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Brief / Technical Note

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Gum Cordia: A Novel Matrix Forming Material for Enteric resistant and Sustained Drug Delivery—A Technical Note

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INTRODUCTION

Sustained drug delivery systems can improve patient compliance and provide extended periods of effective blood levels. In an approach, polymers and their blend are used in various formulations to achieve sustained drug release. The authors investigated various natural, semisynthetic and synthetic polymeric materials. Most thoroughly investigated and used synthetic polymers for sustained release drug delivery are methylcellulose, ethylcellulose, methacrylic acid copolymers (Eudragit; 1), hydroxypropylmethylcellulose (2,3,4), polyoxyethyleneglycol (macrogol; 5), sodium carboxymethylcellulose and carboxypolymethylene (carbopol-934; 6). Some natural gums such as gum karaya (7), chitosan (8), gum copal and gum dammar (9) were also investigated as hydrophilic matrices for sustained drug delivery. However the gums were found to be unable to sustain the drug release for a longer period of time even at higher concentration beyond 12 h. Therefore the study of new materials for retarding drug release is the motive of research even after the advent of synthetic, semi-synthetic and natural polymers.

The past research acknowledged the use of gum cordia as a potential non-toxic and safe pharmaceutical excipient (binding agent) in tablet (10). These particulars explicate the rationale, why proposed article concerns the evaluation of natural gums for sustained drug delivery.

In the present study, an effort has been made to evaluate the efficacy of gum cordia (obtained from *Cordia Obliqua*, Willed., Fam.: *Boraginaceae*) as a novel sustained release matrix forming material in tablet formulations using diclofenac.

Diclofenac is used for long-term treatment of various arthritic conditions (11). However the drug has a short biological half-life (11) which needs multiple dosing regimens of immediate-release formulations and requires sustained release formulation for patient compliance. Therefore, it was chosen as a model drug for the present study.

MATERIALS AND METHODS

Diclofenac sodium was procured from Macleods Pharmaceuticals Ltd., Mumbai, India as a gift sample. Sustained release marketed formulation of diclofenac sodium (Voveran SR-100 tablet, B.No.-6Z033H, Novartis, Mumbai, India) was procured from the local market. All other chemicals such as dicalcium phosphate, magnesium stearate, hydrochloric acid and trisodium phosphate, used for the preparation of tablets and their analysis were of analytical grade and obtained from E. Merck (India) Ltd., Mumbai, India.

Extraction of Gum Cordia

Fresh and raw fruits were collected from the tree *Cordia Obliqua* willed, family *Boraginaecae* in April 2005 from Borigumma, Village of Koraput District (Orissa), India. The fruits only occur once in a year and gum content is found to be much less in ripe fruits. The tree was identified by Dr. M. S. Mondal, Joint Director Botanical Survey of India, Govt. of India, Central National Herbarium, Botanical Garden, Howrah, West Bengal, India. The mucilage was expressed from fruits by tincture press and precipitated with 1% hydrochloric acid and dried in an oven at 50°C.

Preparation of Matrix Tablets

Mathematical Considerations

Absorption, distribution, metabolism and excretion are the important factors for mathematical design (9) of the sustained release dosage forms. Pharmacokinetic studies showed that a dose of 25 mg of diclofenac sodium produces an effective blood level of 0.7–1.5 μg/ml within 1.5–2.5 h with the half-life of 1.1–4.0 h. The elimination rate constant $k=$

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Table I. Composition of 100 mg Diclofenac Sodium Matrix Tablet Formulation

Excipients (in mg)	Formulation Code			
	C1	C2	C3	C4
Calcium carbonate	100	100	100	100
Lactose	91	88	79	64
Gum cordia	3	6	15	30
Magnesium stearate	6	6	6	6

$0.693/t_{1/2}=0.693/4h=0.1732\ h^{-1}$. The bioavailability rate $R=K\times D=0.1732\ h^{-1}\times 25$ mg=4.3 mg/h, where D is the usual dose of the drug. The maintenance dose $Dm=R\times h=4.3$ mg/h$\times 20h=86$ mg, where h is the number of hours for which sustained action is intended. Thus total dose$=D+Dm=25$ mg $+86$ mg$=111$ mg. $D_{corrected}=D-Rt_p=25$ mg$-(4.3$ mg/h$\times 2h)=16.4$ mg, where t_p is the time period required to achieve a peak plasma level. Therefore, total dose$_{corrected}=D_{corrected}+Dm=16.4$ mg$+86$ mg$=102.4$ mg.

Method Used

The preliminary formulation and dissolution studies showed that the formulation containing 2% (*w*/*w*) gum prolonged the drug release up to 24 h. Therefore, in all cases, drug content was maintained at 100mg and gum concentrations of 1%, 2%, 5% and 10% w/w with respect to total drug content were utilized to examine the effect of gum on drug release profile of the tablets.

The composition of different gum matrix tablets (Table I) with almost constant theoretical weight of 300 mg and diameter 9 mm were produced. In all the formulations, ingredients were passed through sieve no #120. Then the ingredients were accurately weighed and granulated using wet granulation technique, using non-aqueous solvent such as isopropanol and dichloromethane in which the gum was mixed to form a sticky paste and then utilized as granulating agent. Granules were allowed to dry in an oven at 50±2°C.

Dried granules lubricated with magnesium stearate (2% *w*/*w*) were compressed between 9 mm round flat faced punches on a hand operated single punch tablet machine (Cadmach Ltd., Mumbai, India).

Analytical Tests for Matrix Tablets

The diameter and thickness of matrix tablet were measured with vernier calipers and the hardness by Stokes–Monsanto hardness tester. The friability test was conducted using Roche friabilator. For each batch, 20 randomly drawn tablets were checked for weight uniformity using a Sartorius high precision balance (Electronic Gem Scale, Sartorius, Göttingen, Germany).

Drug Content Determination

For drug content, 20 tablets were weighed accurately and powdered. Powder equivalent to 50 mg of diclofenac sodium was shaken with 60 mL of methanol in 200 mL volumetric flask and the volume was further adjusted with methanol to 200 mL. Then 5 mL of this solution was diluted to 100 mL in volumetric flask and drug contents were determined by UV–Vis spectrophotometer (UV-1700, Shimadzu, Japan) at 276 nm using calibration curve based on the prepared standard solutions (12).

In Vitro Drug Release Study

Drug release study was determined in USP Apparatus II (Lab India, Disso-2000), paddles, at 100 rpm and 37±0.5°C. Dissolution medium was 900 mL 0.1 N HCl for 0 to 2 h and phosphate buffer pH 6.8 for 2 to 24 h. After each hour 5 mL of sample was withdrawn and analyzed for diclofenac sodium content by UV–Vis Spectrophotometer at 276 nm. The drug content assay was conducted as per the method specified in The United States Pharmacopoeia (13). The experiments were repeated three times and the results were taken as average of three test readings with standard deviations. The accuracy and precision of the standard curve was sufficiently accurate with a validated linearity for determination of drug in dissolution media.

In-vitro Drug Release Kinetics

In order to study the exact mechanism of drug release from the matrix tablets, drug release data was analyzed according to Zero order, First order, Matrix and Hixon–Crowell kinetic equation. The drug release data were compared by one-way ANOVA followed by Tukey HSD test using Vassar stats software.

RESULTS AND DISCUSSION

In this study different formulations of matrix tablet such as C1, C2, C3 and C4 were prepared with 1%, 2%, 5% and 10% *w*/*w* of gum cordia with respect to total tablet weight respectively (Table I). The pharmacotechnical properties of

Table II. Properties of Diclofenac Sodium Matrix Tablets

Formulation code	Diameter (in mm; $n=10$)	Thickness (in mm; $n=10$)	Weight in mg ($n=20$)	Hardness (kg/cm^2; $n=6$)	% Friability ($n=10$)	% Drug content
C1	9.09±0.01	1.28±0.00	298±6.15	5.54±0.24	0.65	99.29±0.85
C2	9.07±0.08	1.29±0.00	304±7.53	6.91±0.20	0.33	99.29±0.84
C3	9.07±0.00	1.29±0.00	298±5.23	7.5±0.00	0.20	98.82±0.74
C4	9.08±0.01	1.28±0.00	298±5.23	5.91±0.12	0.06	99.13±0.13
M	9.08±0.01	4.38±0.10	295±7.6	3.46±0.05	0.05	99.29±0.84

Data show mean±SD
M marketed formulation, Voveran SR

Table III. Cumulative Release and Release Rate Constants of Experimental and Commercial Tablets

Formulation	Zero order		1st order		Matrix		Hix. Crow		$T_{1/2}$ (h)	Q (t) at 24 h
	R	K (h^{-1})	R	K (h^{-1})	R	K (h^{-1})	R	K (h^{-1})		
C1	0.9108	4.72	0.9875	−0.08	0.9399	17.11	0.9859	−0.0230	8	90
C2	0.9165	4.49	0.9924	−0.07	0.9363	16.26	0.9820	−0.0211	9	85
C3	0.9289	4.16	0.9923	−0.06	0.9324	14.97	0.9821	−0.0188	10	80
C4	0.8798	3.33	0.9477	−0.04	0.9363	12.19	0.9281	−0.0137	12.5	59
M	0.9000	4.55	0.9920	−0.07	0.9403	16.55	0.9753	−0.0214	8.5	84

Correlation coefficient 'R', 'K'—rate constant values (rate of release), '$t_{1/2}$' and $Q(t)$ at 24 h (cumulative release at 24 h) according to different kinetic equations for matrix and commercial tablet. *M*: commercial tablets. All the rate data (K) were found to be significant at the level of $p<0.05$ assessed by one-way ANOVA followed by Tukey HSD test
Hix. Crow Hixon–Crowell

matrix tablets were studied (Table II) and compared with commercial formulation such as Voveran SR tablet and found to be having consistent quality. The thickness did not vary much among the formulations. Again average weight variations and drug content in all the formulations were well within the pharmacopoeial limits (14).

From the *in vitro* drug release studies of the matrix tablets and commercial Voveran SR-100 tablets, it was found that all the formulations were effective to sustain the release of diclofenac sodium up to 24 h. With the increasing percentage of gum in the formulations, the drug release from the formulations retarded. All data were significant at $P<0.05$, except when C1 was compared with C2 and M; and C2 was compared with C3 and M up to first 4 h, when compared by one-way ANOVA followed by Tukey HSD test. Although there is a similar trend of release pattern, the matrix tablets of C1, C2, C3 and C4 were able to deliver drug about 90%, 85%, 80% and 60%, respectively at 24 h. However, by that time, commercial tablet M released 84% of its drug. The swelling of the gum containing matrix seems to be a likely factor responsible for the overall rate of delivery. Increasing amount of gum caused increasing amount of swelling which might reduce the drug diffusion pathways from the tablet matrix. As a result, drug release was retarded more with the increasing percentage of gum. The cumulative release and release rate constants (Table III) of the matrix tablets as well as the tested commercial tablets were compared and found that all formulations followed first-order drug release profile. Fig. 1 suggests that both the prepared matrix formulations as well as the commercial tablets showing resistant to release the drug in the simulated gastric fluid i.e. in 0.1 N HCl, favor to drugs which cause acidity to the stomach or deteriorate in stomach pH by inhibiting their release in the stomach.

Drug release from the experimental tablets was comparable to that from the commercial tablets. With the increasing percentage of gum in the matrix tablets (C1, C2, C3 and C4) drug release retarded. The slowest release was observed in case of formulation, C4. The gum may be a suitable option as an excipient for matrix forming agent to impart enteric resistant and sustained drug delivery in tablet or similar formulations.

SUMMARY AND CONCLUSIONS

The study describes the evaluation of gum cordia as a novel sustained release matrix forming material in tablet formulations. Matrix tablets were prepared by wet granulation technique using non-aqueous solvents such as isopropanol and dichloromethane. Diclofenac sodium was used as model drug. The effect of gum (1, 2, 5 and 10% *w*/*w* with respect to total tablet weight) on *in-vitro* drug release profile was examined and compared with a commercial sustained release diclofenac formulation (Voveran SR-100). The results showed that the gum formulations retarded the dissolution of diclofenac sodium in 0.1 N HCl and the formulation C2 (containing 2% *w*/*w* gum) gave a similar dissolution profile to the marketed product. Further, the drug release profiles obeyed 1st order kinetics. The gum might be useful for producing matrix forming agent for enteric resistant and sustained drug delivery in tablet formulations for other drugs too.

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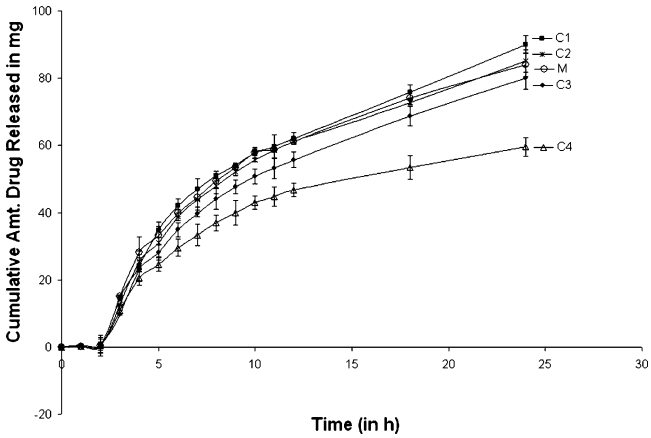

Fig. 1. Diclofenac sodium release profile of gum cordia matrix tablets along with commercial formulation (Voveran SR-100); Data show mean ± SD (n=5); *C1*, *C2*, *C3* and *C4* had 1%, 2%, 5% and 10% (*w*/*w*) gum cordia, respectively. *M* commercial tablet

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