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# PEGylated Rosin Derivatives: Novel Microencapsulating Materials for Sustained Drug Delivery

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## ABSTRACT

The aim of this study was to investigate PEGylated rosin derivatives (PRDs) as microencapsulating materials for sustained drug delivery. PRDs (D1, D2, and D3) composed of a constant weight of rosin and varied amounts of polyethylene glycol (PEG) 400 and maleic anhydride were synthesized in the laboratory. Microparticles were prepared by the O/O solvent evaporation technique using the acetone/paraffin system. Diclofenac sodium (DFS) and diltiazem hydrochloride (DLTZ) were used as model drugs. The effect of the type of PRD, drug, PRD:drug ratio, viscosity of external phase, stirring speed, concentration of magnesium stearate (droplet stabilizer), and method of preparation on particle size, drug loading, and drug release profiles of microparticles was investigated. PRDs could produce discrete and spherical microspheres (with DFS) and microcapsules (with DLTZ). The drug loading value for microparticles was found to be in the range of 37.21% to 87.90%. The microparticle size range was 14 to 36 μm. The particle size and drug loadings of microparticles were substantially affected by the concentration of magnesium stearate and the type of drug, respectively. Most of the formulations could sustain the DFS and DLTZ release for 20 hours. DFS and DLTZ release from PRD microparticles followed Hixson-Crowell and first-order kinetics, respectively. The results suggest that PRDs can be used successfully to prepare discrete and spherical microparticles with DFS and DLTZ for sustained drug delivery.

**KEYWORDS:** PEGylated rosin derivatives, diclofenac sodium, diltiazem hydrochloride, microspheres, microcapsules, solvent evaporation, release kinetics.

## INTRODUCTION

Rosin is a clear, pale yellow to dark amber thermoplastic solid resin that occurs naturally in oleoresins of pine trees (family Pinaceae). It has an excellent film-forming property, fair biodegradation and biocompatibility characteristics, and a low cost.[1] So, rosin has been investigated for its applicability in the field of drug delivery.[2] Although native rosin produces brittle films, it can be modified into a worthy film former for pharmaceutical applications.[3] For modification, rosin provides 2 reactive centers: a carboxyl group and a double bond.[3] Using these, researchers have synthesized and evaluated numerous rosin ester-adduct derivatives as microencapsulating, coating, and matrix-forming materials for sustained drug delivery.[3,4] But so far only polyhydric alcohols such as glycerol, mannitol, sorbitol, and pentaerythritol have been employed to prepare the ester derivatives of rosin. Also, most of these derivatives have a complex composition.[5] Because of the complex composition and the presence of polyhydric alcohols, it has been difficult to pinpoint the precise chemistry of the final product and to recognize the impact of derivates' components on derivatives' physicochemical and film properties. In view of this, an attempt was made to synthesize new rosin derivatives of simple composition with a monohydric alcohol, polyethylene glycol 400 (PEG 400). PEG 400 was selected because of its ester-forming ability, excellent plasticizing activity, and fair biodegradation and biocompatibility characteristics.[6] However, the ester derivative of rosin with PEG 400 was a tacky product, and addition of maleic anhydride (MA) was essential to improve the product's handling property. Notably, rosin reacts with MA to form a Diels-Alder adduct, which usually exhibits higher softening and melting temperatures.[7] The final derivatives, composed of a constant weight of rosin and varied amounts of PEG 400 and MA, were synthesized. These were designated as PEGylated rosin derivatives (PRDs). Three PRDs—D1, D2, and D3—were synthesized. The composition of the PRDs is given in Table 1.

In a previous study, PRDs were synthesized, their physicochemical properties were characterized, and their precise chemistry was proposed.[8] Moreover, their film-forming ability was investigated. Results suggest that PRDs have an excellent film-forming ability and can be used as film-coating materials for sustained drug delivery. Few earlier rosin derivatives could be used successfully as microencapsulating materials.[9] But because of the presence of PEG 400, PRDs might be expected to have enough energy of curvature to produce highly spherical microparticulate systems. Moreover,

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the microparticles of PRDs might have better biocompatibility and biodegradability than did all earlier rosin derivatives because PEGs can improve the in vivo performance of numerous therapeutic substances, including proteins, peptides, and some drug delivery devices like nanoparticles and microparticles.[10] In view of the above, the present study was undertaken to investigate PRDs as novel microencapsulating materials for pharmaceutical applications.

Diclofenac sodium's (DFS's) low oral bioavailability (60%), short biological half-life (1.1-4.0 hours), and low therapeutic index,[11] and diltiazem hydrochloride's (DLTZ's) short biological half-life and thus frequent administration (3 or 4 times a day), make DFS and DLTZ suitable candidates for sustained-release preparations. Therefore, DFS and DLTZ were the drugs used in the present study.

## Materials and Methods

### *Materials*

PRDs were synthesized in the laboratory. Rosin N grade (Swastik Acids and Chemicals, Nagpur, India); PEG 400, acetone, and petroleum ether (Qualigenes Fine Chemicals, Mumbai, India); sodium hydroxide and liquid paraffin (Ranbaxy Fine Chemicals, New Delhi, India); DFS (M/s H-Joules and Co Ltd, Nagpur, India); and DLTZ (Zydus-Cadila Healthcare Ltd, Ahmedabad, India) were used. All other materials and chemicals used were of pharmaceutical grade.

### *Synthesis of PRDs*

The composition of PRDs is given in Table 1. Rosin was heated with PEG 400 at 220°C in the presence of zinc for 5 hours in a glass reactor (1 L) with constant stirring. During the reaction, the acid value of the product was determined hourly; 2 successive constant acid values indicate that all PEG 400 molecules have formed an ester with the rosin. The ester was then treated with MA for 2 hours at 160°C to form PRDs. The scheme to synthesize PRDs using abietic acid as a model compound is shown in Figure 1. The esterification and adduct formation in PRDs was verified by a Fourier transform infrared (FT-IR) spectrophotometer (FT-IR-8101 A, Shimadzu, Kyoto, Japan). PRDs were characterized by their acid value as per the method described in the Indian Pharmacopoeia (1996). Softening and melting temperatures were observed by the conventional Herculus drop technique. Solubility was determined by placing PRDs in 10 mL of different organic solvents and pH buffers for 24 hours. The average molecular weight (MW) and polydispersity were determined by a gel permeation chromatography system (Perkin-Elmer, Norwalk, CT) equipped with a refractive index detector (La Chrom Detector L-7490, Merk, Germany). The Tg was determined by differential scanning calorimetry (Mettler-Toledo Star System, CEM Corporation, Matthews, NC).

**Table 1.** Composition of PEGylated Rosin Derivatives*

| Product Code | Rosin (g) | PEG 400 (g) | MA (g) |
|---|---|---|---|
| D1 | 570 | 28.5 (5% of rosin wt) | 29.92 (5% of rosin + PEG wt) |
| D2 | 570 | 57.0 (10% of rosin wt) | 31.35 (5% of rosin + PEG wt) |
| D3 | 570 | 114.0 (20% of rosin wt) | 82.08 (12% of rosin + PEG wt) |

*PEG indicates polyethylene glycol; MA, maleic anhydride; wt, weight.

### *Viscosity Measurement*

The viscosities of 20% wt/vol solutions of the PRDs in acetone were measured at 25ºC ± 2ºC by a Brookfield viscometer using spindle no 4 (Brookfield Engineering Laboratories, Inc, Stoughton, MA).

### *Preparation of PRD Microparticles*

The PRD microparticles were prepared by the O/O emulsion solvent evaporation (ESE) method and modified emulsion solvent evaporation (MESE) method.[12] The various microparticle formulations are summarized in Table 2. In the ESE method, PRDs (1 g) and drug (500 mg or 1 g) were dissolved/dispersed in 10 mL of acetone. Then magnesium stearate was added. This dispersion was stirred with a magnetic stirrer for 5 minutes and emulsified into 160 mL of rotating liquid paraffin in a 250-mL glass beaker. The glass beaker had an internal diameter of 6.3 cm and a height of 9.5 cm, and the mechanical stirrer (REMI, Mumbai, India) had a blade of 3.5 cm in diameter. The above system was stirred for 8 hours at 29°C ± 2°C. The microparticles formed were collected by vacuum filtration and washed 2 times with 20 mL of petroleum ether (60-80) to remove the adhered liquid paraffin. These microparticles were dried at room temperature and stored in desiccators maintained at 0% relative humidity (RH) before study.

If the rate of solvent extraction from the emulsified polymer could be enhanced, then the ESE method might become more common. Thus, the MESE method was also attempted by adding a polymer nonsolvent that is miscible with solvent from both the internal phase and the external phase but that does not dissolve the polymer. The MESE procedure was similar to the ESE method described above except that after 30 minutes, petroleum ether (60-80) was added to liquid paraffin containing the internal phase (IP). The ratio of acetone

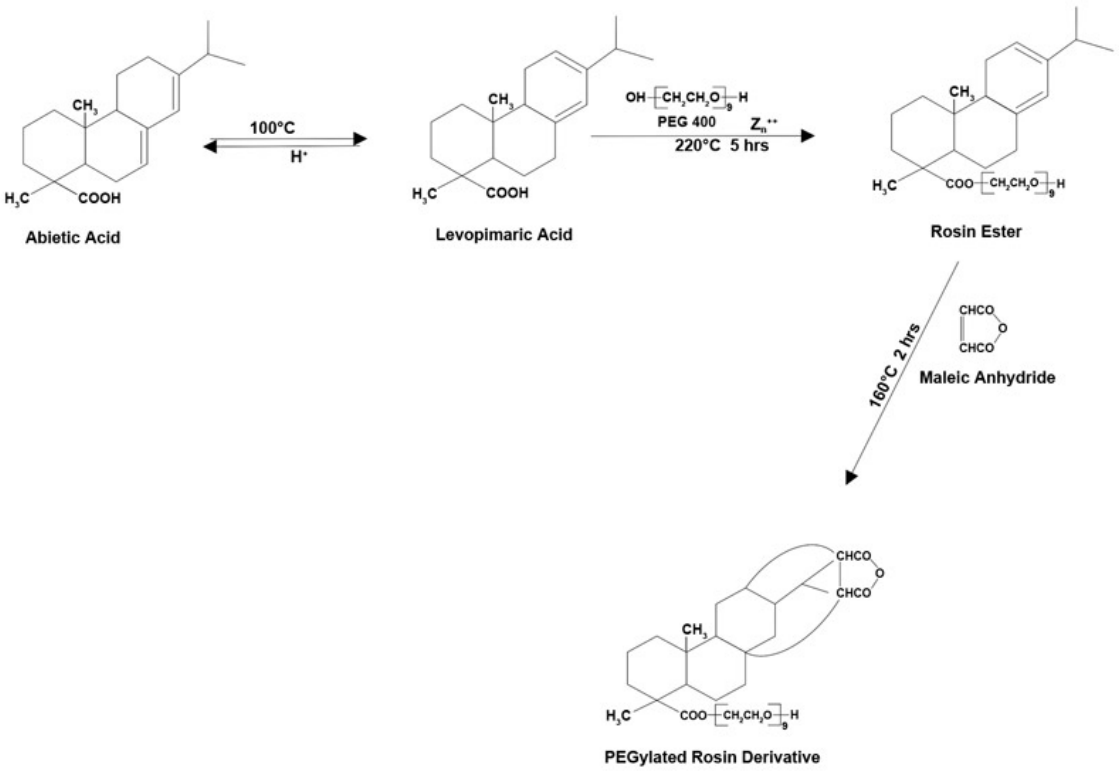


**Figure 1.** Scheme to synthesize PEGylated rosin derivatives using abietic acid as a model compound.

to petroleum ether was 8:1. The petroleum ether and the acetone were evaporated in conditions similar to those of the ESE method. The microparticles were collected as they would be in the ESE method.

### *Particle Size and Surface Morphology*

The morphology and surface properties of microparticles were examined by scanning electron microscopy (SEM) (JEOL, JXA-840A, Tokyo, Japan). The microparticles were examined by an optical microscope (Leica LaborLux Leitz S bright-field microscope, Berlin, Germany), and the mean particle diameter was determined by measuring ~100 particles using a 1-mm stage micrometer.

### *Drug Loading Efficiency*

About 100 mg of microparticles was triturated in a mortar, and drugs were extracted in a total of 250 mL of phosphate buffer pH 6.8 (DFS) or distilled water (DLTZ) during

**Table 2.** Formulations of PRD Microparticles*

| Formulation | PRD | Drug | PRD:Drug Ratio | Viscosity of LP (cps) | Stirring Speed (rpm) | Detackifier Conc (% wt/wt)† |
|---|---|---|---|---|---|---|
| F1 | D1 | DFS | 2:1 | 188 | 2000 | 10 |
| F2 | D2 | DFS | 2:1 | 188 | 2000 | 10 |
| F3 | D3 | DFS | 2:1 | 188 | 2000 | 10 |
| F4 | D2 | DLTZ | 2:1 | 188 | 2000 | 10 |
| F5 | D2 | DFS | 1:1 | 188 | 2000 | 10 |
| F6 | D1 | DFS | 1:1 | 188 | 2000 | 10 |
| F7 | D1 | DFS | 1:1 | 140 | 2000 | 10 |
| F8 | D1 | DFS | 1:1 | 94 | 2000 | 10 |
| F9 | D1 | DFS | 2:1 | 188 | 3000 | 10 |
| F10 | D1 | DFS | 2:1 | 188 | 2000 | 20 |
| ‡F11 | D1 | DFS | 2:1 | 188 | 2000 | 10 |

*PRD indicates PEGylated rosin derivatives; LP, liquid paraffin; Conc, concentration; DFS, diclofenac sodium; DLTZ, diltiazem hydrochloride.
†Magnesium stearate was used as a detackifier, and the % wt/wt of total PRD weight is presented.
‡Petroleum ether was added after 30 minutes.

3 washings. After suitable dilutions, the samples were analyzed spectrophotometrically (UV visible spectrophotometer 1601, Shimadzu, Kyoto, Japan) at 276 nm (DFS) or 237 nm (DLTZ) for drug content determination.

### *In Vitro Drug Release*

The in vitro drug release profile was determined using US Pharmacopeia 25 dissolution apparatus 2 (paddle type). About 100 mg of microparticles was taken in a muslin cloth (mesh 400) and tied to the paddle rotating at a speed of 100 rpm.[13] Phosphate buffer pH 6.8 for DFS and distilled water for DLTZ (900 mL for each sample maintained at 37°C ± 0.5°C) were the dissolution media. Hourly, 5 mL of the sample was withdrawn and replaced with the same volume of medium. Samples were diluted to 50.0 mL and analyzed spectrophotometrically at 276 nm or 237 nm for drug content. Each sample was run in triplicate, and using these results a mean was calculated. The data obtained for drug loading and release were subjected to a 1-way analysis of variance test to analyze statistical differences using the software PRISM (Graphpad, San Diego, CA).

### *Release Kinetics*

To study the exact mechanism of drug release from microparticles, dissolution data were computed in the light of different kinetic equations[14] by PCP Disso V3 software (Poona College of Pharmacy, Poona, India).

## Results and Discussion

### *Synthesis and Characterization of PRDs*

The structure of PRDs and the reaction scheme are depicted in Figure 1. Since the carboxyl groups of rosin are structurally hindered, PEG 400 was treated with rosin at an elevated temperature (220°C) in the presence of Zn. The PEG ester of rosin was then treated with MA to produce PRDs, which were characterized by FT-IR spectroscopy. The FT-IR spectra are shown in Figure 2. The absorption bands at 1693.7 $cm^{-1}$, 2860 $cm^{-1}$, and 3431.5 $cm^{-1}$ for C=O, –CH, and –OH stretching, respectively, indicate the presence of carboxyl groups in rosin as well as in PRDs. The peak intensity of band at 2860 $cm^{-1}$ was much higher in PRDs as compared with rosin. This was due to the presence of PEG 400 in PRDs. The prominent absorption band at around 3430 $cm^{-1}$ for –OH stretching also confirms the presence of PEG 400 in PRDs. The absorption band at 1725 $cm^{-1}$ for C=O stretching of ester was present in PRDs but not in rosin. Notably, the peak intensity of band at 1725 $cm^{-1}$ for C=O stretching of ester was lowest and highest in D1 and D3, respectively.

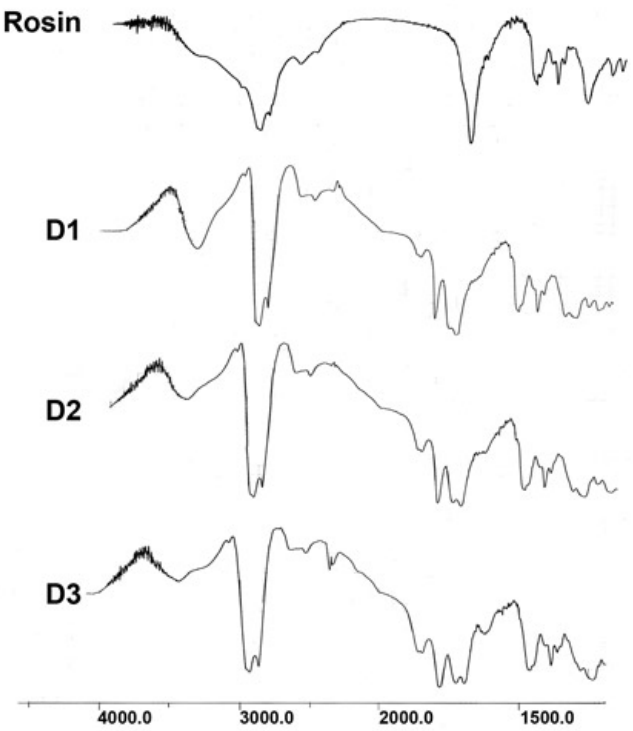


**Figure 2.** Fourier transform infrared spectra of rosin and PEGylated rosin derivatives.

### *Physicochemical Properties of PRDs*

The acid value of PRDs decreased as the amount of PEG 400 increased (Table 3). The MW of PRDs increased proportionally with the amount of PEG 400. The polydispersity index values indicated a narrow range of MW distribution in D1 and D2 as compared with D3. An increase in the amount of PEG 400 decreased the Tg of PRDs. All PRDs were freely soluble in the organic solvents. The effect of pH was clear: PRDs showed greater solubility at an alkaline pH than at an acidic pH (at pH 1.2, the solubility of D1, D2, and D3 was 1.80, 2.30, and 2.60 mg/mL, respectively; and at pH 6.8 the solubility of D1, D2, and D3 was 17.40, 20.02, and 20.85 mg/mL, respectively). This may be attributed to the ionization of free carboxyl groups of PRDs at an alkaline pH.

### *Preparation of Microparticles*

Pilot experimentation revealed that a PRD:drug ratio above 1:1 encourages the aggregation of microparticles. To avoid the use of organic solvents, an attempt was also made to produce PRD microparticles in the water phase, but no discrete and spherical microparticles could be obtained. To examine the effect of a fast-evaporating solvent, methylene chloride as a solvent of IP for the O/O ESE method was also tried, but a strong aggregation of microparticles was observed after only 10 minutes. The fast solvent removal rate

**Table 3.** Characterization and Physicochemical Properties of PEGylated Rosin Derivatives*

| Derivative | MW | PI | Tg | Acid Value | Softening Point | Melting Point |
|---|---|---|---|---|---|---|
| D1 | 470 | 1.2 | 48.24 | 134.09 | 58-60 | 92-94 |
| D2 | 585 | 1.4 | 37.46 | 116.87 | 52-54 | 78-80 |
| D3 | 795 | 1.6 | 35.55 | 90.44 | 44-47 | 62-64 |

*MW indicates molecular weight; PI, polydispersity index.

probably encouraged the coalescence of "embryonic" microparticles. Among various droplet stabilizers, the capability of magnesium stearate, talc, glyceryl monostearate, Span 60, and Span 80 to produce PRD microparticles was investigated. But none of these alone except magnesium stearate was effective in developing the discrete and spherical microparticles of PRDs. Also, ESE and MESE processes were attempted at 40°C to reduce the processing time, but D2 and D3 could not produce spherical and discrete microparticles, probably because of their low Tg values. It was observed that at high RH (above 70%), PRDs could not produce free-flowing microparticles; after filtration and washing with petroleum, they were stuck to the filter paper. This was perhaps due to the presence of PEG 400, which is a hygroscopic material. Also, it is possible that at high RH, petroleum ether softens PRDs, as microparticles became soft and stick to the filter paper only after washing with petroleum ether. Therefore, the microparticles were prepared at RH 40% to 45% and temperature 29°C ± 2°C.

### *Surface Morphology*

The SEM images are shown in Figure 3. The images reveal that PRDs produced a matrix (microspheres) with DFS and encapsulated DLTZ to form microcapsules. The clear difference in the surface texture of microparticles—DFS's rough (Figures 3A, 3B, and 3C) and DLTZ's smooth and shiny (Figure 3D)—can be seen in the SEM images. During the preparation of IP, it was noted that DFS was completely soluble in PRDs' solution in acetone, whereas DLTZ formed a dispersion in the acetone. Thus, dispersed DLTZ particles were encapsulated by the PRDs' wall, and DFS precipitated together with PRDs to form a homogeneous drug-polymer matrix after solvent evaporation. Pores were seen on the surface of PRD microspheres produced with DFS (Figures 3A, 3B, and 3C). The highest numbers of pores was observed in D3 microspheres (Figure 3C).

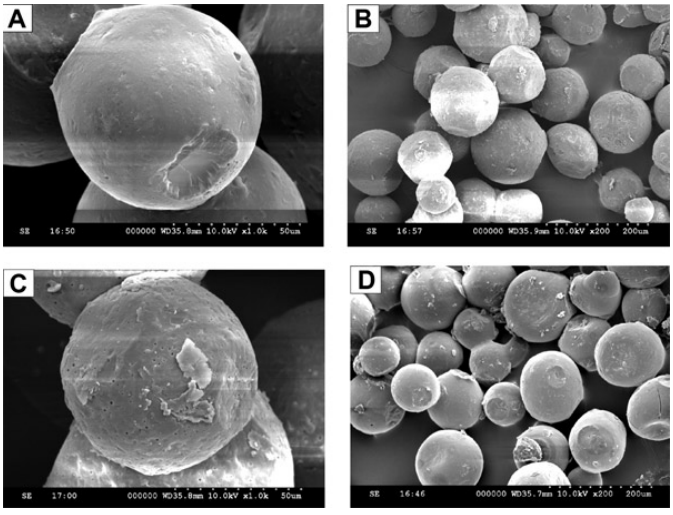


**Figure 3.** Scanning electron microscopy images of diclofenac sodium microparticles prepared with (A) D1, (B) D2, and (C) D3, and (D) diltiazem hydrochloride microparticles prepared with D2.

### *Particle Size*

#### *Effect of Type of PRD*

Microparticles prepared with D1, D2, and D3 with a derivative:DFS ratio of 2:1 had a similar particle size, in the range of 36 to 38 μm (Table 4). Type of PRD did not alter the microparticle size, because the PRD type did not substantially alter the viscosity of IP (20% wt/vol solutions of D1, D2, and D3 in acetone exhibited almost similar viscosities of 6.5 cps, 6.0 cps, and 7.0 cps, respectively).

#### *Effect of PRD:Drug Ratio*

D1 with DFS in ratios of 2:1 and 1:1 (F1 and F6) produced microparticles with a size range of 36 to 38 μm and 26 to 28 μm, respectively (Table 4). An increase in the PRD:drug ratio decreased the microparticle size, possibly because of a reduction in the viscosity of IP at the higher drug ratio,[15] which might have formed a fine emulsion of IP in the external phase (EP) and thus might have produced the smaller microparticles.

**Table 4.** Effect of Formulation Variable on Drug Loading and Particle Size of PEGylated Rosin Derivative Microparticles

| Formulation | Particle Size (μm) | Drug Loading* (%) |
|---|---|---|
| F1 | 36-38 | 79.42 |
| F2 | 36-38 | 60.39 |
| F3 | 36-38 | 40.62 |
| F4 | 28-30 | 30.21 |
| F5 | 24-26 | 38.46 |
| F6 | 26-28 | 46.16 |
| F7 | 40-42 | 75.21 |
| F8 | 62-64 | 87.19 |
| F9 | 30-32 | 76.18 |
| F10 | 14-16 | 71.70 |
| F11 | 28-30 | 79.10 |

*Each value is a mean of 3 determinations.

*Effect of Viscosity of Paraffin*

The microparticle size was significantly decreased with the increase in viscosity of liquid paraffin (Table 4). It is acknowledged that the tangential, radial, and axial flows (TRA flows) exist in the rotating EP.[16] In the highly viscous EP, TRA flows probably were less intense (because of the resistance of EP itself) and could not facilitate the coalescence of dispersed droplets of IP. This resulted in the formation of smaller microparticles. Also, in this study the viscosity of paraffin was reduced by adding light liquid paraffin to heavy liquid paraffin; light liquid paraffin can extract more acetone.[12] Additionally, magnesium stearate was incorporated as a droplet stabilizer in all formulations. These factors also should not be ignored and might have contributed to the microparticle size.

*Effect of Stirring, Concentration of Magnesium Stearate, and Method of Preparation*

An increase in stirring speed decreased the microparticle size (F1 and F9 in Table 4). Magnesium stearate of a higher concentration prevented the coalescence of dispersed droplets[17] and thus produced smaller spheres. Type of method (eg, MESE) did not significantly alter the microparticle size. The small quantity of petroleum ether seems the probable reason for insignificant effect of method of preparation on microparticle size.

*Effect of Type of Drug*

D2:DFS in a 2:1 ratio produced microparticles with a size range of 36 to 38 μm. At the same ratio, D2:DLTZ produced microparticles with a wide size range distribution, from a minimum of 28 to 30 μm to a maximum of 576 ± 40 μm (F2 and F4 in Table 4). However, the 576 ± 40 μm microparticles were few and could be separated easily by sieving. Unlike DFS, DLTZ showed partial solubility in PRD solution in acetone, so it could not be incorporated into all emulsion droplet size fractions homogeneously. The droplets enclosing/entrapping DLTZ particles of different sizes thus produced microparticles of different sizes. Next, DLTZ microparticles of a size range comparable with DFS microparticles' were selected by sieving. SEM images illustrate the particle size uniformity of DLTZ microparticles collected by sieving (Figure 3D).

***Drug Loading Efficiency***

*Effect of Type of PRD*

Type of PRD significantly ($P < .05$) affected the drug loading of microparticles. Microparticles of D1 and D3 with DFS in a ratio of 2:1 showed 79.42% and 40.62% drug loading, respectively (Table 4). D1 and D3 contain the lowest and the highest amount of PEG 400 and MA, respectively. As the particle size of D1 and D3 microparticles was comparable, it can be stated that an increase in the amounts of PEG 400 and MA in PRDs reduced the drug loadings of microparticles. Higher amounts of PEG 400 and MA probably facilitate the diffusion of parts of the entrapped drug to the surrounding medium during microparticle formation. Also, it is possible that the greater hydrophobicity of D1 could favor the entrapment of DFS.

*Effect of PRD:Drug Ratio and Viscosity of Paraffin*

An increase in the PRD content of IP significantly ($P < .05$) increased the drug loading of microparticles (Table 4). Perhaps the amount of PRD at a PRD:drug ratio of 1:1 was not enough to entrap all the drug material. Microparticles prepared in EP of viscosity 188, 140, and 94 cps showed 46.16%, 75.21%, and 87.19% drug loadings, respectively (F6, F7, and F8 in Table 4). This significant difference ($P < .05$) can be ascribed to the proportional change in particle size of microparticles with the viscosity of EP. In highly viscous EP, small spheres were obtained, which provided a greater surface area for drug loss.[18]

*Effect of Stirring, Concentration of Magnesium Stearate, and Method of Preparation*

An increase in the stirring speed and the concentration of magnesium stearate slightly reduced the microparticle size and thus the drug loading; the difference was statistically insignificant ($P > .05$). The type of method also did not significantly alter the drug loading of microparticles. The probable reasons are the small quantity of petroleum ether and the lack of substantial change in microparticle size with the type of method.

*Effect of Type of Drug*

D2:DFS and D2:DLTZ in a ratio of 2:1 produced microparticles with 60.39% and 30.21% drug loadings, respectively (F2 and F4). The loading efficiency was significantly ($P < .05$) low for the hydrophilic drug. This may be attributed to the difference in solubility of DFS and DLTZ in the PRD matrix, since the particle size of both was comparable (Figures 3B and 3D). PRDs are hydrophobic materials. DFS probably has higher solubility than DLTZ and thus remained entrapped in the PRD matrix during microparticle formation, whereas DLTZ escaped in EP. To pinpoint the exact reason, the solubility of both drugs in paraffin was determined spectrophotometrically. DLTZ showed greater solubility (2.76 mg in 160 mL in 12 hours) than DFS (0.73 mg in 160 mL in 12 hours) in liquid paraffin.

Moreover, the crystals of DLTZ were observed in EP under the light microscope during microparticle preparation. This suggests that a greater amount of DLTZ, as compared to DFS, was lost to EP during microparticle formation.

### *In Vitro Drug Release*

#### *Effect of Type of PRD*

D1 and D3 microparticles with DFS in a ratio of 2:1 (F1 and F3) showed complete drug release in 20 and 18 hours, respectively (Figure 4A). The difference between the amounts of drug released was statistically significant ($P < .05$). D3 contained the greatest amount of hydrophilic components (PEG 400 and MA), so it seems that higher amounts of PEG 400 and MA in PRDs increased the hydration rate and thus the drug release rate of microparticles. A similar finding with regard to PEG 400 was reported by Huang et al.[19] A similar increase in the nifedipine release rate from ethyl cellulose (EC) microparticles was reported by Guyot and Fawaz.[20] Also, SEM images revealed the high porosity of D3 microparticles (Figure 3). This may be ascribed to the greater polydispersity index of D3. Because of polydispersity, D3 might have precipitated less homogeneously from the dispersed droplets of IP to form the porous microparticles, and the pores could have facilitated the drug release further.

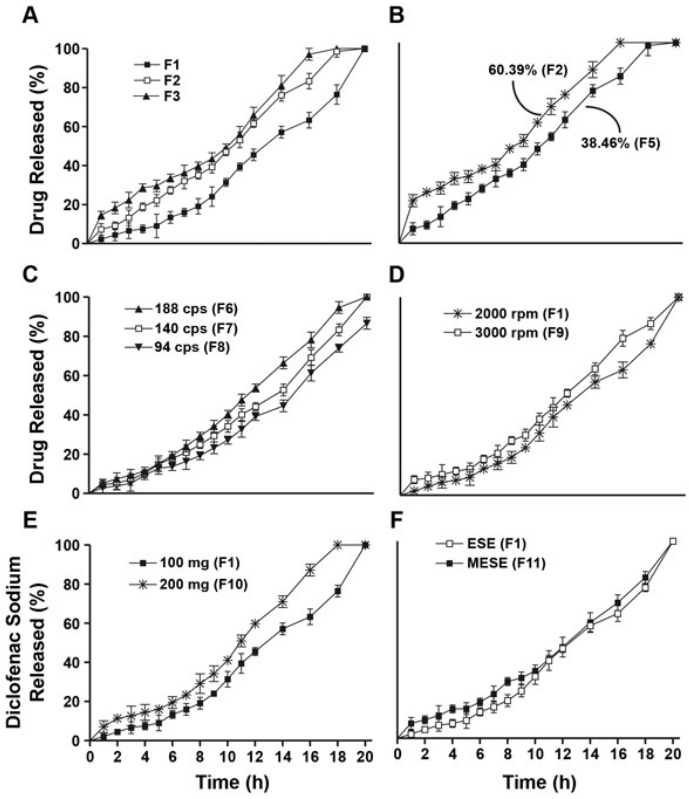


**Figure 4.** Effect of (A) type of PRD, (B) drug loading, (C) viscosity of paraffin, (D) stirring speed, (E) concentration of magnesium stearate, and (F) method of preparation on drug release profile of PRD microparticles. PRD indicates PEGylated rosin derivatives; ESE, emulsion solvent evaporation; MESE, modified emulsion solvent evaporation.

#### *Effect of PRD:Drug Ratio*

D1:DFS in a ratio of 2:1 and 1:1 showed complete drug release in 20 and 18 hours, respectively, while D2:DFS in a ratio of 2:1 and 1:1 showed complete drug release in 20 and 16 hours, respectively (Figure 4B). Although the difference was statistically insignificant ($P > 0.05$) in the case of D1, the PRD:drug ratio significantly affected the drug release profile of D2 matrices. This perhaps was due to the higher hydrophilic content of D2. In both cases, an increase in drug load increased the drug release rate. It has also been revealed that an increase in drug load increases the porosity of microparticles, which provides faster drug delivery.[21]

#### *Effect of Viscosity of Paraffin*

A decrease in the viscosity of liquid paraffin decreased the drug release rate of DFS microspheres (Figure 4C). The decrease in the viscosity of liquid paraffin produced larger spheres, which provided less surface area for drug release. Also, it must be noted that in the present study, the viscosity of paraffin was reduced by adding light liquid paraffin to heavy liquid paraffin; light liquid paraffin extracts more acetone from IP.[12] Thus, the greater amount of light liquid paraffin in EP in this study would increase the extraction rate of acetone from IP droplets. Yang et al have systematically studied the effect of solvent removal rate from IP droplets on microparticle properties.[22] Their results suggest that sphere porosity tends to decrease with an increasing solvent removal rate until a limiting value is reached. Thus, it seems that higher amounts of light liquid paraffin in EP in the present study might have increased the acetone removal rate to the extent that less porous microparticles were obtained, which meant that drug was released more slowly.

#### *Effect of Stirring Speed*

PRD microparticles prepared with DFS at 2000 and 3000 rpm showed 76.45% and 86.71% drug release at the end of 18 hours, respectively (Figure 4D). This slight increase in the drug release rate with an increase in the stirring speed was due to the fact that higher stirring speed produced relatively smaller microparticles.

#### *Effect of Concentration of Magnesium Stearate*

PRD microparticles prepared with 100 mg and 200 mg of magnesium stearate (F1 and F10) showed complete drug release at the end of 20 hours and 18 hours, respectively

(Figure 4E). This was due to the reduction in microparticle size with an increase in the amount of magnesium stearate (Figure 4E).

*Effect of Method of Preparation*

When the PRDs and the drug were allowed to precipitate rapidly by adding petroleum ether in the MESE method, the microparticles showed faster drug delivery (Figure 4F). However, the difference was statistically insignificant ($P > 0.05$). The slight increase in drug release rate with the addition of petroleum ether may be due to the fact that the fast solvent evaporation rate after a limiting value produces more porous and permeable spheres through which drug can escape more quickly.[22] Also, Jeyanthi et al[23] have investigated sphere porosity at variable solvent removal rate, and their findings support the above explanation.

*Effect of Type of Drug*

DLTZ release from PRD microparticles was slow as compared with that of DFS (Figure 5). The drug release study of DLTZ and DFS microparticles was executed in distilled water and phosphate buffer pH 6.8, respectively. PRDs have very low solubility in distilled water. Thus, to see if the distilled water affected DLTZ release from PRD microparticles, dissolution of PRD microparticles containing DLTZ was also executed in phosphate buffer pH 6.8. However, the release rate of DLTZ was again slow (72% ± 3% in 14 hours). This slow speed, therefore, may be attributed to the structural differences of PRD microparticles. DFS and DLTZ formed microspheres and microcapsules, respectively, with PRDs. Thus, DFS was distributed throughout the PRD matrix, and more of it was available for dissolution. In contrast, DLTZ was inside the PRD coatings, and thus its release was slow as compared with that of DFS.

**Table 5.** Correlation Coefficients ($r$) According to Different Kinetic Equations Used to Describe the Drug Release From PEGylated Rosin Derivative Microparticles*

| | Correlation Coefficient ($r$) for Kinetic Model | | | | |
|---|---|---|---|---|---|
| Formulation | First Order | B-L | H-C | Zero Order | Higuchi |
| F1 | 0.983 | 0.850 | 0.996 | 0.962 | 0.916 |
| F2 | 0.988 | 0.913 | 0.993 | 0.992 | 0.965 |
| F3 | 0.985 | 0.905 | 0.993 | 0.984 | 0.959 |
| F4 | 0.989 | 0.786 | 0.973 | 0.917 | 0.860 |
| F5 | 0.995 | 0.906 | 0.994 | 0.975 | 0.937 |
| F6 | 0.993 | 0.900 | 0.997 | 0.982 | 0.943 |
| F7 | 0.985 | 0.919 | 0.995 | 0.989 | 0.956 |
| F8 | 0.976 | 0.885 | 0.993 | 0.981 | 0.945 |
| F9 | 0.996 | 0.882 | 0.996 | 0.965 | 0.918 |
| F10 | 0.994 | 0.857 | 0.992 | 0.959 | 0.911 |
| F11 | 0.994 | 0.915 | 0.993 | 0.982 | 0.946 |

*B-L indicates Baker-Lonsdale kinetic model; H-C, Hixson-Crowell kinetic model.

***Release Kinetics***

The correlation coefficient values for linearity according to different kinetic equations are given in Table 5. The drug release data from all PRD microparticles containing DFS followed the Hixson-Crowell kinetic equation. When this model is used, it is assumed that the release rate is limited by the drug particle dissolution rate and not by the diffusion that might occur through the polymeric matrix. This model has been used to describe the release profile, keeping in mind the diminishing surface area of drug particles

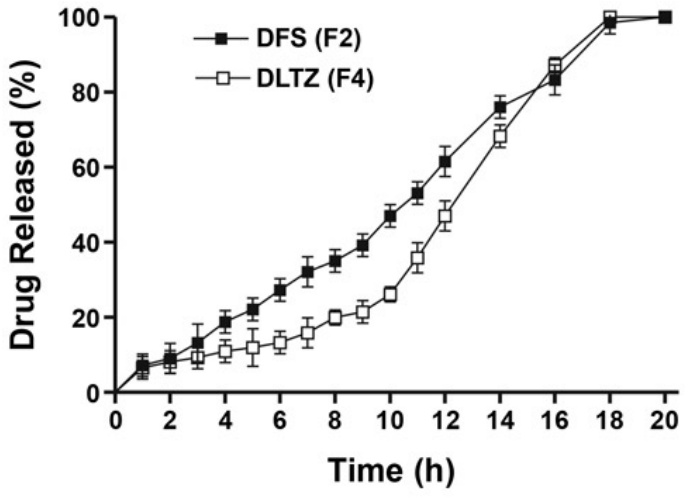


**Figure 5.** Effect of type of drug on drug release profile of PEGylated rosin derivative microparticles. DFS indicates diclofenac sodium; DLTZ, diltiazem hydrochloride.

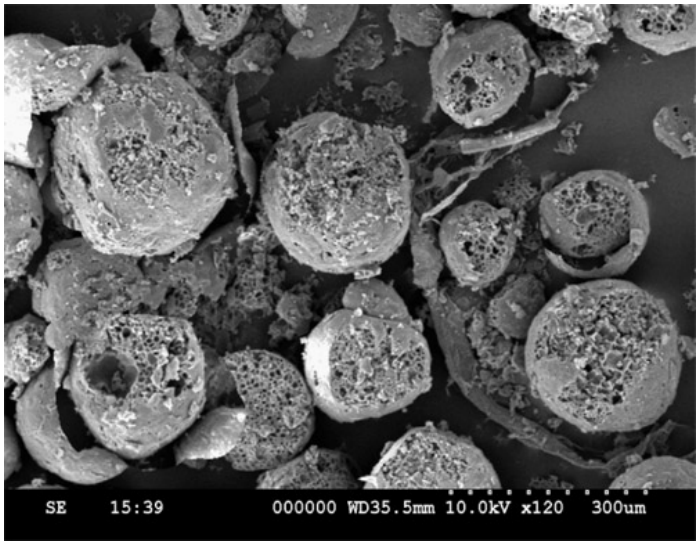


**Figure 6.** Scanning electron microscopy image of diclofenac sodium–D2 microparticles after dissolution.

and the device during dissolution.[24,25] Thus, the drug dissolution as well as matrix erosion seems responsible for DFS release from microparticles. The SEM images clearly show PRD-DFS matrix erosion (Figure 6). On the other hand, PRD microparticles containing DLTZ showed drug release by first-order kinetics, which indicates that the drug release was dependent on the drug load in these matrices.

## CONCLUSIONS

PRDs can be used efficiently to produce microparticles of DFS and DLTZ for sustained drug delivery. A change in the hydrophilic content of PRDs substantially alters the drug content and drug release rate of microparticles. DFS and DLTZ release from PRD microparticles follows Hixson-Crowell and first-order kinetics, respectively. Rosin and PEG 400 both have fair biodegradation and biocompatibility characteristics; thus, experimental work is in progress to examine the in vivo performance of PRD microparticles.

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