Drug Development and Industrial Pharmacy, 27(8), 759–766 (2001)

RESEARCH PAPER

Formulation and Evaluation of Diclofenac Sodium Using Hydrophilic Matrices

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ABSTRACT

Controlled-release tablets (having near zero-order release) of diclofenac sodium, a water-soluble drug, were prepared using hydrophilic polymers like hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (NaCMC), and Carbopol 934. Tablets were also prepared with mixtures of polymers of NaCMC, HPMC, and Carbopol 934. The optimum ratio of drug : HPMC : NaCMC was found to be 1 : 2 : 1. A combination of nonionic polymer HPMC and anionic NaCMC polymer matrix resulted in near zero-order release of diclofenac sodium. The results obtained were in agreement with the earlier reports. It is observed that increasing polymer content produces more sustained effect. A combination of nonionic polymer HPMC and anionic polymer NaCMC as the polymer matrix resulted in near zero-order release of diclofenac sodium. Drug release from the matrix did not follow Fick's law of diffusion and exhibited near zero-order release. Results of the bioavailability studies indicated that formulation 4 with drug : HPMC : NaCMC equal to 1 : 2 : 1 was similar to the marketed product Dicloran SR and showed better bioavailability than Voveran SR. A statistically significant difference was seen between Voveran SR and the other two products. A good in vitro–in vivo correlation was observed for these products.

Key Words: *Carbopol 934; Controlled drug delivery; Diclofenac; HPMC; NaCMC*

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INTRODUCTION

Sustained-release dosage forms provide medication over an extended period. Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether of a temporal or spatial nature or both. In other words, the system attempts to control the drug concentration in the target tissue; often, this is blood serum (1).

In general, the goal of a sustained-release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period of time. This is generally accomplished by attempting to obtain zero-order release from the dosage form. Sustained-release systems generally do not attain this type of release; they usually try to mimic zero-order release by providing drug in a slow first-order fashion. Controlled release, although resulting in a "zero-order" delivery system, may also incorporate methods to promote localization of the drug at an active site.

The most important reason for sustained drug delivery is improved disease management. The use of less total drug to treat a condition has been illustrated with sustained drug delivery. The net effect of this reduction in drug is usually a decrease or elimination of systemic or local side effects. This also minimizes drug accumulation with chronic dosing. Economy and greater patient compliance are other advantages. Sustained-release dosage forms would be most applicable for drugs having low therapeutic indices and short elimination half-lives. Marketed sustained-release diclofenac sodium tablets are available and are frequently used (2,3). The aim of this work was to prepare diclofenac sodium controlled-release tablets and to study the release behavior in vitro and in vivo.

EXPERIMENTAL

Materials

Hydroxypropylmethylcellulose (HPMC; 100 cps) (Cadila Laboratories, Bangalore, India); sodium carboxymethylcellulose (NaCMC), a high-viscosity polymer of Reliance Cellulose Products Limited (Hyderabad, India); Carbopol 934 (Wilson Labs, Bombay, India); diclofenac sodium (Cipla Labs, Bangalore, India); naproxen (Reddy's Labs, Hyderabad, India); lactose monohydrate, magnesium stearate, talc, glacial acetic acid (AR grade), sulfuric acid (AR grade), chloroform (AR grade), potassium dihydrogen phosphate (AR grade), sodium hydroxide (AR grade), and potassium ferricyanide (SD Fine Chemicals Limited, Bombay, India); acetonitrile (high-performance liquid chromatography [HPLC] grade), and methanol (HPLC grade) (Qualigens Fine Chemicals, Bombay, India) were used.

Methods

Preparation of Tablets

The formulations evaluated consisted of diclofenac sodium as a model drug with HPMC 100 cps and NaCMC as rate-controlling polymers. Lactose monohydrate was used as a compression aid, and magnesium stearate and/or talc were employed as lubricants.

All formulation components except magnesium stearate and talc were dry blended and then granulated by addition of water in all studies. Then, wet screening was done using a 20-mesh screen. Granules were dried at 50°C for 1 h. Lubrication was performed by mixing the dried granules with talc and magnesium stearate. Tablets were compressed using a single-punch hand/motor-operated tablet machine (Cadmach, Ahmedabad, India) fitted with 13-mm concave punches. The various formulations prepared are shown in Table 1 along with their compositions, hardnesses, and average weights.

In Vitro Dissolution Studies

Drug release studies of compressed tablets were carried out on a USP 22 dissolution apparatus with a paddle stirrer at 100 rpm. The dissolution medium was 1000 ml of phosphate buffer at pH 7.4, and it was maintained at $37^{\circ}C \pm 0.5^{\circ}C$. Samples were withdrawn at predetermined intervals, and drug was estimated spectrophotometrically using an ultraviolet-visible (UV-Vis) spectrophotometer (ELICO Pvt. Ltd., Hyderabad, India) at 545 nm. To 1 ml of filtered sample, 1 ml of 6% sodium hydroxide and 1 ml of 1% potassium ferricyanide were added. Absorbance of the sample was read at 545 nm within 30 min of color development (4). Dissolution studies were performed six times for each batch of tablets. The mean values and standard deviations were calculated.

Table 1

Physical Parameters of Diclofenac Sodium Formulations

Formulation Number or Marketed Products	Matrix Composition	Average Weight (mg)	Hardness (Kg/cm^2)	Release Exponent *n*	Correlation Coefficient *r*
Drug : HPMC : NaCMC					
1	1 : 3 : 0	508	6.5	0.788	0.996
2	1 : 0 : 3	505	6.0	0.744	0.836
3	1 : 2.25 : 0.75	498	10.0	0.810	0.995
4	1 : 2 : 1	503	9.0	0.932	0.998
5	1 : 1 : 2	510	7.5	0.906	0.997
6	1 : 1.5 : 1.5	507	7.8	1.140	0.998
7	1 : 0.75 : 2.25	495	6.7	0.745	0.998
Drug : HPMC : Carbopol 934					
8	1 : 2 : 1	512	7.0	0.807	0.999
9	1 : 2 : 0	503	6.5	0.850	0.993
Dicloran SR		330	6.0	0.950	0.993
Voveran SR		305	5.0	0.595	0.994
Nac-SR		300.7	4.5	0.900	0.992

Assay

About 150 mg of tablet powder was taken into a 100-ml volumetric flask and dissolved in pH 7.4 phosphate buffer. The sample was filtered. To 1 ml of clear filtrate, 1 ml of 6% sodium hydroxide and 1 ml of 1% potassium ferricyanide were added, and absorbance was measured at 545 nm against a reagent blank. Corresponding concentrations were calculated from a standard graph.

In Vivo Bioavailability Study

Six healthy human volunteers of ranging between 21 and 23 years of age participated in the study. The subjects were given selected formulations in a randomized crossover design.

In the present study, bioavailability of diclofenac sodium from two commercially available sustained-release products and a formulation made in the laboratory that was considered to be the best from the dissolution was investigated in a randomized crossover design. The subjects fasted overnight and received a single oral administration of (1) 100 mg Dicloran SR, (2) 100 mg Voveran SR, or (3) 100 mg formulation 4.

The washout period was 7 days. No food or liquid other than water was allowed for 3 h following ingestion of the dose. Blood samples were collected at regular intervals for 24 h, and serum samples were frozen until analyzed by the modified method of El-Sayed et al. (5).

High-Performance Liquid Chromatographic Determination of Diclofenac Sodium in Human Serum

To 0.5 ml of human serum in dried test tubes was added 0.1 ml of naproxen (1 μg) standard solution as an internal standard. The solution was vortexed for 1 min. Proteins were precipitated by the addition of 0.5 ml 1 N sulfuric acid. A pinch of sodium chloride was added to prevent emulsification during the extraction process. The serum was extracted with 3 ml of chloroform by vortexing for 3 min. About 2.5 ml of chloroform layer was separated after centrifugation and dried under vacuum. The residue was reconstituted with 75 μl of acetonitrile. The operating HPLC conditions were set, and a stable baseline was obtained on the recorder at a flow rate of 1.5 ml/min. Then, 20 μl of the reconstituted solution was spiked; the peak heights of drug and the internal standard were measured, and their ratios were computed. The retention times of diclofenac and naproxen were 3.6 min and 6.4 min, respectively.

Treatment of Bioavailability Data

The pharmacokinetic parameters of diclofenac sodium were calculated using a computer program

(RAMKIN) written in advanced basic. This program enables the computation of the area under the zero and first moment curves.

Statistical Treatment of Data

The results of the diclofenac sodium study were analyzed using a computer program by a paired t test ($p = .05$) to compare bioavailability and by the F test to compare the variance of bioavailability.

RESULTS AND DISCUSSION

Dissolution Studies

Dissolution profiles of the different tablet formulations prepared are shown in Figs. 1 and 2. Of all the formulations prepared, formulation 4, with a matrix composition of drug : HPMC : NaCMC in the ratio of 1 : 2 : 1, showed sustained and near zero-order release, releasing the drug in 8 h. From Fig. 1, it can be seen that the combination of HPMC and Carbopol 934 in the 2 : 1 ratio showed the fastest release, followed by formulations 7 and 5, which had HPMC : NaCMC ratios of 1 : 3 and 1 : 2, respectively. All the formulations contained drug : polymer ratios of 1 : 3 except formulation 9, for which the drug : polymer ratio was 1 : 2. Examination of Fig. 2 indicates that formulation 9 released drug at a faster rate compared with the other formulations. By this observation, we can conclude that, by increasing the polymer content, drug release can be sustained. This result is in agreement with general principles (6–8).

The individual release rates of tablets made of HPMC and NaCMC are shown in Fig. 2; they were faster compared to those of tablets made of the two polymers combined. The release of drug from the tablet of HPMC polymer was found to be more sustained when compared to that of the NaCMC polymer. These findings are in agreement with the earlier report of Baveja et al. (9), who found that a combination of anionic NaCMC with nonionic HPMC produced a synergistic increase in viscosity. This was attributed to the stronger hydrogen bonding between the carboxyl groups of NaCMC and hydroxyl groups of the HPMC, leading to stronger cross-linking between two gums.

The release rates of marketed diclofenac sodium sustained-release tablets along with formulation 4 are shown in Fig. 3. In the case of marketed products, the release rate from Dicloran SR was more regular (approaching zero order) and the release of drug was sustained for 7 h when compared with the release rates of Voveran SR and Nac SR. The dissolution profile of Dicloran SR is almost comparable with that of the test formulation 4.

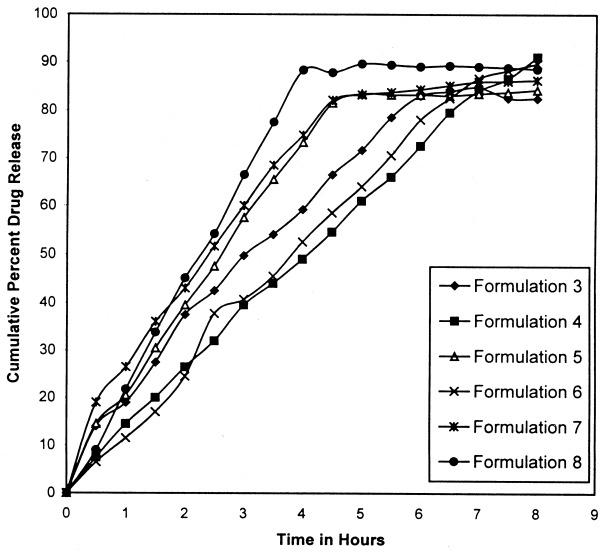

Figure 1. Dissolution profiles of diclofenac sodium from matrix tablets containing a combination of polymers.

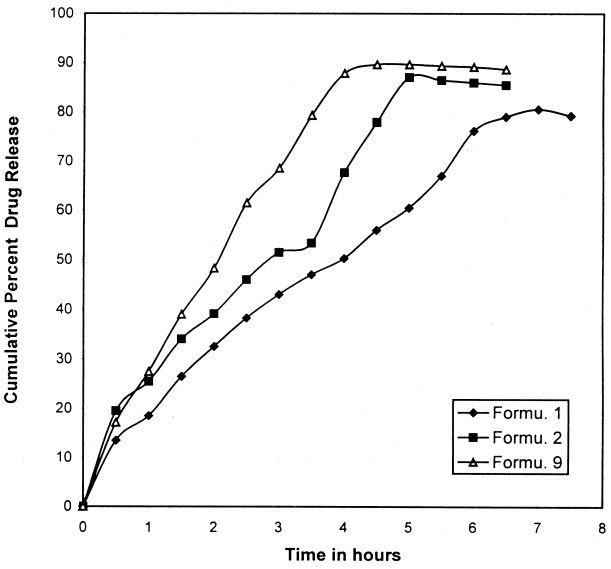

Figure 2. Dissolution profiles of diclofenac sodium from matrix tablets containing a single polymer.

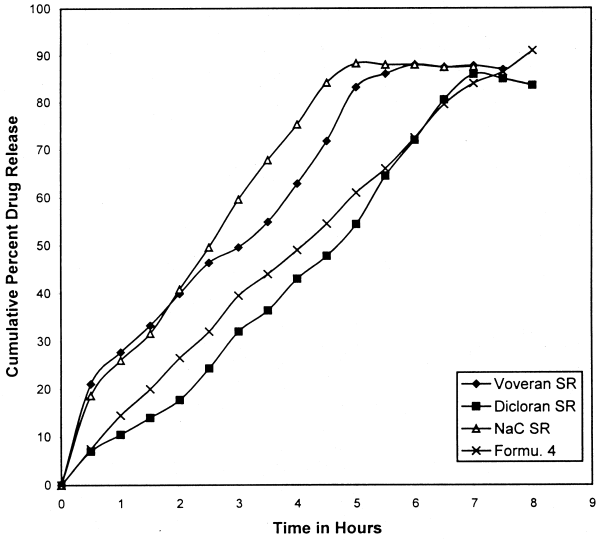

Figure 3. Dissolution profiles of diclofenac sodium marketed products and formulation 4.

On comparing formulation 8 with formulation 1 and formulation 4, it is observed that addition of Carbopol 934 to the HPMC matrix tablet increased the release rate of diclofenac sodium.

To study the release mechanism, the dissolution data obtained were plotted as the percentage of diclofenac sodium released against the square root of time. Linearity was not observed, with the plots showing that the release was not following Fick's law of diffusion.

To analyze the release mechanism of the drug from these formulations, the dissolution data obtained were fit to the equation of Korsmeyer and Peppas (10), given as

$$Mt/M\infty = Kt^n$$

where $Mt/M\infty$ is the fractional release of drug in time t, K is a constant incorporating structural and geometric characteristics of the controlled-release device, and n is the diffusional release exponent indicative of mechanism of release. The value of n is 0.5 for Fickian transport, more than 0.5 and less than 1 for non-Fickian transport, and 1 for case II transport (zero order); when the value of n approaches 1, it may be concluded that the release is approaching zero order.

The dissolution data were fit to the above equation by drawing a log-log plot of the fraction released versus time. The values of diffusion release exponent n (slope) and coefficient of correlation r following linear regression of dissolution data are shown in Table 1. For all the test formulations and marketed products, the value of n was greater than 0.5, indicating non-Fickian transport. Formulation 4 and Dicloran SR exhibited an n value greater than 0.9, indicating near zero-order release. Therefore, these two products were selected for the bioavailability study along with Voveran SR, which is a brand leader with huge popularity.

Table 2

Average Serum Concentrations and Related Parameters of Diclofenac Sodium Following Oral Administration of 100 mg Sustained-Release (SR) Tablets

Sl. No.	Time (h)	Dicloran SR	Voveran SR	Formulation 4
1	0.5	123.7	123.3	111.3
2	1.0	292.6	273.5	265.6
3	1.5	370.0	365.9	375.0
4	2.0	481.5	457.0	455.4
5	2.5	548.0	447.0	549.8
6	3.0	491.0	340.0	467.0
7	5.0	444.0	356.0	385.0
8	7.0	334.0	244.0	325.0
9	10.0	212.0	146.0	214.0
10	13.0	123.0	95.8	133.0
11	24.0	46.0	43.0	36.0

Bioavailability Studies

The mean serum levels of diclofenac sodium and the mean pharmacokinetic parameters, like peak serum concentration C_{max}, peak serum time T_{max}, area under the curve AUC, half-life $t_{1/2}$, mean residence time (MRT), along with statistical details (one-way analysis of variance [ANOVA] test) are given in Table 2 and Table 3, respectively. The profiles of serum concentration versus time are given in Fig. 4. From Table 3, the differences in C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2}$ between Dicloran SR and formulation 4 were found to be statistically insignificant, whereas the difference in all of these pharmacokinetic parameters between Voveran SR and formulation 4 were found to be statistically significant. Fig. 4 shows that the profiles of serum drug concentrations versus time of Dicloran SR and formulation 4 were found to be similar with respect

Table 3

Mean Pharmacokinetic Parameters of Diclofenac Sodium Marketed Products (Dicloran SR and Voveran SR) and Formulation 4

Sl. No.	Pharmacokinetic Parameter Mean	Voveran SR A	Dicloran SR B	Formulation 4 C
1	C_{max}	472.00[a]	554.60	538.00
2	T_{max}	2.08	2.41	2.30
3	AUC_{0-t}	3698.00[a]	4871.00	4554.00
4	$AUC_{0-\infty}$	4156.00[a]	5279.00	4872.00
5	$t_{1/2}$	7.29[a]	6.20	5.38
6	MRT	10.49	9.44	9.09

Statistical analyses were carried out using one-way analysis of variance (ANOVA) test.
MRT, mean residence time; SR, sustained release.
[a]Statistical significant ($P < .05$).

Table 4

In Vitro–In Vivo Correlation of Diclofenac Sodium Marketed Products (Dicloran SR and Voveran SR) and Formulation 4

Sl. No.	Time (h)	Formulation 4		Dicloran SR		Voveran SR	
		A	B	A	B	A	B
1	0.5	7.5	18.8	7.0	21.1	21.1	24.6
2	1.0	14.5	45.7	10.5	50.5	27.7	59.8
3	1.5	20.0	65.7	14.0	65.3	33.3	76.5
4	2.0	26.5	81.3	17.7	98.4	39.9	97.9
r		0.994		0.991		0.989	

A, % released in vitro; B, % absorbed; *r*, correlation coefficient; SR, sustained release.

to AUC and C_{max}, whereas the profile of serum drug concentration versus time of Voveran SR does not follow the pattern of formulation 4 with respect to AUC and C_{max}. This is also supported by the statistically significant difference of pharmacokinetic parameters between Voveran SR and formulation 4 (shown in Table 4).

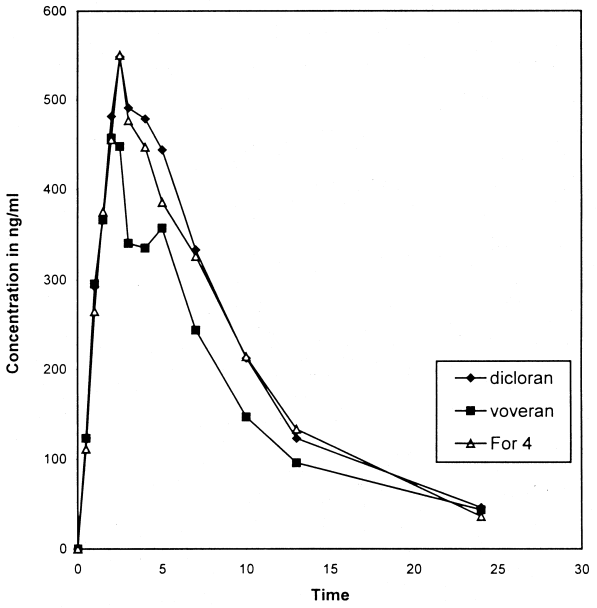

Figure 4. Profiles of mean serum concentration versus time of diclofenac sodium tablets.

The results obtained from the bioavailability study showed that Dicloran SR and formulation 4 were similar in their bioavailability profile and at the same time significantly different from Voveran SR.

In the case of formulation 4, the drug diclofenac sodium was embedded in an HPMC : NaCMC polymeric matrix. During transit of the dosage form through the gastrointestinal tract, the drug was released slowly from this polymeric matrix. The polymer HPMC was swellable and formed a coating over the drug particles, thereby delaying the release of the drug. The HPMC and NaCMC physical mixture tablet, because of its slow release of drug into the gastrointestinal fluids, caused more complete absorption of the drug. The increase in AUC must have been due to the larger residence time of the dosage form in the gastrointestinal tract, resulting in complete and effective absorption of the drug. This increased residence time of the dosage form may be due to mucoadhesion, which might have occurred since HPMC has good mucoadhesive properties (11). Earlier work (X-ray studies) done in our laboratories with the same polymer has proved conclusively that HPMC does have good mucoadhesive properties.

Hence, it is concluded that the resultant increase in AUC_{0-t} and $AUC_{0-\infty}$ for formulation 4 must have been due to prolonged release of the drug due to the higher viscosity of the polymer combination and possible mucoadhesion of the tablet to the gastrointestinal tract because of the mucoadhesive polymer HPMC.

In Vitro–In Vivo Correlation

Percentage of drug absorbed at different times was determined by the Wagner Nelson (12) method using a computer program. In vitro–in vivo correlation was done by plotting percentage drug absorbed versus in vitro drug release. The plots were linear for the three products tested (i.e., formulation 4, Voveran SR, and Dicloran SR), with a correlation coefficient of 0.994 for formulation 4, 0.991 for Dicloran SR, and 0.989 for Voveran SR (Table 4). For the formulations tested, the r value was greater than 0.989, indicating high correlation. This in vitro–in vivo correlation is of great use in development of sustained-release matrix tablets.

SUMMARY AND CONCLUSIONS

The results from in vitro dissolution studies showed that prolonged release can be achieved by formulating drugs in matrix devices using HPMC and NaCMC polymers. The optimum ratio of drug : HPMC : NaCMC was found to be 1 : 2 : 1. A combination of nonionic polymer HPMC and anionic polymer NaCMC as the polymer matrix resulted in near zero-order release of diclofenac sodium. It was observed that increasing the polymer content produced a more sustained effect. The results obtained were in agreement with earlier reports (13–15).

Drug release from the matrix did not follow Fick's law of diffusion and exhibited near zero-order release following case II transport.

Critical analysis of the results reveals that one of the marketed formulations (Voveran SR) was not able to maintain the sustained-release pattern, and the bioavailability of formulation 4 was similar to that of the marketed formulation Dicloran SR. A good in vitro–in vivo correlation was observed for these products.

Matrix tablets are easy to prepare and have sound technology. They are cost-effective and exhibit predictable release behavior. We therefore presume that future controlled-release products could be developed along these lines rather than as multiunit pellet preparations, which not only are sophisticated in their technology, but are comparatively less economical than matrix products.

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