the plasticizers were sufficiently flexible to be bent in the dried state without breaking. Due to increasing elongation, the modulus at break (calculated from the ratio of stress to strain) of PR films decreased with increasing plasticizer concentration. A poor adhesion between the film and coating surface is due to high internal stress in the film coating. Young's modulus is the constant of proportionality of stress to strain and increases

Table 3
Relative solubility of PR

Solubility in different solvents[a]		Solubility in different pH solutions[a]	
Solvent	Solubility (g/ml)	pH	Solubility (g/ml) $\times 10^{-4}$
Chloroform	0.52 ± 0.017	1.6	1.1 ± 0.08
Dichloromethane	0.49 ± 0.023	4.6	5.4 ± 0.17
Acetone	0.42 ± 0.036	6.8	12.2 ± 0.64
Isopropyl alcohol	0.16 ± 0.029	8.0	28.0 ± 0.17
Ethanol	0.12 ± 0.018	10.4	62.4 ± 0.30
Water	Insoluble		

[a] Each value is mean ± S.D. of four determinations.

with increasing internal stress. In our studies, addition of plasticizers to the film decreased the values of Young's modulus consequent to increased percent elongation. This may contribute to increased adhesion between film and coating surface. These results reveal that addition of hydrophobic plasticizers like DBS and TBC are efficient for positively modifying the free films of PR.

The presence of plasticizers can also affect the permeability of polymeric films (Donbrow and Friedman, 1975; Benita et al., 1986). The results of WVTR study are depicted in Table 5. The WVTR is strongly dependent on the experimental humidity, hence, humidity conditions of 43 and 93% were employed for all the studies. The humidity transmitted through PR films decreased with increasing plasticizer concentrations. As the film thickness is likely to affect the WVTR, Utsumi's equation was employed for determination of transmission rate taking the film thickness into consideration. The decrease in WVTR may be attributed to the increased hydrophobicity due to plasticizers.

In addition to the polymer and type and concentration of plasticizer, the mechanical properties are considerably influenced by the storage conditions. Results of the moisture absorption study conducted at different RH conditions are shown in Table 6. Decrease in the moisture absorption was associated with increasing plasticizer concentration. The results are in accordance with the decreased WVTR due to addition of plasticizers used in the present study. All non-plasticized films which were initially brittle showed slight change in the physical appearance along with the plasticized films. Films became sticky and soft at the end of the study schedule as revealed by visual observation.

3.2. Coating and drug release

Slight cracking and agglomeration of film surfaces was observed with formulation F1 resulting in longer coating time. This was successfully prevented by addition of plasticizers. Using formulations F3 and F5 coating could be achieved

Table 4
Mechanical properties of free films of various formulations

Film formulation	F1	F2	F3	F4	F5
Thickness (mm)	0.40	0.41	0.43	0.45	0.47
Tensile strength (MN m^{-2})	0.248	0.271	0.397	0.253	0.312
Elongation (%)	9.837	26.120	40.060	15.420	34.190
Young's modulus (MN m^{-2})	2.521	1.011	0.830	1.600	0.800

Average of four determinations.

Table 5
WVTR of free films of various formulations

Film formulations	Thickness (cm)	Area (cm^2)	WVTR (g cm/cm^2)/24 h $\times 10^{-5}$ at RH	
			43%	93%
F1	0.040	4.34	1.21 ± 0.09	4.24 ± 0.14
F2	0.043	4.32	1.10 ± 0.12	3.47 ± 0.60
F3	0.042	4.34	0.90 ± 0.06	3.07 ± 0.56
F4	0.041	4.32	1.12 ± 0.10	4.01 ± 0.35
F5	0.043	4.33	1.10 ± 0.07	3.92 ± 0.27

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

Table 6
Moisture absorption study of free films of various formulations

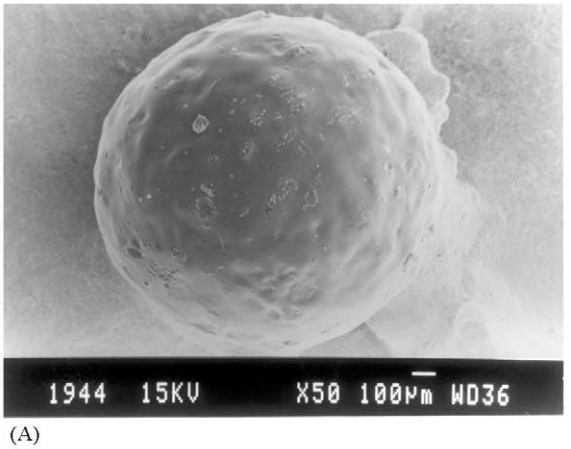
Film formulation	Percent moisture absorbed at RH			
	23%	43%	75%	93%
F1	0.113	0.426	0.972	1.132
F2	0.098	0.392	0.921	1.077
F3	0.075	0.314	0.857	0.967
F4	0.107	0.407	0.944	1.099
F5	0.094	0.371	0.894	1.013

Average of four determinations.

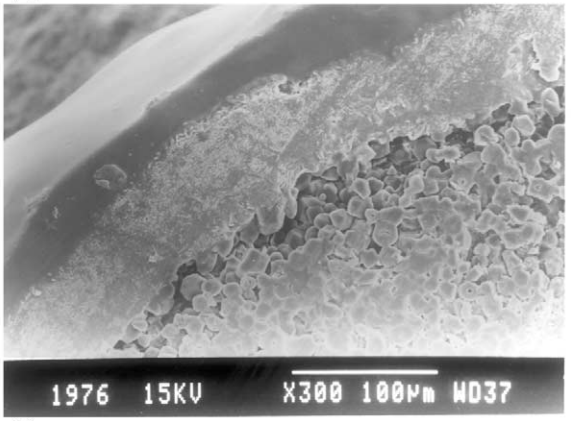
without any significant agglomeration of the pellets which may be due to lower values for Young's modulus resulting in increased adhesion between film and coating surface. Scanning electron microscopy studies were performed on drug loaded non-pareils coated with film formulations F3 and F5. SEM views are shown in Figs. 1 and 2, respectively. As illustrated in these figures, coated pellets show a continuous and uniform appearance. At a higher magnification the cross-sectioned coated pellets show distinct layers of coat, drug and NPS. The physical nature of each of the three distinct layers is clearly visible. The non-pariel core is a porous granular material. The drug layer appears compact and grained separating the core and the film coat. The surface of coated pellets is smooth and homogenous which may facilitate the sustained drug release observed in the present study. The drug release profile from coated pellets is shown in Figs. 3–5 for coating formulations F1, F3 and F5, respectively. Sustained drug release was observed for upto 10 h with increased coat build-ups. Addition of plasticizers seems to have positively favoured the sustained drug release demonstrating that slight variation in coating composition may influence drug release from coated forms.

4. Conclusions

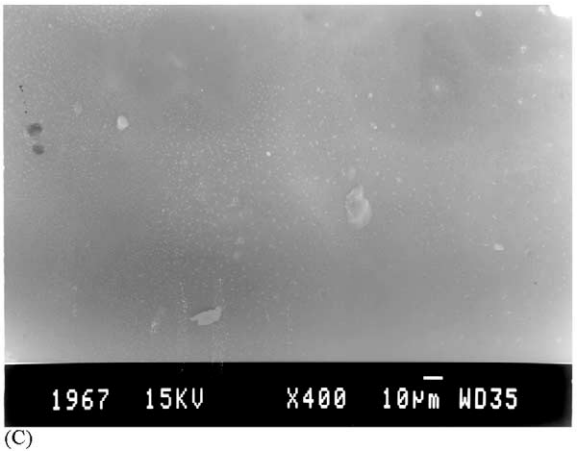
A low molecular weight film forming biopolymer, PR was examined for its drug delivery applications. Films prepared from the novel polymer, containing different proportions of plasticizers, were studied to assess the mechanical, WVT and moisture absorption characteristics. Free PR films have low mechanical properties and plasticizers are required to positively modify these properties. Both DBS and TBC were observed to improve the film characteristics. The release of diclofenac sodium from PR coated pellets could be satisfactorily sustained for upto 10 h. The release observed was pH dependent which may partly be due to poor solubility of the drug in acidic milieu. In view of the overall results reported in the present study, it may be proposed that the hydrophobic plasticizers viz. DBS and TBC (20% w/w) are effective plasticizers in PR film formulations. The plasticized films can be used in coating processes for the design of sustained release dosage forms.



(A)

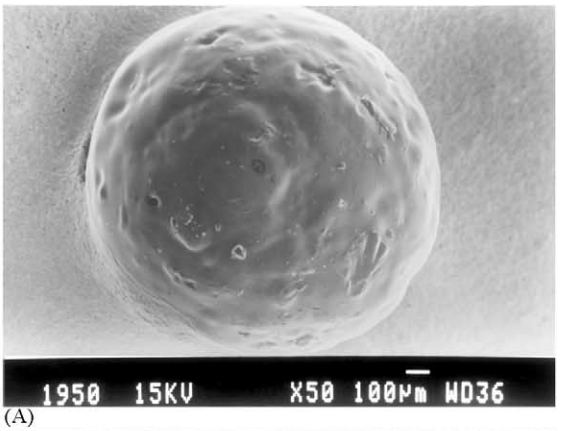


(B)

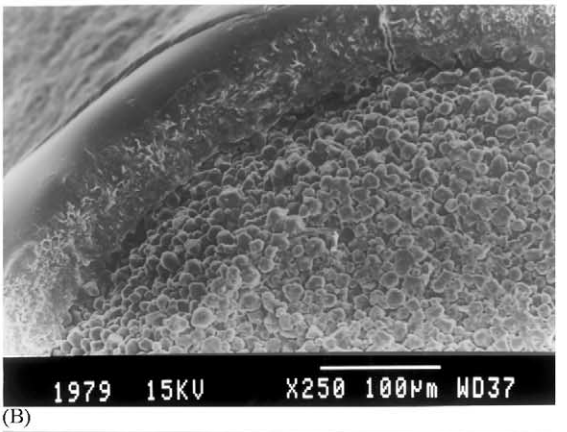


(C)

Fig. 1. Scanning electron micrographs of pellets coated with formulation F3 (A) coated pellet (B) cross-section of coated pellet (C) surface of coated pellet.



(A)



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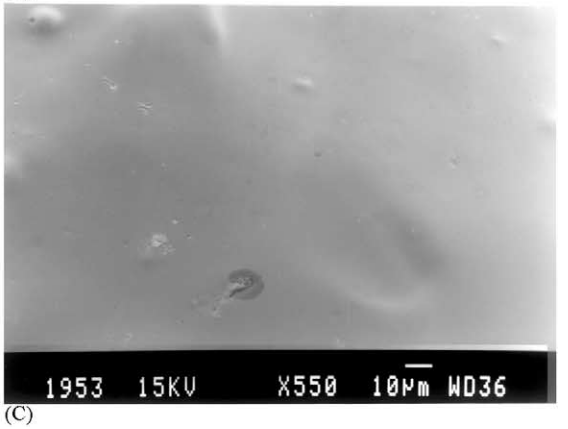

(C)

Fig. 2. Scanning electron micrographs of pellets coated with formulation F5 (A) coated pellet (B) cross-section of coated pellet (C) surface of coated pellet.

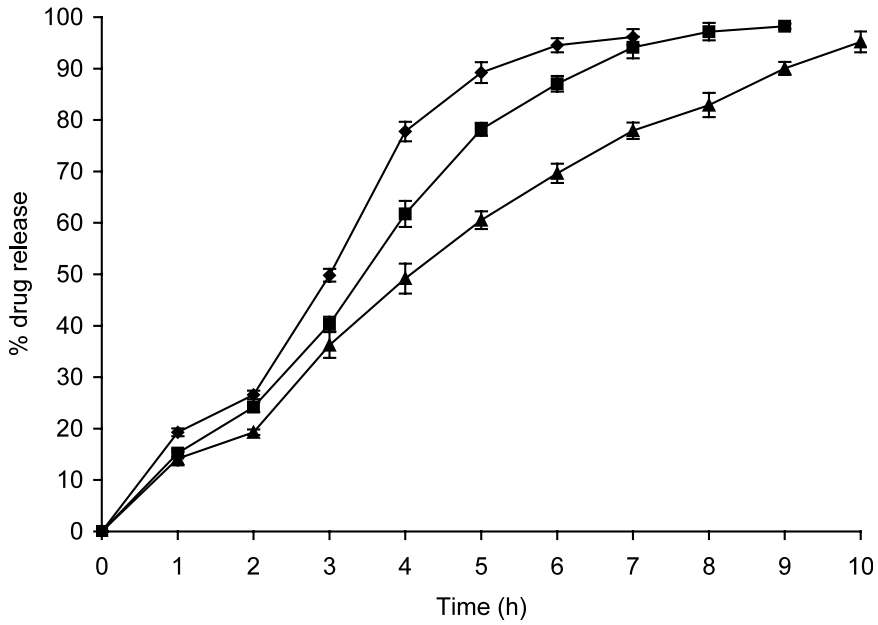

Fig. 3. Release of diclofenac sodium from pellets coated with PR film formulation F1 at various percent coating; ◆, 4% w/w; ■, 6% w/w; ▲, 8% w/w.

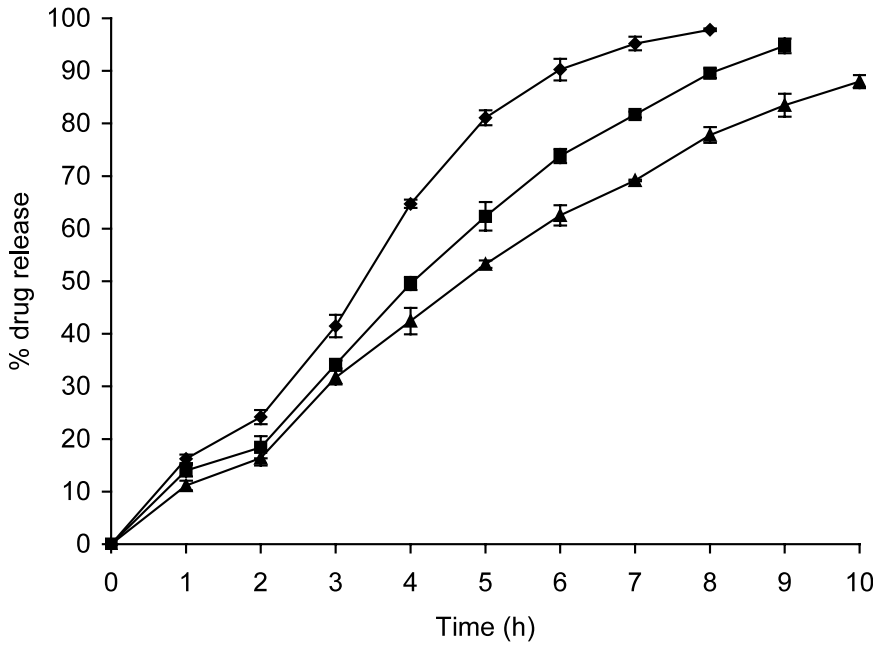

Fig. 4. Release of diclofenac sodium from pellets coated with PR film formulation F3 at various percent coating; ◆, 4% w/w; ■, 6% w/w; ▲, 8% w/w.

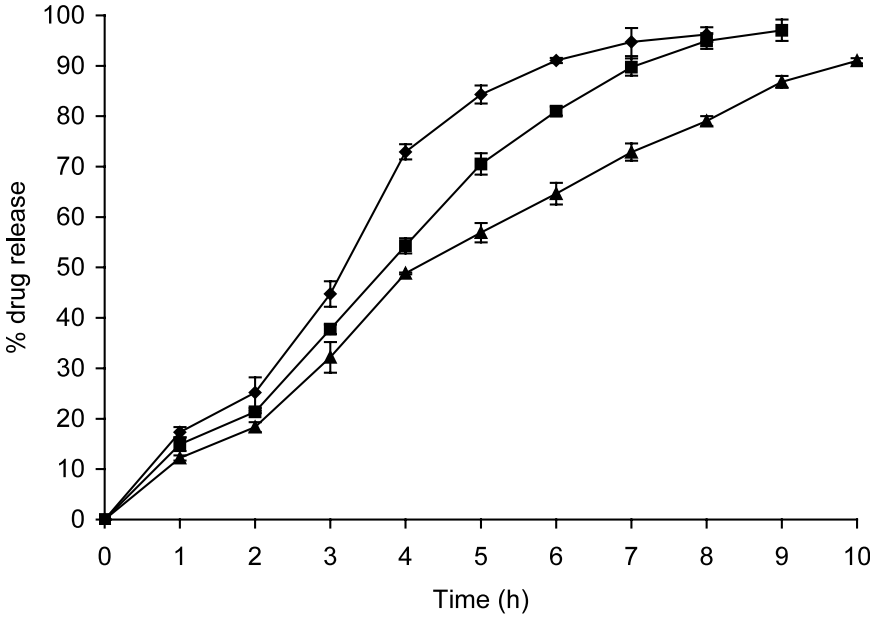

Fig. 5. Release of diclofenac sodium from pellets coated with PR film formulation F5 at various percent coating; ◆, 4% w/w; ■, 6% w/w; ▲, 8% w/w.

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