IJPSR (2017), Vol. 8, Issue 1 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 14 July, 2016; received in revised form, 12 September, 2016; accepted, 13 September, 2016; published 01 January, 2017

DEVELOPMENT AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF DICLOFENAC SODIUM USING DIFFERENT GRADE HYDROPHILIC POLYMER & PEG 6000 AS RELEASE RETARDANT

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Keywords:

Diclofenac sodium, HPMC, Release retardant, Hydrophilic polymer, PEG 6000

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ABSTRACT: Diclofenac Sodium, being NSAID, its oral administration restricted due to its inherent problems. Hence in the present study, attempt has been made to design oral sustained release once daily matrix tablets of Diclofenac Sodium using combination of hydroxyl propyl methyl cellulose (HPMC) & PEG 6000 and to study the effect of various process and formulation variables like polymer properties and polymer viscosity on in-vitro release of drug. Sustained release tablets of Diclofenac sodium were prepared using different proportion of HPMC 4000 cps and PEG 6000 (F1, F2, F3……..F6). The physical properties of prepared tablets like hardness, friability, weight variation, thickness and drug content were studied and were found to be within the acceptable limits. *In-vitro* release studies were performed in Simulated Gastric Fluid (SGF) pH-1.2 for two hours and Simulated Intestinal Fluid (SIF) pH-6.8 for subsequent 10 hours by USP-I dissolution apparatus, in 900 ml at 37.5±0.5^{o}C (stirring speed was 70 rpm). As amount of HPMC was increased from 5% to 30%, released rate was decreased. However, no appreciable change occurred, when the amount of HPMC was increased to 30% matrix tablets containing 25% HPMC4000 cps and 5% PEG 6000 were found to show good initial release (32% in 2 hours) and extended the release upto 10 hours. The "n" value was found to be 0.89, indicating anomalous (non-fickian) behavior of the drug release.

INTRODUCTION: Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic reducing pain in conditions such as arthritis or acute injury [1]. It can also be used to reduce menstrual pain, dysmenorrhea [1]. The name is derived from its chemical name: 2-(2,6-dichloranilino) phenylacetic acid. Diclofenac is available as a generic drug in a number of formulations [1]. Over the counter (OTC) use is approved in some countries for minor aches and pains and fever associated with common infections [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(1).251-53

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (1).251-53

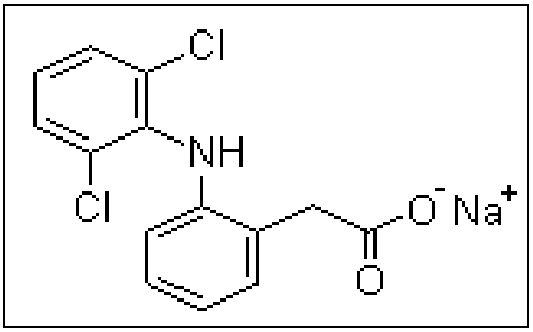

FIG. 1: STRUCTURE OF DICLOFENAC SODIUM

The goal of any drug delivery system is to deliver a therapeutic amount of drug to the proper site in the body and to maintain a desired concentration [2]. The development of oral controlled release dosage forms has attracted much attention in the recent years and hydrophilic matrix tablets are among the most widely used of the numerous controlled releases dosage forms [3].

Hydroxypropylmethylcellulose (HPMC) is hydrophilic cellulose ether widely used as excipients in controlled release preparation, due to their release behavior of the drug [4]. When these formulations meet water there is a rapid hydration of the macromolecules in the solid liquid interface, followed by a formation of a viscous layer [5]. The matrix system produced as a result of this process can pass along the gastrointestinal tract without breaking up, releasing the drug progressively [6].

Hence, in the present investigation, an attempt has been made to fabricate a controlled release dosage form of theophylline using HPMC as matrix material with other commonly used tablet excipient. The *in vitro* release studies were conducted for all the formulations and an attempt has been made to study the drug release kinetics from the formulations.

MATERIALS AND METHODS:

Drug: The standard sample of Salmeterol was obtained as gift sample from Dr. Reddy's Laboratory Pvt. Ltd., Hyderabad, A.P., India. The commercial preparation was obtained from local market.

HPMC POLYMER K100, PEG 6000 Polymer & release modifier, Microcrystalline cellulose NF (Avicel pH 102), Starch-binder, Magnesium stearate, PVP polymer, Talc and Distilled water were procured from local market.

Preparation of SR matrix tablets:

- Sustained release tablets of Diclofenac sodium were prepared by using drug and different polymer concentration such as 5, 10, 15, 20, and 25%w/w of tablet by wet granulation technique.
- HPMC was used as a matrix forming material, while microcrystalline cellulose (Avicel pH102) was used as a diluent.
- Talc and magnesium stearate was used as lubricant. All the ingredients were passed through sieve no 100.
- Required quantities of drug, polymer and diluents were mixed thoroughly and sufficient quantity of granulating agent (Starch and water) was added to get dough mass.
- The mass was sieved through 22/40 mesh and dried at 50° for 2 hour. The dried granules retained on 40 meshes were mixed with 10% fines, 2% talc and 1% magnesium stearate.
- Tablets were compressed using 10 mm flat faced punches on a rotary tablet press at an appropriate compression pressure (hardness 5-6 kg/cm^2).

Evaluation of Granules: The following parameters were used;

- Angle of repose
- Bulk density
- Compressibility index

Evaluation of Diclofenac sodium matrix tablets; Following parameters were used for evaluation.

- Weight variation test
- Hardness test
- Friability test
- Dissolution test

RESULT AND DISCUSSION: The present investigation was undertaken to design, formulate and evaluate Diclofenac sodium matrix tablets for sustained release dosage form. IR studies indicated good compatibility between drug, polymer and excipients.

The granules of different formulations were evaluated for angle of repose, LBD, TBD and compressibility index. The granules indicated good flowability with the angle of repose values 25-30° according to fixed funnel and free standing cone method. The results of compressibility index lies between 10.34±0.03 and 12.36±0.05%, which is below 15% indicating good to excellent flow properties (**Table 1**).

TABLE 1: COMPARATIVE COMPOSITION OF DICLOFENAC SODIUM MATRIX GRANULES

Formulation batch code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility Index (%)
F1	0.461±0.04	0.526±0.03	12.36±0.05
F2	0.473±0.05	0.535±0.04	11.59±0.04
F3	0.479±0.04	0.547±0.02	12.43±0.03
F4	0.510±0.02	0.574±0.04	11.15±0.06
F5	0.487±0.04	0.530±0.04	12.55±0.05
F6	0.520±0.05	0.580±0.05	10.34±0.03

All tablet formulations were subjected to various evaluation parameters and the results obtained were within the range (**Table 2**).

TABLE 2: EVALUATION PARAMETERS

Formulation code	Drug content (%)	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	% Cumulative Diclofenac Sodium released
F1	99.6±0.5	0.20	5.5±0.9	3.2±0.41	91.30
F2	99.8±0.4	0.26	5.3±1.1	3.2±0.47	85.10
F3	99.5±0.9	0.30	5.4±0.8	3.2±0.43	80.10
F4	101.2±0.3	0.39	5.5±0.9	3.2±0.42	75.20
F5	99.8±0.4	0.49	4.2±0.8	3.4±0.45	98.20
F6	99.8±0.4	0.41	5.5±0.8	3.2±0.40	70.90

The weight variation test indicates that all the tablets were uniform with low standard deviation values. The tablets mean thickness and mean diameter values ranged from 3.2±0.40 mm and 3.4±0.45 mm, respectively. The hardness of all the tablets was within the range of 4.2±0.8 to 5.5 ±0.9 kg/cm^2. The loss in friability test was in a range of 0.20 to 0.41%. The percentage drug content for different tablet formulations were varied from 99.5% to 101.2%, were found to be within range.

The incorporation of water soluble carrier to improve the dissolution rate and bioavailability has been reported frequently. Poly ethylene glycol (PEG 6000) at 10% of tablet weight was incorporated into formulation F6, and 100% of drug release was observed in 12 h. This revealed that there was a significant increase in drug release using water soluble carrier.

Dissolution was also carried out by using paddle method, keeping the rotation at 50 rpm. It was observed that the tablets in buffer solution settled down at bottom of the flask and swelled considerably to release the drug from matrix tablet (**Fig.1**).

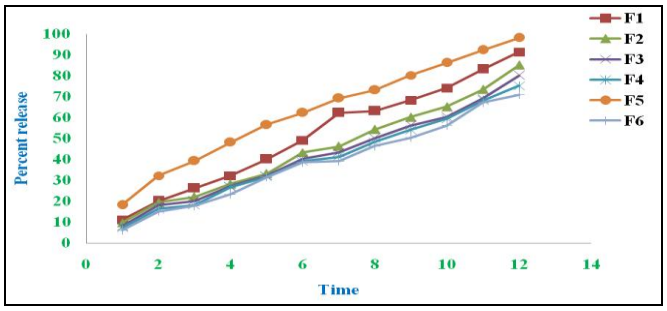

FIG. 1: *IN VITRO* DISSOLUTION PROFILES OF VARIOUS BATCHES OF DICLOFENAC SODIUM MATRIX TABLETS

There was no significant difference observed between basket and paddle method under same experimental conditions ($p>0.05$) using student 't' test method of data analysis. From the above results it can be concluded that, HPMC can be used as an effective matrix material to retard the release of Diclofenac sodium for prolonged period of time. In turn, this could be useful for cost effectiveness and better patient compliance. However, *in vivo* studies are needed to carry out its potential effect by conducting the bioavailability studies.

As per the study it was found that the F5 shows the best results of in-vitro test of friability, hardness, thickness and dissolution characteristics. F5 formulation shows the prolong dissolution up to 24 hrs due to HPMC polymer with PEG 6000 as release retardant.

ACKNOWLEDGMENTS: Author (Rahul Singh) acknowledges Mr. Vijendra Suryavanshi, Asst. Prof. SRIP, Kumhari for his kind and valuable guidance in making this research work a success and all others involved in this research work.

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How to cite this article:
Kalyani G, Singh R and Parihar AKS: Development and *in vitro* evaluation of sustained release matrix tablets of diclofenac sodium using different grade hydrophilic polymer & peg 6000 as release retardant. Int J Pharm Sci Res 2017; 8(1): 251-53.doi: 10.13040/IJPSR.0975-8232.8(1).251-53.