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Design and Evaluation of Matrix-Based Controlled Release Tablets of Diclofenac Sodium and Chondroitin Sulphate

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ABSTRACT

The purpose of the present study was to develop and characterize an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxypropylmethylcellulose (HPMC) was developed using wet granulation technique to contain 100 mg of DS and 400 mg of CS. Formulations prepared were evaluated for the release of DS and CS over a period of 9 hours in pH 6.8 phosphate buffer using United States Pharmacopeia (USP) type II dissolution apparatus. Along with usual physical properties, the dynamics of water uptake and erosion degree of tablet were also investigated. The in vitro drug release study revealed that HPMC K100CR at a concentration of 40% of the dosage form weight was able to control the simultaneous release of both DS and CS for 9 hours. The release of DS matched with the marketed CR tablet of DS with similarity factor (f_2) above 50. Water uptake and erosion study of tablets indicated that swelling followed by erosion could be the mechanism of drug release. The in vitro release data of CS and DS followed Korsmeyer-Peppas and zero-order kinetics, respectively. In conclusion, the in vitro release profile and the mathematical models indicate that release of CS and DS can be effectively controlled from a single tablet using HPMC matrix system.

KEYWORDS: Chondroitin sulphate, diclofenac sodium, hydroxypropylmethylcellulose, controlled release.

INTRODUCTION

Chondroitin sulfate (CS) belongs to a family of heteropolysaccharides called glycosaminoglycans or GAGs. Glycosaminoglycans were formerly known as mucopolysaccharides. GAGs in the form of proteoglycans comprise the ground substance in the extracellular matrix of connective tissue. CS is made up of linear repeating units containing D-galactosamine and D-glucuronic acid. CS is found in humans in cartilage, bone, cornea, skin, and the arterial wall. This type of CS is sometimes referred to as chondroitin sulfate A or galactosaminoglucuronoglycan sulfate. The molecular weight of CS ranges from 5000 to 50 000 d and contains ~15 to 150 basic units of D-galactosamine and D-glucuronic acid.

The mechanism of action and absorption of orally administered CS has not been clearly understood. Possible actions include promotion and maintenance of the structure and function of cartilage (referred to as chondroprotection), pain relief of osteoarthritic joints and anti-inflammatory activity.[1-4] CS in combination with hyaluronic acid is available as a combination product in the United States. It is used as a viscoelastic agent in cataract surgery. CS is available generically from numerous manufacturers.

Diclofenac sodium (DS) is usually prescribed as once-a-day controlled release tablets for management of painful arthritis conditions to reduce the inflammation and thereby reduce pain. CS is coprescribed in many instances for its chondroprotective action and cartilage rebuilding. It was hypothesized that combining both drugs in a controlled release dosage form would reduce pill burden and increase patient compliance.

An effort was therefore made to develop simple and effective controlled release DS and CS tablets using a polymer matrix system with uniform in vitro release properties. Hydroxypropylmethylcellulose (HPMC) is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems.[5] The transport phenomena involved in the drug release from hydrophilic matrices are complex because the microstructure and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly.[6] The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution.[7,8] As reported by Ford et al,[9] as the proportion of the polymer in the formulation increases, the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix. Narasimhan and Peppas[10] showed that the dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer swelling and

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Table 1. Different Tablet Compositions*

Name of Component	Quantity (mg) per Tablet†			
	F1	F2	F3	F4
Diclofenac sodium	100	100	100	100
Chondroitin sulfate	400	400	400	400
HPMC K100	100	134	235	360
Isopropyl alcohol	qs	qs	qs	qs
PVP K90	10	10	12	14
Magnesium stearate	8	7	7	8
Talc	8	8	8	9
Aerosil	8	8	8	9
Total	634	667	770	900

* HPMC indicates hydroxypropylmethylcellulose; qs, quantity sufficient; PVP, polyvinylpyrrolidone.
† Formulations: F1, 15% HPMC; F2, 20% HPMC; F3, 30% HPMC; and F4, 40% HPMC.

dissolution as well as the corresponding rate of drug release are found to increase with either higher levels of drug loading or with use of lower viscosity grades of HPMC.[11] The aim of this study was to develop a controlled release dosage form of DS and CS and to evaluate the drug release kinetics from the HPMC matrix.

Materials and Methods

Diclofenac sodium United States Pharmacopeia (USP) was supplied by Lupin Ltd (Pune, India). HPMC (Methocel K100M CR) was procured from Colorcon (Dartford, UK). Chondroitin sulfate was procured from Biocon (Banglore, India) and polyvinylpyrrolidone (PVP) K90 USNF was purchased from BASF (Ludwigshafen, Germany). All other ingredients used throughout the study were of USP grade and were used as received.

Preparation of Tablets

Matrix tablets were prepared by wet granulation method. The composition of various formulations is given in Table 1. DS, CS, and HPMC K100 were mixed in a polybag, and the mixture was passed through mesh (No. 40). Granulation was done using a solution of PVP K90 in sufficient isopropyl alcohol. The wet mass was passed through mesh No 8. The wet granules were air dried for ~2 hours. The granules were then sized by mesh No. 16 and mixed with aerosil (Aerosil-200, Degussa Corp, Dusseldorf, Germany) and talc. Tablets were compressed at 900 mg weight on a 10-station mini rotary tableting machine (General Machinery Co, Mumbai, India) with 18-mm oval-shaped punches. Four different formulas, having different concentrations of HPMC K100 (15%, 20%, 30%, and 40%), were developed to evaluate the drug release and to study the effect of polymer concentration on drug release.

Evaluation of Tablets

As mentioned in the Preparation of Tablet section, to study the effect of polymer concentration on drug release, 4 different formulas, having different concentrations of HPMC K100, were developed. Because determination of CS is a complex process, the optimized formula was selected on the basis of DS release characteristics only. As shown in Figure 1, F4 formulation showed prolonged release and thus was chosen for further studies.

The prepared tablets were tested as per standard procedure for weight variation (n = 20), hardness (n = 6), drug content, thickness (n = 20), friability, water uptake, and erosion characteristics. Hardness of tablet was determined by using a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). Friability test (n = 20) was conducted using Roche friabilator (F. Hoffmann-La Roche Ltd, Basel, Switzerland). Thickness of the tablets was measured by digital Vernier caliper (Mitutoyo Corp, Kawasaki, Japan). Drug content of DS was analyzed by measuring the absorbance of standard and samples at λ = 275 nm using UV/Visible spectrophotometer (Jasco model V-530, Tokyo, Japan). Drug content of CS was analyzed by using method described by Zhang et al[11] and measuring the absorbance of complex at λ = 662.5 nm and comparing the content from a standard calibration curve. Further the similarity factor (f_2) for the release of DS between the test product and that of marketed formulation, Voveran SR (Novartis, Basel, Switzerland), was performed.

Quantification of the Water Uptake and Erosion Determination

For conducting water uptake studies, the dissolution jars were marked with the time points of 0.5, 1, 2, up to 9 hours.

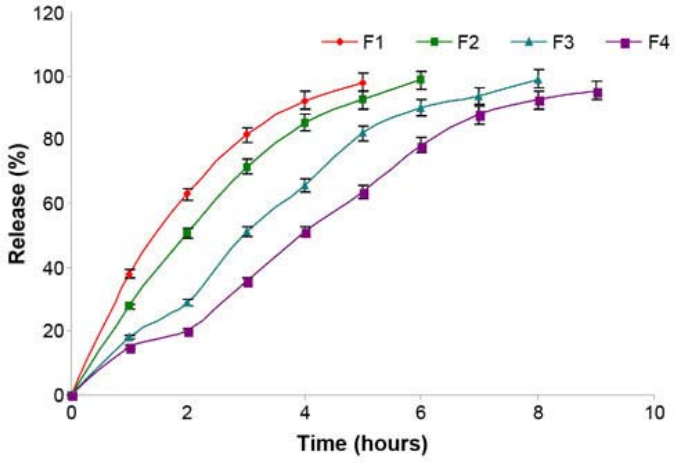

Figure 1. Percentage average release of diclofenac sodium from matrices containing different concentrations of hydroxypropylmethylcellulose. Error bars represent the standard deviation ±<3%.

One tablet was placed in each dissolution jar containing 1000 mL of phosphate buffer pH 6.8 at 37°C ± 0.5°C, and the apparatus was run at 100 rpm using paddle. The tablets were taken out after completion of the respected stipulated time span as mentioned above and weighed after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an oven at 40°C up to constant weight. The increase of the weight on the tablet reflects the weight of the liquid uptake. It was estimated according to Equation 1:

$$Q = 100(W_w - W_i)/W_w \quad (1)$$

where Q is the percentage of the liquid uptake, and W_w and W_i are the masses of the hydrated samples before drying and the initial starting dry weight, respectively.[12]

The degree of erosion (expressed as percentage erosion of the polymer content, E) was determined using Equation 2:

$$E = 100(W_i - W_f)W_i \quad (2)$$

where W_f is the final mass of the same dried and partially eroded sample.

The entire process was repeated to get 3 values for each time point, and the average was calculated.

In Vitro Drug Release Characteristics

Drug release was assessed by dissolution test under the following conditions: n = 6 (in triplicate), USP type II dissolution apparatus at 100 rpm in 1000 mL of phosphate buffer at pH 6.8 maintained at 37°C ± 0.5°C. Ten milliliters of the sample was withdrawn at regular intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No. 1, Whatman, Maidstone, UK) and drug content in each sample was analyzed after suitable dilution. DS was analyzed at λ = 275.0 nm. Release of CS was studied by means of a dye complexation method[11] using methylene blue (MB), a cationic dye; and absorbance of complex was measured at 662.5 nm.

The suitability of several equations, which have been reported in the literature to define drug release mechanism(s),[13] was tested with respect to the release data. Some diffusion models (Korsmeyer-Peppas) are expected to be valid up to ~60% cumulative drug released,[14] therefore the data for analysis were restricted to that range. To analyze the mechanism of drug release from the matrix tablets, data obtained from the drug release studies were analyzed according to Equations 3, 4, and 5 of the zero-order model,[15-17] Higuchi model, and the Korsmeyer-Peppas model,[18,19] respectively:

$$M_t = M_o + K_o t \quad (3)$$

$$M_t = M_o + K_H t^{0.5} \quad (4)$$

$$M_t = M_o + K_k t^n \quad (5)$$

In all mathematical expressions, M_t is the amount of the drug dissolved in time t; M_o is the initial amount of drug in the solution; K_o is the zero-order release constant; K_H is the Higuchi rate constant; K_K is the release constant; and n is the release exponent, which characterizes the mechanism of drug release.

Similarity Factor (f_2) Analysis

In vitro release profile of the marketed DS sustained release (SR) tablets, (Voveran SR, Novartis) was performed under similar conditions as used for in vitro release testing of the test product for the release of DS. The similarity factor between the 2 formulations was determined using the data obtained from the drug release studies. The data were analyzed by the formula[20] shown in Equation 6.

$$= 50\log\left\{\left[1 + (1/N)\sum(Ri - Ti)^2\right]^{-0.5} \times 100\right\} \quad (6)$$

where N = number of time points, Ri and Ti = dissolution of reference and test products at time i. If f_2 is greater than 50 it is considered that 2 products share similar drug release behaviors.

Results and Discussion

The combination product of DS and CS was conceptualized based on the fact that, in clinical practice, DS is used as an anti-inflammatory agent in the treatment of osteoarthritis, and CS is usually supplemented for its reported cartilage-rebuilding ability. DS is known to be effective when taken once daily, and the mechanism of action of CS and its pharmacokinetics after oral administration is not clearly understood; hence, the controlled release form of DS and CS together was expected to be more beneficial. Because CS is a mucopolysaccharide with a higher molecular weight, there is difficulty in transportation of drug across the gastrointestinal mucosa; therefore it was thought that if this drug were released slowly, the absorption would be better.

Direct compression is the preferred technique for making controlled release tablet formulations; however, in the

Table 2. Physical Properties of Formulations Prepared*

Test	Results			
	F1	F2	F3	F4
Weight (mg) mean ± SD	634 ± 1.3	667 ± 2.0	770 ± 1.6	900 ± 1.0
Hardness (kp)	17–19	17–20	16–18	17–20
Drug content (%) DS	99.5	98.9	99.3	99.6
Thickness (mm)	4.9 ± 0.02	5.2 ± 0.02	5.8 ± 0.04	6.3 ± 0.03
Friability (%)	0.19	0.22	0.35	0.15

*SD indicates standard deviation; kp, kilopascals; DS, diclofenac sodium.

authors' experience, when the tablet contains a higher percentage of active substance and especially when this active substance is water soluble, the direct compression technique is less effective. In this case, CS is a water-soluble, hydrophilic material, which allows quicker penetration of water in the system, resulting in faster drug release. This characteristic has been controlled by adding HPMC to the system and further adopting aqueous granulation.

Physical Properties

The results of the uniformity of weight, hardness, drug content, thickness, and friability of the tablets are given in Table 2. All the samples of the test product complied with the official requirements of uniformity of weight. The drug content was found to be close to 100% of the label claim for DS and CS in all formulations. The low friability indicates that the matrix tablets are compact and hard. The results were reproducible, even on tablets that had been stored for about 6 months at 25°C and 60% relative humidity.

Liquid Uptake and Erosion

Since the rate of swelling and erosion is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and the erosion of the hydrated tablets were determined. Simultaneously with the liquid uptake study, the degree of polymer erosion was measured. The percentage liquid uptake and erosion of tablet at various time intervals is shown in Figures 2 and 3.

During swelling of the HPMC tablets, an anisotropic swelling phenomena (ie, more swelling in the axial direction than in the radial direction on exposure to water) was seen. Similar phenomena were observed by Lopes et al[12] and Papadimitriou et al,[21] who related the predominantly axial relaxation of the HPMC compacts to the relief of stress induced during compaction and the unidirectional swelling to the orientation of the molecules during compression. The reason for such preferential swelling in an axial direction must be due to the need for the directional stresses, imposed on HPMC during tableting, to relax. It follows that the area change in the swollen system is directly related to the area exposed to water access.

In Vitro Release Studies

Low molecular weight HPMC is used predominantly for tablet film coating, while high molecular weight HPMC is used as a rate-controlling polymer to retard the release of drugs from a matrix at levels of 10% to 80% wt/wt in tablets and capsules.[22,23] Therefore, prototype formulations with

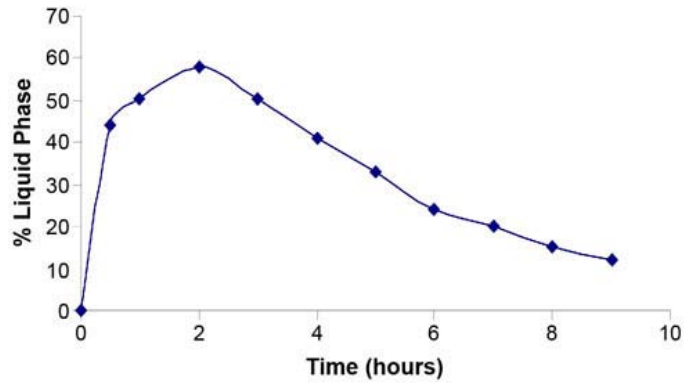

Figure 2. Percentage of liquid uptake by hydroxypropylmethylcellulose at various time intervals (hours) after contact with aqueous medium.

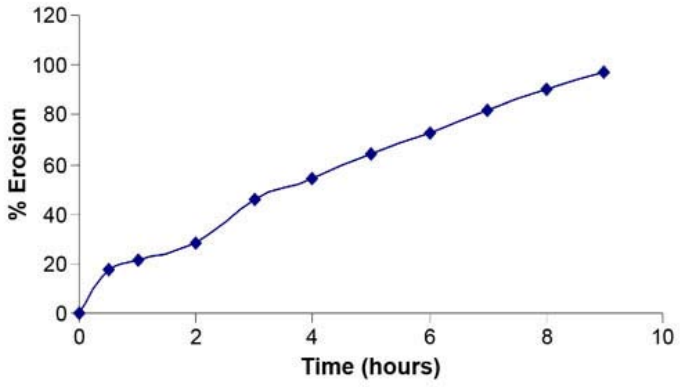

Figure 3. Percentage erosion resulting from hydroxypropylmethylcellulose erosion of tablet at various time intervals (hours) after contact with aqueous medium.

Table 3. Dissolution Parameters for Diclofenac Sodium and Chondroitin Sulfate From Formulation F4*

	Korsmeyer-Peppas Equation		Zero-Order Equation		Higuchi Equation	
Drug	n	R^2	K_0	R^2	K_H	R^2
DS	0.9438	0.9871	11.8000	0.9878	29.3380	0.9415
CS	0.8773	0.9931	12.0741	0.9851	30.1612	0.9557

* DS indicates diclofenac sodium; CS, chondroitin sulfate.

drug content of DS (100 mg) and CS (400 mg) were developed by simple wet granulation method using HPMC K100 MCR USNF. The effect of polymer level on the release of DS and CS was studied for tablets containing 15%, 20%, 30%, and 40% HPMC K100 (formulations F1, F2, F3, and F4 respectively). Figure 1 shows that the amount of HPMC affects the release rate of drug. Tablets containing 15% and 20% HPMC showed 97.8% and 98.6% release after 5 and 6 hours, respectively. These formulations (F1 and F2) underwent erosion before complete swelling could take place, resulting in faster release of drug. F3 formulation showed faster dissolution rate in intermediate time of 2 to 6 hours, which did not match with the reference product. On increasing the quantity of HPMC to 40%, prolonged release of both the drugs was achieved up to 9 hours.

Identification of the Mechanism by Which the Drug Is Released

Based on various mathematical models, the magnitude of the release exponent "n" indicates the release mechanism (ie, Fickian diffusion, case II transport, or anomalous transport). In the present study, the limits considered were n = 0.45 (indicates a classical Fickian diffusion-controlled drug release) and n = 0.89 (indicates a case II relaxational release transport; non-Fickian, zero-order release). Values of n between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport.[13] From the release exponent in the Korsmeyer-Peppas model (n = 0.8773), it can be suggested that the mechanism that led to the release of CS was an anomalous transport with constant release rate adequate for a sustained release dosage form. The correlation (R^2) was used as an indicator of the best fitting for each of the models considered (Table 3). The release of CS and DS (Figure 4) apparently follows Korsmeyer-Peppas model ($R^2 > 0.9931$) and zero-order kinetics ($R^2 > 0.9878$), respectively. However, looking at the negligible variation of R^2 values for the release of DS, the release data analysis applying these mathematical models can be purely empirical, and no definitive conclusion can be drawn concerning the dominating mass transport mechanism.

Similarity Factor

The principal purposes of dissolution testing are 3-fold: (1) for quality control, to ensure the uniformity of product from batch to batch; (2) to help to predict bioavailability for formulation development; and (3) as a measure of change when formulation changes are made to an existing formulation. The so-called f_2 method can be used to compare 2 dissolution profiles. Similarity factor analysis between the prepared tablets and Voveran SR tablet for the release of DS showed an f_2 factor (f_2 = 68.98) greater than 50. As shown in Table 4 and

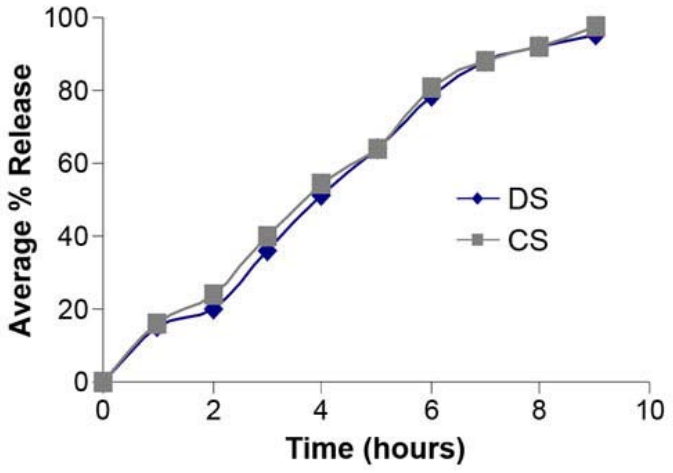

Figure 4. In vitro release profiles of diclofenac sodium (DS) and chondroitin sulfate (CS) from Formulation F4.

Table 4. f_2 Factor Results

	Average % Release		
Time	Reference*	Test†	f_2‡
0	0.00	0.00	0.00
1	18.79	14.87	76.54
2	29.16	20.08	61.84
3	38.30	35.69	64.15
4	56.10	51.05	64.20
5	67.32	63.70	65.10
6	76.35	78.21	66.45
7	86.51	87.71	67.73
8	91.38	92.39	68.87
9	99.08	95.22	68.98

* Voveran SR tablet.
† Prepared Tablet.
‡ Average value of f_2 = 68.98.

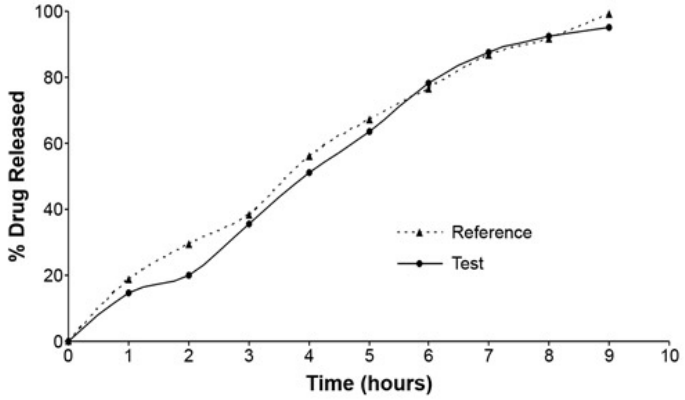

Figure 5. Comparative in vitro diclofenac sodium release profile for f_2 test: reference is Voveran SR tablet and test is prepared tablet.

Figure 5, the f_2 factor confirms that the release of DS from the prepared tablets was similar to that of the marketed tablet.

CONCLUSION

Results of the present study demonstrate that CS and DS can be co-administered in the form of a single controlled release matrix tablet. It is evident that the investigated controlled release matrix of HPMC at 40% concentration was capable of prolonging the release of both drugs simultaneously for 9 hours. The mechanism of drug release was observed to be following Korsmeyer-Peppas model and zero-order kinetics for CS and DS, respectively.

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