RESEARCH PAPER

Accepted 14 December 2001
Revised 29 October 2001
Received 4 June 2001
Indian J. Pharm. Sci., 2002, 64(2): 138-141

Rosin Derivative as Hydrophobic Matrix Material for Controlled Release of Diclofenac Sodium

P. M. SATTURWAR, S. V. FULZELE*, P. M. MANDAOGADE, G. N. DARWHEKAR AND A. K. DORLE
Department of Pharmaceutical Sciences, Nagpur University Campus,
Amravati Road, Nagpur-440 010.

New rosin derivative (R-1) as a hydrophobic matrix material for the controlled release of drugs is reported, using diclofenac sodium as model drug. Matrix tablets were prepared by wet granulation method using R-1 as matrix forming material in different proportions and combinations. The matrix tablets were evaluated for thickness, hardness, friability, weight variation, drug content uniformity and *in vitro* dissolution. The results suggest that the new rosin derivative (R-1) is useful in developing sustained release matrix tablets, with drug release being prolonged for upto 10 h. R-1 thus promises considerable utility in the development of oral sustained release drug delivery systems.

Sustained and controlled release formulations have been developed for a variety of therapeutic agents[1]. Embedding a drug within an insoluble matrix provides a convenient means of controlling the drug release. In such a system, drug release is preceded by penetration of dissolution medium into the porous matrix to dissolve the drug, followed by diffusion/leaching of the dissolved molecules out of the matrix[2]. Two types of materials are used as matrix carriers: water-insoluble, hydrophobic materials such as wax or ethyl cellulose and water-soluble hydrophilic materials such as hydroxy propyl methylcellulose or sodium carboxy methylcellulose. Various types of polymers, waxes and gums have been used as matrix materials for preparing controlled release dosage forms[3-7].

Rosin is a solid resinous material obtained naturally from pine trees. Rosin and rosin esters have been widely evaluated for pharmaceutical applications such as coating,[8] microencapsulating[9] and as matrix materials[10] in tablet formulations. Derivatives of abietic acid, the principle component of rosin have also been evaluated as matrix forming material[11,12]. Rosin derivatives are mostly hydrophobic in nature and have excellent film forming property. The present communication deals with the evaluation of a new rosin derivative as hydrophobic matrix material for the controlled release of drugs, using diclofenac sodium as a model drug.

*For correspondence
Email: fsuniket@yahoo.com

MATERIALS AND METHODS

Rosin N grade was purchased from Swastik Acids and Chemicals, Nagpur. Maleic anhydride and fumaric acid were purchased from S.D. Fine Chemicals, Mumbai. Glycerol was purchased from Qualligen Laboratories, Mumbai and castor oil was purchased from Apex Laboratories, Mumbai. Microcrystalline cellulose (Avicel, pH 101) was received as a gift sample from Chemfields Pharma, Nagpur. All other excepients, chemicals and solvents were of either analytical or pharmacopoeial grade. Diclofenac sodium was obtained as gift sample from Zim Laboratories, Nagpur and used as received.

Synthesis of rosin derivative:

Rosin derivative (R-1) was prepared in laboratory and the composition of which is as follows: Rosin-60.0%, maleic anhydride-5.0%, fumaric acid-5.0%, glycerol-10.0% and castor oil-20.0%. Rosin along with other ingredients was charged into a four-neck glass reactor (2 l) fitted with a condensor, stirrer and temperature control arrangement.

Xylene (5%) was added as a solvent. The reaction was progressed by heating the ingredients at 225° (1 h), 210° (2 h), 200° (2 h) and 190° (2 h) with constant stirring at 60 rpm. The final product was removed and strained through a fine mesh and used for further studies.

Characterization of rosin derivative (R-1):

Various physiochemical parameters such as colour, acid value, softening point and percent loss on drying (%LOD) of R-1 were evaluated. R-1 is highly soluble in all organic solvents and insoluble in water. Molecular weight of R-1 was determined along with its polydispersity by size exclusion chromatography coupled with a laser light scattering detector (DAWN-DSP, Wyatt Technology, USA). These measurements were done using K-5 type cell at a wavelength of 633 nm. Methylene chloride was used as the mobile phase with a flow rate adjusted to 1 ml/min. Molecular weight (Mw) and polydispersity index (Mw/Mn) was computed by software ASTRA 4.70.07 (Wyatt Technology, USA).

Preparation of matrix tablets:

Matrix tablets of diclofenac sodium were prepared by wet granulation process. Accurately weighed quantity of drug, microcrystalline cellulose and matrix material (R-1) were mixed in a mortar. Required quantity of solvent (acetone) was added to the same and mixed thoroughly to form a mass suitable to form granules. The dough mass was passed through a sieve # 12 to obtain granules, which were then dried at 50°. The granules were mixed with lubricants and compressed to form tablets on a single punch tablet machine using 9 mm diameter punches. Twelve formulations were prepared using different formulae by varying the concentration of R-1 and microcrystalline cellulose. The total weight of each tablet was 200 mg containing 50 mg of diclofenac sodium.

Evaluation of matrix tablets:

The hardness of six tablets from each type of formulation was determined using a Monsanto Tablet Hardness tester. Thickness and diameter was measured using a Vernier Calipers while the friability was estimated using a Roche Friabilator. Weight variation test was carried out as per official method[13]. For the estimation of drug content, six tablets representing each formulation were taken and powdered in a mortar. Powder equivalent to 50 mg of diclofenac sodium was weighed accurately in a 250 ml volumetric flask and dissolved in 60 ml of methanol. The contents were shaken for about 30 min and diluted to volume with methanol. From this, 5 ml was further diluted to 100 ml with methanol and absorbance measured at 275 nm using spectrophotometer (Shimadzu UV-150-02, Kyoto, Japan).

In vitro dissolution studies were conducted in 900 ml phosphate buffer (pH 7.4) using USP XXIII dissolution apparatus 1 (Veego Scientific, Mumbai) at 37° at a speed of 100 rpm. The dissolution studies were carried in triplicate. At predetermined time intervals, aliquots were withdrawn and the amount of drug released was monitored by measuring the UV absorbance at 275 nm.

RESULTS AND DISCUSSION

R-1 was synthesized in laboratory and evaluated as matrix forming material. Results of the preliminary characterization are shown in Table 1. The Mw of R-1 was found to be 1937 with a narrow polydispersity index (Mw/Mn) of 1.655. R-1 is soluble in most of the organic solvents and insoluble in water. R-1 is dark yellow in colour with acid value 94.07 and softening point between 73-79°.

TABLE 1: CHARACTERIZATION OF ROSIN DERIVATIVE (R-1).

Parameter	R-1
Colour	Dark yellow
Acid value	94.07
Softening Point (°)	73-79
% LOD	3.63
Molecular weight (Mw)	1937
Polydispersity (Mw/Mn)	1.655±0.166*

Each value represents a mean of 3 determinations. Asterisk indicates mean ± standard deviation.

Various formulations (F_1–F_{12}) prepared to evaluate the matrix forming ability of R-1 are shown in Table 2. Matrix tablets equivalent to 200 mg containing 50 mg of diclofenac sodium were prepared. Tablets of four different hardnesses, 4, 5, 6 and 7 kg/cm² were prepared by varying the ratio of R-1 and microcrystalline cellulose as shown. Preliminary characteristic features of matrix tablets are shown in Table 3. The drug content in all the formulations was found to be fairly uniform. The percent friability showed gradual decline with increase in hardness of tablets as desired.

The *in vitro* release of diclofenac sodium from various matrix tablets is shown in fig. 1 and fig. 2. Matrix tablets with hardness 4.0 kg/cm² showed significant effect of the ratio of R-1:micro crystalline cellulose on the drug release pattern

TABLE 2: FORMULAE OF MATRIX TABLETS.

Ingredients (mg)	Formulation											
	Hardness 4.0 kg/cm²			Hardness 5.0 kg/cm²			Hardness 6.0 kg/cm²			Hardness 7.0 kg/cm²		
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Diclofenac sodium	50	50	50	50	50	50	50	50	50	50	50	50
Matrix material (R-1)	20	40	60	20	40	60	20	40	60	20	40	60
Microcrystalline cellulose	126	106	86	126	106	86	126	106	86	126	106	86
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2

F_1-F_{12} are various formulations of diclofenac sodium matrix tablets. In each formulation 50 mg diclofenac sodium was taken. Quantity of R-1 and microcrystalline cellulose was varied and mixed with 2 mg of talc and 2 mg of magnesium stearate.

with formulation F_3 showing sustained release upto 10 h. Similar release pattern is seen in tablets with hardness 5 kg/cm² where formulation F_6 shows sustained release. Increase in the tablet hardness to 6 kg/cm² and 7 kg/cm² respectively shows correspondingly better sustained release profile. In formulations F_8, F_9, F_{11} and F_{12} drug release from matrix tablets was delayed upto 10 h as shown. Thus using R-1 as matrix forming material, the release profile suggests significant effect of tablet hardness on the release pattern.

Similarly, increase in the concentration of R-1 shows better sustained release property using 10% concentration

TABLE 3: EVALUATION OF MATRIX TABLETS.

Formulation	Thickness (mm)*	Diameter (mm)*	Hardness (kg/cm²)*	Percent friability*	Weight variation		Drug content
					Average*	% deviation	mg ± S.D.
F_1	3.3	9	4	0.69	200.1	± 2.81	48.3 ± 1.42
F_2	3.3	9	4	0.62	199.3	± 2.21	47.0 ± 1.12
F_3	3.3	9	4	0.57	202.1	± 3.12	45.2 ± 1.15
F_4	3.3	9	5	0.67	198.9	± 4.12	49.1 ± 1.64
F_5	3.2	9	5	0.51	199.1	± 3.81	48.4 ± 1.10
F_6	3.3	9	5	0.45	202.4	± 3.75	46.7 ± 0.91
F_7	3.3	9	6	0.49	199.7	± 4.35	48.9 ± 0.85
F_8	3.3	9	6	0.41	201.4	± 3.50	47.1 ± 1.30
F_9	3.2	9	6	0.29	198.4	± 3.20	45.5 ± 1.21
F_{10}	3.2	9	7	0.31	200.7	± 4.20	48.0 ± 1.85
F_{11}	3.1	9	7	0.25	201.5	± 2.75	47.3 ± 0.75
F_{12}	3.1	9	7	0.19	202.7	± 3.60	47.1 ± 0.90

F_1-F_{12} are various formulations of matrix tablets. *Each value represents mean of six determinations.

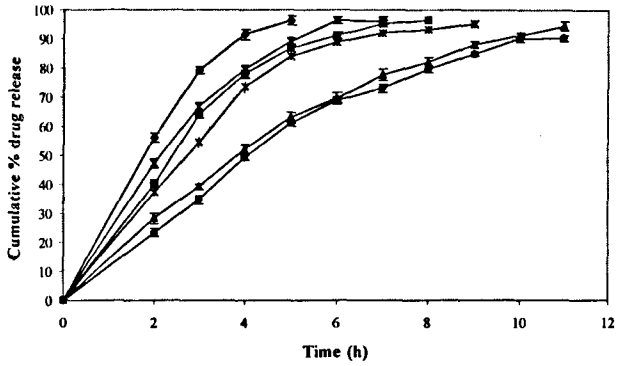

Fig. 1: *In vitro* release of diclofenac sodium from tablets containing matrix material R-1.

Formulations F_1 (◆), F_2 (■), F_3 (▲), F_4 (x), F_5 (✱) and F_6 (●). Each point represents a mean of three determinations.

(F_1, F_4, F_7 and F_{11}) of matrix forming material where drug was released in about 4-6 h. Increasing the concentration to 20% shows good sustained release property in formulations F_8 and F_{11} only. However, using 30% concentration of R-1 sustained release pattern is observed with all the four representative hardness of the tablets.

The above study indicates that matrix tablets prepared using the new rosin derivative (R-1) as matrix forming material successfully sustained the release of diclofenac sodium up to 10 h employing 20% and 30% concentration. Rosin is widely available in India, it would therefore be possible to produce a novel, cost effective matrix forming material, R-1 for sustained release dosage forms.

ACKNOWLEDGEMENTS

The authors thank the Head, Department of Pharmaceutical Sciences, Nagpur University, Nagpur for providing the facilities. One of the authors (P.M.M.) also wishes to thank the CSIR, New Delhi, for providing financial assistance.

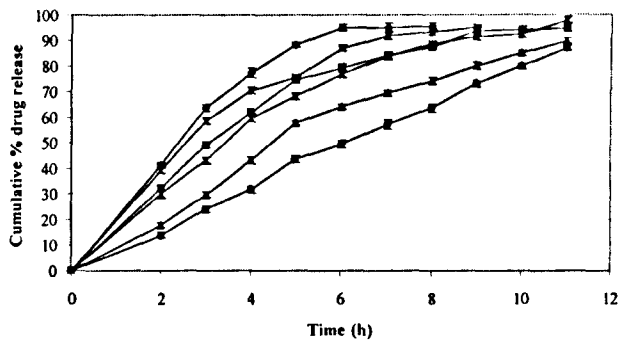

Fig. 2: *In vitro* release of diclofenac sodium from tablets containing matrix material R-1.

Formulations F_7 (◆), F_8 (■), F_9 (▲), F_{10} (x), F_{11} (✱) and F_{12} (●). Each point represents a mean of three determinations.

REFERENCES

1. Mandal, T.K., **Drug Develop. Ind. Pharm.**, 1998, 24, 623.
2. Billa, N., Yuen, K.H. and Pen., K. K., **Drug Develop. Ind. Pharm.**, 1998, 24, 45.
3. Nagoji, K.E., Rao, S.S. and Rao, M.E., **Indian J. Pharm. Sci.**, 2000, 6, 482.
4. Nath, B.S., Venkatesh and Hiremath, D., **Indian J. Pharm. Sci.**, 2000, 1, 33.
5. Misra, A.N. and Baweja, J.M., **Indian Drugs**, 1997, 34, 216.
6. Satoh, K., Takayama, K., Machida, Y., Suzuki, Y. and Nagai, T., **Chem. Pharm. Bull.**, 1989, 37, 1642.
7. Adikwu, M.U., **Acta Pharm.**, 1997, 47, 31.
8. Pathak, Y.V., Nikore, R.L. and Dorle, A.K. **Int. J. Pharm.**, 1985, 24, 351.
9. Sheorey, D.S. and Dorle, A.K., **J. Microencapsulation.**, 1991, 8, 243.
10. Pathak, Y.V. and Dorle, A.K., **Drug Design Delivery.**, 1990, 6, 223.
11. Ramani, C.C., Puranik, P.K. and Dorle, A.K., **Int. J. Pharm. Adv.**, 1996, 1, 344.
12. Ramani, C.C., Puranik, P.K. and Dorle, A.K., **Int. J. Pharm.**, 1996, 137, 11.
13. Pharmacopoeia of India, 4th Edn., Ministry of Health, The Government of India, New Delhi, 1996, 513.