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Research Article

Formulation and *In-vitro* Evaluation of Diclofenac Sodium Controlled Release Drug Delivery System

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ABSTRACT

Diclofenac sodium is a potent non-steroidal drug with potent analgesic and anti-inflammatory activity. Its oral administration is associated with a high risk of adverse effects such as irritation, ulceration and also bleeding of gastrointestinal tract. The present study focuses on the development of five formulations which were prepared by granulation using two viscosity grades of HPMC (hydroxylpropylmethylcellulose) in varying ratios with water in a planetary mixer. The *in-vitro* release tests indicate that the larger the amount of high viscosity grade HPMC used, the slower the resultant release rate of diclofenac sodium. Infra-red (IR) investigations revealed that there was no interaction between the drug and the polymers used. There was no significant degradation of diclofenac sodium or change in drug release rate in any of the prepared formulations during a six-month period of stability testing. The effect of various formulations as well asprocess variables on the flowabilityof drug loading and *in-vitro* drug release was studied. The flow characteristic showed Hausner's ratios of <1.25 and Carr's index of 5-16 % of the systems prepared while those of the drug alone were >1.25 and > 40% respectively indicating good and excellent flow of the systems and extremely poor flowability of the drug. Diclofenac sodium content in different formulations was not affected by neither the polymer type nor drug to polymer ratio and ranged between 98 - 100 %.The *in-vitro* release studies showed that the release rate of the drug has been modified. This study presents a new approach for obtaining modified release drug delivery system.

Keywords: Diclofenac sodium, controlled delivery, HPMC, In vitro study.

1. INTRODUCTION

Diclofenac sodium is one of the classes of non-steroidal drugs which has potent anti-inflammatory, analgesic as well as antipyretic action. Diclofenac sodium is a phenylacetic acid derivative with a pKa value of 4.0. As a result, diclofenac sodium is practically insoluble in acidic medium but dissolves in intestinal fluid and water[1]. It is generally known that diclofenac sodium migrates into blood within 30 min and reaches the maximum blood concentration (Cmax) within 1.5 to 2.5 h following oral administration of a50 mg enteric coated tablet[2]. The maximum average concentration in blood is between 0.7 and 1.5 mg L^{-1}. The oral bioavailability is around 60% with an excretion half-life of between 1.1 and 1.8 h[3]. HPMC is the material most widely used as a matrix to control drug release. The influence of technological variables on drug release from HPMC matrices has been reviewed[4]. However, due to the poor flow of the powder blend, it is common to use less desirable methods such as direct die-filling or double compression. Wet-granulation with water as a simple binding aid has not been employed, probably because of the tendency of HPMC to gel and form lumps in the presence of water. In previous studies[5], it was shown that HPMC granules suitable for compression into matrix tablets could be produced by spraying the powder blend with water and granulating in a planetary mixer. Employing the same granulation process in this study, the combination of high and low viscosity grades of HPMC at various ratios was used as the matrix base to prepare diclofenac sodium sustained-release tablets. The in-vitro dissolution tests were performed to evaluate the control characteristics of these matrix tablets.

2. MATERIALS AND METHODS

2.1. Materials

Diclofenac sodium (Sigma-Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Amriya pharmaceuticals industries, Alexandria, Egypt. Two viscosity grades of hydroxy-propylmethylcellulose (HPMC, Metolose 60-SH, 50 and 4000 CPs) were purchased from RÖhm Pharma GMBH, Darmstadt (Germany). All other reagents were analytical or pharmaceutical grade.

2.2. Preparation of diclofenac sodium- HPMC granules:

The two grades of HPMC (total 50 mg) at five different ratios (Table 1) were mixed with 50 mg diclofenac sodium in a planetry mixer. While stirring, water was added using a spray system (nozzle size 0.012 inches). After the measured amount of water was added, the wet granules were discharged and dried for 10 h at 50^{o}C in a hot air oven. All granules batches had loss on drying value of less than 2% (measured with an ohaus moisture determination balance, model MB-200). The dried granules were passed through a No 20 mesh screen.

2.3. Infrared spectral analysis:

The IR spectrum was used to determine the interaction of the drug with the polymers used. The infrared spectra of samples were obtained using a spectrophotometer (FTIR, Jusco, Japan). Samples were mixed with potassium bromide (spectroscopic grade) and compressed into discs using hydraulic press before scanning from 4000 to 400 cm^{-}1 [6,7].

2.4. Flowability testing:

The flowability of the prepared powders was tested by measuring their angle of repose. The calculations of Carr's compressibility index as well as Hausner's ratio were also tested. The experiments are done in triplicate, the average ±S.D were recorded.

2.4.1. Measuring the angle of repose:

The fixed height cone method was adopted[8] where the diameter of the formed cone (d) was determined according to the following equation:

$$Tan\,\theta = \frac{2h}{d}$$

Where (h) and (d) are the height and the diameter of the formed cone respectively.

2.4.2. Determination of the initial and tapped bulk densities:

A fixed weight of the powder either the drug or the prepared granules was poured into a 25 ml graduated cylinder , the powder was allowed to settle with no outer force and the volume occupied was measured as V_I (initial bulk volume).The cylindrical graduate was then tapped on a plan surface at a one inch distance till a constant volume was obtained . The tapped volume of the powder was then recorded as (V_T). The initial and tapped bulk densities were then calculated according to the following equation[9]:

Initial Bulk Density $\rho_I = M / V_I$

Tapped Bulk Density $\rho_T = M / V_T$

Where (M) is the mass of the powder. The percentage compressibility (Carr's index) was then determined from the following equation[10]:

$$\text{Carr's index} = \frac{\rho_T - \rho_I}{\rho_T}$$

Finally the Hausner's ratio was obtained by dividing V_I by V_T[11].The experiments were carriedout in triplicate and the average angle of repose; Carr's index and Hausner's ratio of each of the prepared formulae were then calculated.

2.5. Drug content determination:

Percentage yield can be determined by calculating the initial weight of raw materials and the finally obtained weight of granules. Percentage yield can be calculated by using the formula[12]:

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoritical yield}} \times 100$$

An accurately weighed amount of the prepared granules was taken in a stoppered test tube and extracted with 5 ×10 ml quantities of phosphate buffer (pH 7.4).The extracts were filtered and collected into 100 ml of volumetric flask and made up to the volume with phosphate buffer (pH 7.4). The solutions were subsequently diluted suitably with pre warmed phosphate buffer (pH 7.4) and spectrophotometric absorbance was taken at 276nm [13].(UV-Visible recording spectrophotometer), SHIMADZU (UV-160A) (Japan). Percentage drug entrapment as well as the percentage entrapment efficiency (PEE) were calculated by the formula given below [14-16].

$$\text{PEE} = \frac{\text{Drug loading in the prepared granules}}{\text{Theoritical drug loading}} \times 100$$

2.6. *In-vitro* drug release studies:

The USP dissolution test apparatus employing paddle type(Paddle type , Copley , England) was used to measure the dissolution rate of diclofenac sodium from HPMC delivery system at 37^{o}C± 0.2. The dissolution of the drug was conducted in two media pH 1 (0.1 N HCL) as well as pH 7.4 (Phosphate buffer) representing stomach and intestinal conditions respectively.

At predetermined time intervals up to 12 hours, aliquots (5ml) were withdrawn, filtered through

0.45µ membrane filter and replaced with equal volumes of pre warmed fresh medium to maintain constant volume and keep sink condition. After appropriate dilution, the sample solution was analyzed for diclofenac sodium by UV absorbance method at 276 nm[17].

2.7. Stability study:

A stability test was conducted by storing the prepared formulation in amber bottles at ambient temperature, 31, 37, 43°C (the relative humidity was controlled at 75%, except at ambient temperature). The content of diclofenac sodium as well as the release of drug from the proposed formulation were tested monthly for six months. The dissolution study of the tested formulations followed the same procedures as previously described[18].

3. RESULTS AND DISCUSSION

3.1. Infrared spectral analysis:

The IR spectrums are shown in Figure 1. The IR spectrum of pure drug diclofenac sodium (Fig.1A) shows a characteristic peak at 3386 cm^{-1}due to N-H stretching frequency of secondary amine. The absorption bands at 1305 and 1282 cm^{-1}resulted from C-N stretching and the peaks at 1556 and 1574 cm^{-1}due to C=C stretching and C=O stretching of carboxylate group, respectively. The C-Cl stretching characteristic peak was observed at 746 cm^{-1}. The IR spectra of diclofenac sodium with HPMC 4000 (Fig.1B) and diclofenac sodium with HPMC 50 (Fig.1C) shows all the principal characteristic peaks related to diclofenac sodium without any change in their position, indicating no possibility of chemical interaction between the drug and formulation ingredients**.**

3.2. Flowablity testing:

Table (2) shows the results of the flowablity testing of diclofenac sodium as well as the results of the proposed formulations. From the table it is clear that, Hausner's ratio of the drug alone was found to be 1.86±0.46 which indicates a poor flow property of the free drug. The F1 formula showed 1.07, while F2 formula revealed 0.85. Also, F3 formula showed 1.10.The F4 formula revealed 0.89, while F5 formula revealed 1.12indicating a good flow [11].

Carr's index for the drug alone was found to be 50.21% indicating extremely poor flow of the free drug. The F1 formula showed an index of 16.22%, while F2 formula showed an index of 15.07%. On the other hand, F3 formula showed an index of 14.55%. F4 formula showed an index of 13.05%, while F5 formula showed an index of 12.90% indicating excellent and good flow[10].

It is evident from Table (2) that the angle of repose decreases by using higher ratio of HPMC 50 and when the angle of repose decreases flowability increases.

3.3. Drug content determination:

Table (3) shows the results of diclofenac sodium content in the proposed formulations, it is clear that the percentage yield of different proposed formulations varied from 98.94±0.21 to 100.03±0.87. From the results in the table it is evident that drug to polymer ratios did not play any rule in the entrapment efficiency of the drug. It was proved that the type of the polymers in the delivery system has no effect on the percentage entrapment efficiency[12].

3.4. *In-vitro* drug release studies:

Since diclofenac sodium has a pka value of 4, it is practically insoluble in acidic medium; there was no observable release of diclofenac sodium in 0.1 N HCl[19].

Apparently, the release rate of diclofenac sodium is mainly controlled by the polymer viscosity. Specifically, the drug release rate is inversely proportional to the quantity of the higher viscosity polymer. Basically, drug released from these types of drug delivery systems results from hydration of HPMC, which forms a gelatinous barrier through which drug must diffuse. In addition, the resistance of such a gel layer is controlled by the viscosity grade of the HPMC. In such cases, decreasing HPMC 4000 in the formulations would increase the release rate of diclofenac sodium. The release profile of diclofenac sodium from different prepared formulations is shown in Figure2.

3.5. Stability testing:

Table 3 show the release profile of diclofenac sodium from three different batches constructed, it is clear that there was no significant difference among the release profile for each set of the three batches, indicating that this manufacturing process is reliable and reproducible.The table shows stability of diclofenac sodium in different prepared formulations giving the percentage remaining of the drug in the formulation (F1-F5).

From the table, the stability of diclofenac sodium in these formulations was examined over six months. There was insignificant diclofenac sodium degradation in the prepared five formulations. Apparently, the release of the drug from all formulations didn't change after storage at all temperature utilized for this period of time, suggesting that diclofenac sodium is stable in the HPMC matrices and the controlled release ability of

these matrices is not influenced by the temperature range tested.

4. CONCLUSION

In the present study a satisfactory attempt was made to develop controlled release drug delivery system of diclofenac sodium with improved bioavailability, efficient targeting and dose reduction. From the experiment results it can be concluded that: HPMC polymer is a suitable macromolecule for the preparation of controlled release formulations of diclofenac sodium. The release rate of diclofenac sodium is mainly controlled by the polymer viscosity; decreasing HPMC 4000 in the formulations would increase the release rate of diclofenac sodium. FT-IR studies did not reveal any significant drug interactions between the drug and the polymers used. There was no significant degradation of diclofenac sodium or change in drug release rate in any of the proposed formulations during a six-month period of stability testing. Diclofenac sodium content in different formulations was affected by neither the polymer type nor drug to polymer ratio. Therefore, it is possible to overcome the problem of gastric damage during the use of diclofenac sodium, by avoiding the exposure of the drug to the ulcer-prone area of the GI tract by providing controlled release drug delivery systems.

Table 1
The composition of the prepared formulations

Formulation code	Diclofenac sodium (mg)	HPMC (4000 cps)	HPMC (50 cps)
F1	50	50.00	0.00
F2	50	37.50	12.50
F3	50	25.00	25.00
F4	50	12.50	37.50
F5	50	0.00	50.00

Table 2
Flowability testing of diclofenac sodium and its modified release formulations

Parameter	Pure drug	F1	F2	F3	F4	F5
V_I (ml)	3.4	2.20	1.80	1.40	0.84	0.73
V_T (ml)	1.53	1.90	1.50	1.20	0.63	0.51
P_I(gm.cm^{-3})	0.22±0.46	0.48±0.18	0.54±0.68	0.58±0.51	0.59±0.18	0.58±0.14
P_T(gm.cm^{-3})	0.41±0.81	0.52±0.52	0.639±0.44	0.648±0.23	0.66±0.52	0.712±0.34
P_T / P_I	1.86	1.07	0.85	1.10	0.89	1.12
Carr's index (%)	50.21	16.22	15.07	14.55	13.05	12.90
Angle of repose(ɵ)	55±0.43	25.36±0.22	24.60±0.65	23.20±0.90	21.33±0.23	21.21±0.78

Where,V_I: Initial bulk volume, V_T: Tapped bulk volume, P_I: Initial bulk density, P_T: Tapped bulk density, PT / P_I:Hausner ratio, each formulation containing 50mg of diclofenac sodium. Results show are the ± SD, n=3 for Angle of repose, Bulk density and Tapped density.

Table 3
Diclofenac sodium content in different formulations in phosphate buffer (pH7.4)

Formula	Diclofenac sodium content
F1	100.03±0.87
F2	98.94±0.21
F3	99.84±0.23
F4	99.98±0.54
F5	100.01±0.11

Table 4
Stability of diclofenac sodium in different prepared formulations

Time (months)	% Drug Remaining				
	F1	F2	F3	F4	F5
1	97.12±1.22	99.30±2.23	98..80±1.14	99.59±1.33	99.33±1.34
3	96.70±1.43	98.48±1.58	97.99±0.89	97.79±0.77	98.48±0.65
6	96.08±1.45	96.58±2.11	96.84±1.02	95.64±0.43	96.71±0.46

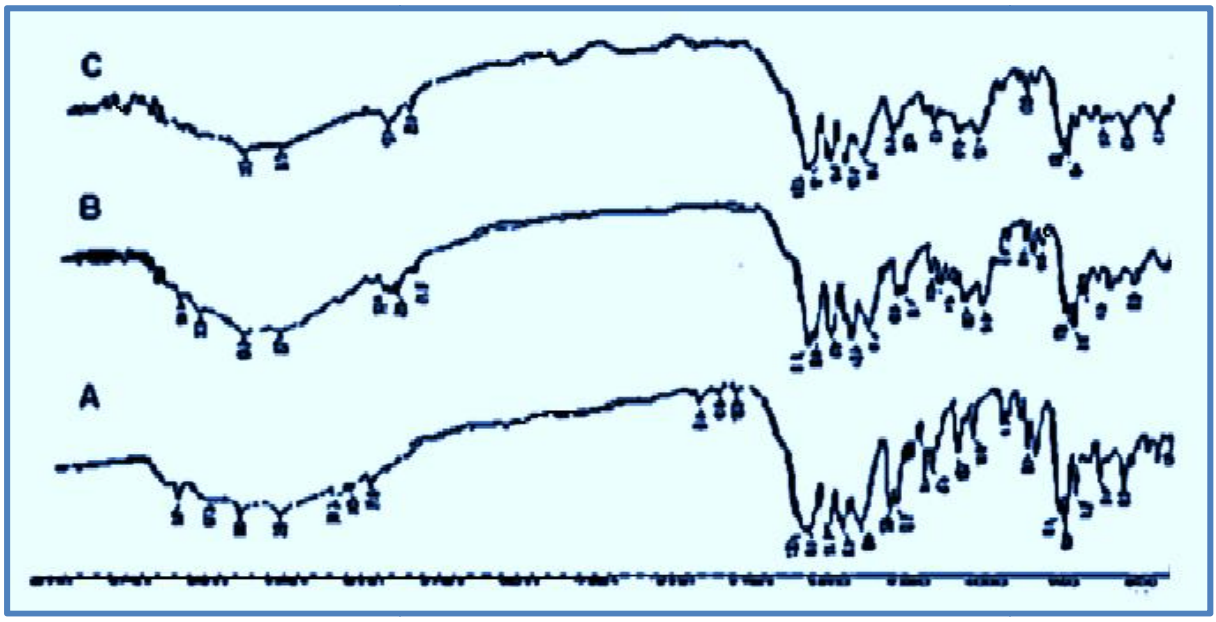

Figure 1
IR spectra of pure drug diclofenac sodium (A), diclofenac sodium with HPMC 4000 (B) and diclofenac sodium with HPMC 50 (C)

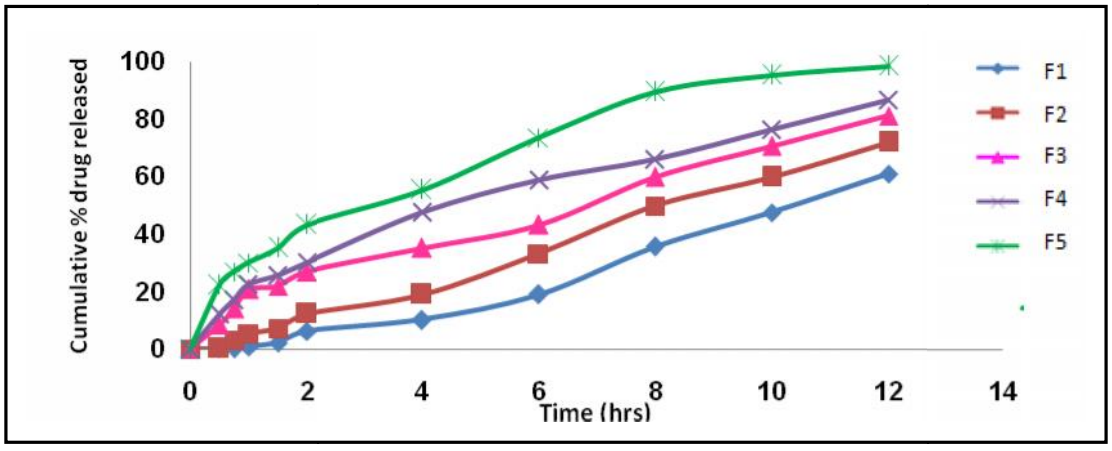

Figure 2

***In vitro* drug release profile of the prepared formulations**

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