Drug Development and Industrial Pharmacy, 27(6), 591–598 (2001)

COMMUNICATION

Formation and Stability Studies of Multiple (w/o/w) Emulsions Prepared with Newly Synthesized Rosin-Based Polymeric Surfactants

V. T. Dhanorkar,[1,*] B. B. Gogte,[2] and A. K. Dorle[1]

[1]Department of Pharmaceutical Sciences, University Campus, Nagpur University, Nagpur 440 010 (MS), India
[2]Laxminarayan Institute of Technology, Nagpur University, Nagpur 440 010 (MS), India

ABSTRACT

The multiple (water-in-oil-in-water, w/o/w) emulsions were prepared using newly synthesized rosin-based polymeric surfactants. The oil phase used was liquid paraffin. These emulsions were evaluated for stability by various methods: conductivity, viscosity, particle size, and visual inspection. The stability studies were carried out at 37°C and 4°C for 1 month. The multiple emulsion prepared with polymer 7 was found to be more stable compared to the emulsions prepared with polymer 2.

INTRODUCTION

Multiple emulsions are emulsions in which drops of the dispersed phases contain smaller droplets with the same composition as the external phase. The potential of these systems for application in pharmaceutical technology has generated increased attention, and comprehensive reviews have dealt with their preparation, stability, and pharmaceutical uses (1–3). The stability of the multiple emulsion is a complex phenomenon, and long-term stabilization is an unsolved problem.

The present study was performed to investigate the formation and stability of multiple (water-in-oil-in-water, w/o/w) emulsions prepared with rosin-based polymeric surfactants. The use of rosin as a surface-active agent and emulsifying agent has been patented (4–6). A literature

*Corresponding author. E-mail: dvipin@usa.net

survey indicated no evidence of the use of rosin-based polymeric surfactants in the preparation of multiple emulsions.

The rosin-based polymeric surfactants were synthesized in the laboratory. The synthesized polymers were used for the preparation of multiple (w/o/w) emulsions. The stability studies of the multiple emulsions prepared with rosin-based polymers were carried out using commonly employed methods: visual inspection, conductivity, viscosity, and particle size measurements.

EXPERIMENTAL

Materials

The procured materials were as follows: rosin N grade (Tayebai Ebrahimji Pettodwala, Mumbai, India); glycerol (Qualigens); sorbitol (Qualigens); pentaerythritol (Qualigens); liquid paraffin (Thomas Baker); Span 80 (S.D. Fine); maleic anhydride (Qualigens); pthaleic anhydride (Qualigens); castor oil (P. J. Chemicals); sodium bisulfate (S. D. Fine); sodium bisulfite (S.D. Fine). Distilled water was used for the preparation of all emulsions.

Methods

Preparation of Rosin-Based Polymers

The polymers were synthesized at Laxminarayan Institute of Technology (LIT), Nagpur, India. The polymer synthesis reaction was conducted in a four-neck 2-L glass reactor. This reactor was fitted with a condenser, stirrer, and temperature control arrangement. The reaction temperature was maintained within ±2°C with the help of an accurate thermometer. First, rosin, part of the maleic anhydride, castor oil, and catalyst (sodium bisulfite and sodium bisulfate) were added to the reactor, and temperature was slowly raised to 160°C. The reaction was maintained at this temperature for 1 h. Next, the temperature was lowered to 120°C, and glycerol (pentaerythritol for the synthesis of polymer 7) and sorbitol were added slowly over about 15 min. The cooking continued for 3 to 4 h at 210°C to 250°C. At the end of this period, calculated solvents (5% xylene), part of the maleic anhydride, and pthaleic anhydride were slowly added over about 15 min. Further cooking was done at a lower temperature (80°C) for 3 to 4 h until the desired acid value was reached. Finally, xylene was stripped totally by heating at a slightly higher temperature (150°C) using a vacuum. The sample was strained through a fine mesh and stored carefully.

During the process, the acid value of the product was determined intermittently, as reported previously by Sahu et al. (7). The composition and physicochemical properties of the prepared rosin-based polymers are presented in Table 1 and Table 2, respectively.

Table 1

Composition of Polymer 2 and Polymer 7

	Weight in Grams	
Composition	Polymer 2	Polymer 7
Rosin	50	50
Castor oil	35	35
Glycerol	2.2	—
Sorbitol	14.7	8.79
Maleicanhydride	6	6
Pthaleicanhydride	2	2
Pentaerythritol	—	6.97

Preparation of Multiple (w/o/w) Emulsion

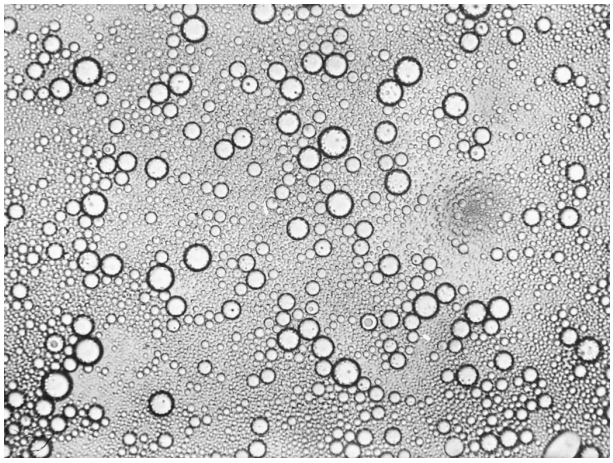
Multiple emulsions were prepared according to the formulas given in Table 3. They were prepared with a two-step emulsification process (8). The internal aqueous phase and oily phase were preheated to 70°C before emulsification. The internal aqueous phase was added to the oil phase by stirring at 3500 rpm for 10 min. The emulsion was then placed in a water bath maintained at 70°C. The viscous primary emulsion formed was emulsi-

Table 2

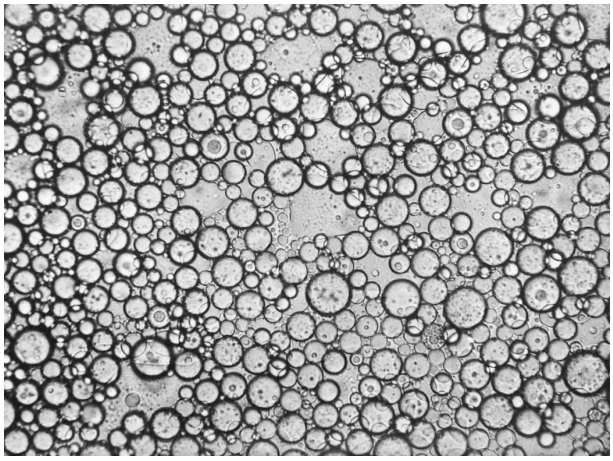
Physicochemical Properties of Polymer 2 and Polymer 7

	Acid Value	Sap Value	HLB	Viscosity[a] (Centipoises)	Weight per ml* (1 g % Solution)	Refractive Index[a] (1 g % Solution)
Polymer 2	0.44	107.35	12.7	72,000	1.5389	1.3335
Polymer 7	2.6	117.16	12.1	45,000	1.055	1.334

[a] Readings taken at 37°C.

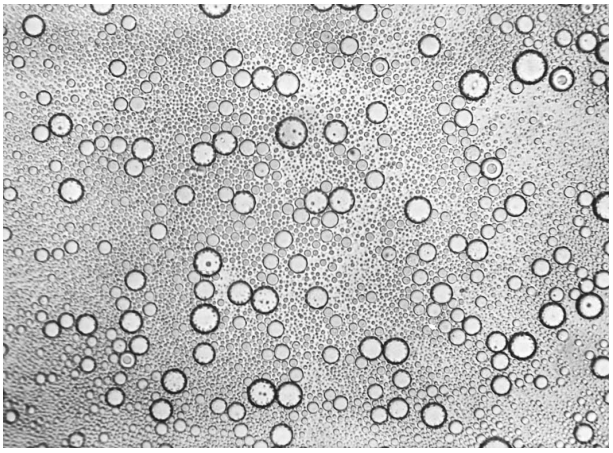


(a)

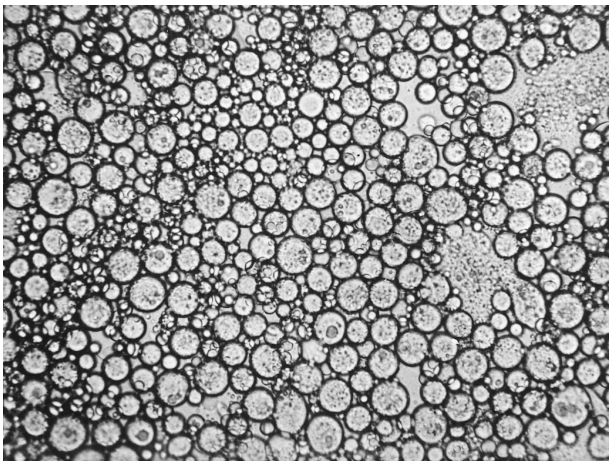


(b)

Figure 1. Photomicrographs of the multiple (w/o/w) emulsions prepared with polymer 2 and Span 80: (a) after 7 days of preparation; (b) after 42 days of storage at 4°C.



(a)



(b)

Figure 2. Photomicrographs of the multiple (w/o/w) emulsions prepared with polymer 7 and Span 80: (a) after 7 days of preparation; (b) after 42 days of storage at 4°C.

fied further in an external aqueous phase at 1500 rpm for 2 min. The temperature was maintained at 70°C for the second emulsification. The emulsion thus formed was allowed to equilibrate by standing overnight.

Emulsion Stability Evaluation

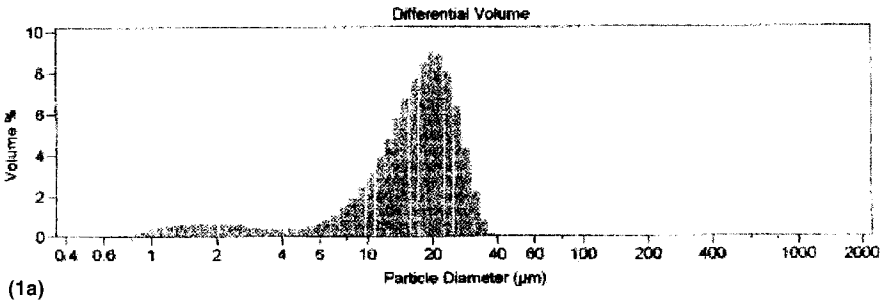
The changes in mean globule size, polydispersibility, conductivity, and viscosity were considered as parameters for evaluation of the stability of the multiple emulsion. The stability was evaluated periodically by visual inspection by cylindrical method and other methods described below at 37°C and 4°C.

Table 3

Composition of Various Multiple (w/o/w) Emulsions

Formulation	Internal Phase (Aqueous)	Middle Oily Phase	External Phase (Aqueous)	PVR
Polymer 2	Water	Liquid paraffin + Span 80	Water + P2	1:1
Polymer 7	Water	Liquid paraffin + Span 80	Water + P7	1:1

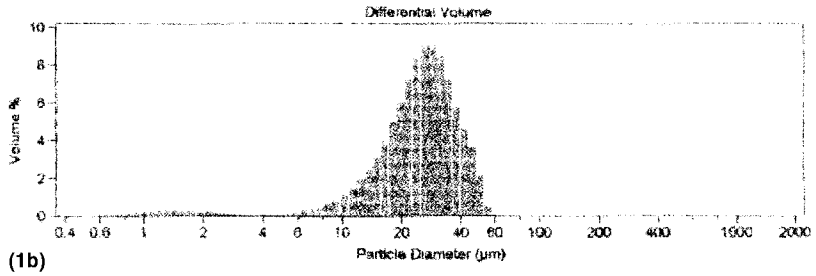
PV, phase volume ratio, Span 80 = 5%; P2, Polymer 2 = 0.53%, P7, polymer 7 = 0.53%; w/o/w, water in oil in water.



(1a)

Volume statistics (Arithmetic)

Volume	100.0 %			S. D.	7.79 µm
Mean	16.51 µm			C. V.	47.2 %
Median	16.90 µm			Skewness	-0.141 left
Mode	19.76 µm			Kurtosis	-0.457 Platykurtic
% <	10	25	50	75	90
Size µm	4.741	11.46	16.90	22.06	26.47

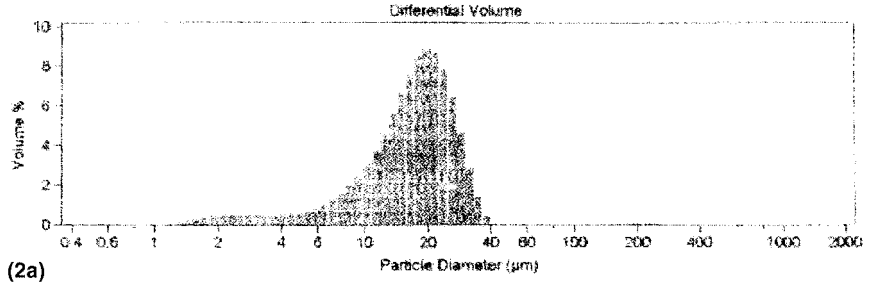


(1b)

Volume statistics (Arithmetic)

Volume	100.0 %			S. D.	11.3 µm
Mean	25.49 µm			C. V.	44.3 %
Median	25.19 µm			Skewness	0.0812 Right
Mode	28.69 µm			Kurtosis	-0.163 Platykurtic
% <	10	25	50	75	90
Size µm	11.40	18.09	25.19	32.71	40.72

Figure 3. Particle size distribution of the multiple emulsions prepared with various emulsifying agents: after preparation (1a) with polymer 2, (1b) with polymer 7.

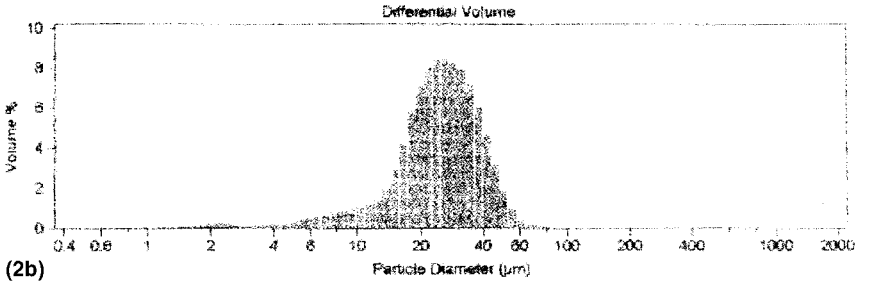


(2a)

Volume statistics (Arithmetic)

Volume	100.0 %	S. D.	19.4 μm
Mean	18.96 μm	C. V.	102 %
Median	17.37 μm	Skewness	8.1 Right Skewed
Mode	19.76 μm	Kurtosis	79.4 Leptokurtic

% <	10	25	50	75	90
Size μm	6.849	12.00	17.37	22.66	27.62



(2b)

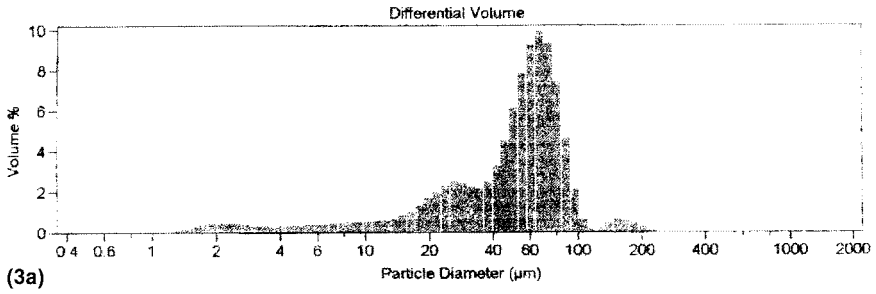
Volume statistics (Arithmetic)

Volume	100.0 %	S. D.	11.7 μm
Mean	25.93 μm	C. V.	45.1 %
Median	24.83 μm	Skewness	0.571 Right
Mode	26.14 μm	Kurtosis	1.05 Leptokurtic

% <	10	25	50	75	90
Size μm	11.64	18.35	24.83	32.97	41.13

Figure 3. Continued. Emulsions stored at 37°C (2a) with polymer 2, (2b) with polymer 7.

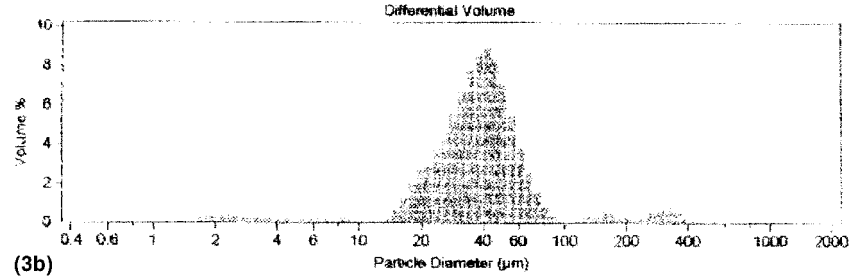
(*continued*)



(3a)

Volume statistics (Arithmetic)

Volume	100.0 %		S. D.	31.8 µm	
Mean	53.83 µm		C. V.	59.1 %	
Median	55.41 µm		Skewness	1.14 left	
Mode	66.44 µm		Kurtosis	3.85 Leptokurtic	
% <	10	25	50	75	90
Size µm	13.03	30.39	55.41	71.17	84.54



(3b)

Volume statistics (Arithmetic)

Volume	100.0 %		S. D.	62.1 µm	
Mean	51.97 µm		C. V.	119 %	
Median	38.18 µm		Skewness	3.94 Right	
Mode	41.67 µm		Kurtosis	17 Leptokurtic	
% <	10	25	50	75	90
Size µm	18.30	27.31	38.18	50.52	69.54

Figure 3. Continued. Emulsions stored at 4°C (3a) with polymer 2, (3b) with polymer 7.

Visual Inspection

The multiple emulsions were placed in 100-ml measuring cylinders. The cylinders were then sealed with aluminum foil on the top and kept undisturbed for further studies. A visual inspection of the emulsion stability was performed at room temperature at regular intervals until phase separation was seen.

Photomicrographs

A Leitz-Larorlux-S microscope with a wild MPS 28/38 photomicrographic attachment was used for photomicrographic studies. The emulsions were subjected to photomicrographic studies immediately after the preparation and after storage at various temperatures for 42 days.

Droplet Size Measurement

Particle size distribution was evaluated using an LS-230 particle size analyzer (Coulter Counter, UK). The particle size distribution was measured initially and after 42 days to evaluate stability.

Viscosity Measurement

The viscosity of the prepared emulsions was calculated using a Brookfield viscometer.

Conductivity

The emulsion conductivity was determined using a digital conductometer (Elico Pvt. Ltd., model CM-180, Hydrabad, India).

RESULTS AND DISCUSSION

Visual Inspection

The visual inspection of the multiple emulsions revealed that emulsions prepared with polymer 7 showed the presence of a little separated oil on top of the cylinder after storage at 37°C and 4°C up to 42 days, as compared to the emulsions prepared with polymer 2.

Photomicrographic Studies

Figures 1a and 1b show the photomicrographs of multiple emulsions prepared using polymer 2 after 7 days of preparation and 42 days of aging at 4°C, respectively. Figures 2a and 2b show the photomicrographs of multiple emulsions prepared using polymer 7 after 7 days of preparation and 42 days of aging at 4°C, respectively. The least polydispersibility was observed for emulsions prepared with polymer 7 compared to polymer 2.

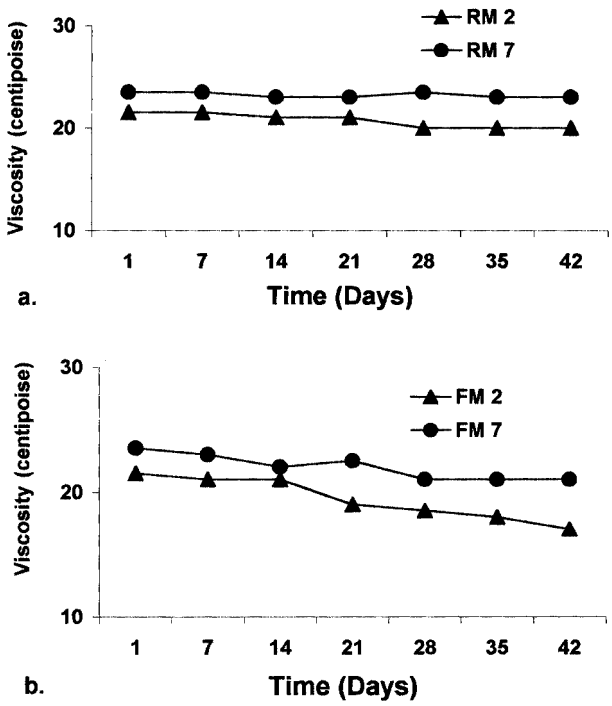


Figure 4. Changes in viscosity of multiple emulsions prepared with various emulsifying agents upon aging. (a) Emulsions stored at 37°C: RM 2, with polymer 2; RM 7, with polymer 7. (b) Emulsions stored at 4°C: FM 2, with polymer 2; FM 7, with polymer 7.

Droplet Size

The emulsions prepared with polymer 2 and polymer 7 showed large globule size. No specific justification at this stage was possible regarding the large initial globule size observed with these polymers. However, particle size can be controlled by modification in the method adopted for the preparation of the multiple emulsions (9). The changes in particle size on aging at 37°C and 4°C show that the increase in particle size was greater with the multiple emulsions prepared with polymer 2 compared to the emulsions prepared with polymer 7. The least changes in particle size of the emulsions prepared with polymer 7 and Span 80 as emulsifiers at 37°C and 4°C may be an indication of the better storage stability of these emulsions. The results are shown in Fig. 3.

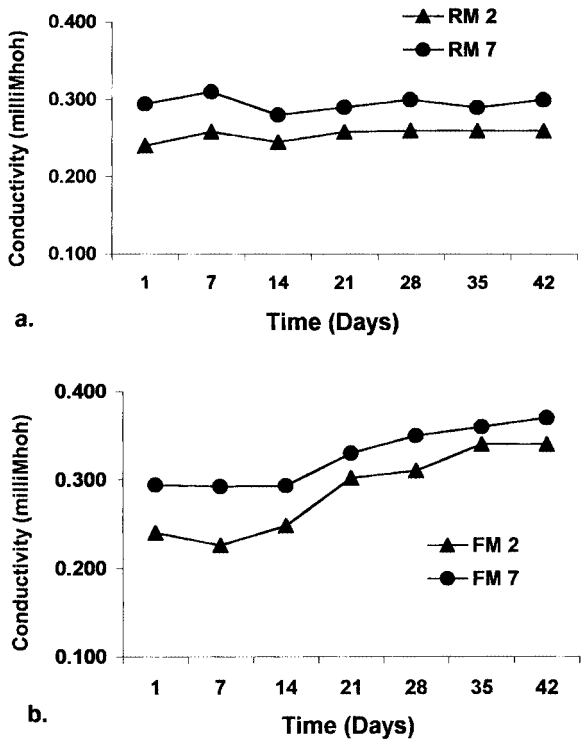


Figure 5. Conductivity pattern of multiple emulsions prepared with various emulsifying agents on aging. (a) Emulsions stored at 37°C: RM 2, with polymer 2; RM 7, with polymer 7. (b) Emulsions stored at 4°C: FM 2, with polymer 2; FM 7, with polymer 7.

Viscosity Measurements

Figure 4 shows the changes in viscosity of multiple emulsions prepared with various emulsifiers during aging at 37°C and 4°C. The decrease in viscosity of both the emulsions stored at 37°C shows a similar pattern. However, there was a larger decrease in viscosity in the case of the multiple emulsion prepared with polymer 2 and Span 80 stored at 4°C. The mention of a decrease of viscosity with time for multiple emulsions was also reported elsewhere (10).

Conductivity Measurements

The conductivity of the multiple emulsions formulated with various emulgents is presented in Fig. 5. The storage of emulsions at 37°C increased the conductivity in such systems. The increase in conductivity showed a similar pattern in both the emulsions prepared. The greater increase in conductivity in the case of multiple emulsions prepared with polymer 2 was observed on storage at 4°C. The conductivity demonstrated an inverse relation with the viscosity of all the emulsions under investigation. A similar relation between viscosity and conductivity was also proposed by Jain et al. (11).

CONCLUSIONS

Rosin-based polymeric surfactants can be used to prepare stable multiple (w/o/w) emulsions. The multiple emulsions prepared with polymer 7 and Span 80 showed good stability compared to the emulsions prepared using polymer 2 and Span 80.

ACKNOWLEDGMENT

We gratefully acknowledge Dr. N. K. Subhedar for assistance with photomicrography and Dr. V. V. Parashar, Head, Department of Pharmaceutical Sciences, Nagpur University, Nagpur, for providing the necessary facilities.

REFERENCES

1. Florence, A.T.; Whitehill, D. Int. J. Pharm. **1982**, *11*, 277.
2. Florence, A.T.; Whitehill, D. Stability and Stabilization of w/o/w Multiple Emulsions. In *Macro and Micro Emulsions: Theory and Applications*; Shah, D.O., Ed.; American Chemical Society: Washington, DC, 1985; 259–388.
3. Davis, S.S. Chem. Ind. **1981**, 684.
4. Price, E.D. U.S. Pat. 2,392,945, 1946.
5. Price, E.D.; May, E.L. U.S. Pat. 2,397,692, 1947.
6. Products Chemiques de la Montogne Noire, Fr. Pat. 946,189, 1949.
7. Sahu, N.H.; Mandaogade, P.M.; Deshmukh, A.M.; Dorle, A.K. Biodegradation Studies of Rosin-Glycerol Ester Derivative. J. Bioactive Compatible Polym. **1999**, *14*, 344–360.
8. Khopade, A.J.; Jain, N.K. Drug Dev. Ind. Pharm. **1998**, *24* (3), 289–293.
9. Lashmar, U.T.; Richardson, J.P.; Erbold, A. Int. J. Pharm. **1995**, *125*, 315–325.
10. Kita, Y.; Matsumoto, S.; Yonezawa, D. J. Colloid Interface Sci. **1997**, *62*, 87.
11. Jain, K.D.; Sharma, M.K. J. Indian Chem. Soc. **1971**, *48*, 1026–1031.