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Development of Diclofenac Sodium Matrix Tablets using Sunflower Stem Residue

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ABSTRACT

Hydrophilic matrix based tablets using different concentration of hydroxypropylmethylcellulose (Methocel K_4M) and treated sunflower stem residues were developed by using wet granulation technique for Diclofenac Sodium (DS) (100mg). Different formulations were prepared and evaluated for the release of DS over a period of 10 hours in phosphate buffer (pH 7.5) using USP type II dissolution apparatus. Along with usual physical properties, tests like friability, weight variation, hardness, drug content, thickness and the dynamic of water uptake and erosion were also studied. The in vitro drug release revealed that the replacement of HPMC by treated sunflower stem residues in tablet dosage form controlled the release of DS for 10 hours. The drug release was comparable with the commercially available Fenbar SR (Diclofenac Sodium 100mg). Tablet friability, weight variation, drug content, thickness and hardness tests were also in conformity with United State Pharmacopeia (USP). Water uptake and erosion study of the tablets indicated that swelling followed by erosion could be the possible mechanism of drug *release. The in vitro release data indicated that DS followed zero-order kinetics. In conclusion, the in vitro release profile and the mathematical models indicate that using HPMC and treated sunflower stem residue in combination can effectively control the release of DS

Keywords: Diclofenac Sodium, Hydroxypropylmethylcellulose, Sunflower stem, Modified, Matrix tablets.

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INTRODUCTION

Sustained release dosage forms are the products that alter the timing and rate of release of drug substance. A sustained-release dosage form is one for which the drug release characteristics of time course and location are chosen to obtain the desired therapeutic or convenience objectives which cannot be achieved with conventional dosage forms such as solutions, ointments, or promptly dissolving dosages forms. Matrix tablets are an important option in the development of oral controlled release formulation[1]. There are number of polymers used to formulate matrix tablets. Water soluble polymers such as polyvinylpyrrolidone (PVP) and polyethylene glycol are used to increase the dissolution rates of poorly soluble drugs. Hydroxypropylmethylcellulose (HPMC) is cellulose ether which is used as the basis for hydrophilic matrices to formulate controlled release oral delivery.[2].Diclofenac Sodium (DS), a non-steroidal anti-inflammatory drug (NSAID), is usually prescribed for management of painful arthritis in order to reduce the inflammation and thereby to reduce pain. The most frequent side effects of DS, on long-term administration, are gastrointestinal disturbances like peptic ulceration and gastrointestinal bleeding.[3].

The short biological half-life of DS (1-2 hours) dictates multiple dosing to maintain therapeutic drug level in the blood, which results in poor patient compliance and increased incidence of adverse effects[4]. To cope with the problem, extensive efforts have been made for the formulation of controlled drug delivery system. Hydroxypropylmethylcellulose (HPMC) is the most commonly used hydrophilic release 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 micro and macrostructure of the release retarding agents exposed to water are strongly time dependent. Upon contact with gastrointestinal fluid, the release-retarding agent (HPMC) swells, gels and finally dissolves slowly[6]. The gel becomes a viscous layer acting as protective barrier to the influx of water and the efflux of drug in solution[7,8]. As the proportion of polymer in a formulation increases, the gel formed is more likely to diminish the diffusion of drug and delay the erosion of the matrix[7,9]. The rate of polymer swelling and dissolution as well as the corresponding drug release are found to increase with either higher level of drug loading or with the use of low viscosity grade polymers [11]. As HPMC is quite expensive, therefore an effort was made to replace HPMC by sunflower stem residue, which is not only cheaper but also widely available in Pakistan.

The objectives of present investigation were to design and evaluate sustained release tablets of

Diclofenac sodium using treated sunflower stem residue as a release retarding polymer to replace HPMC. Hence, an attempt was made to formulate a comparatively cheaper sustained release formulation with increased patient compliance and decreased signs of adverse effects.

MATERIALS AND METHODS:

Diclofenac Sodium (USP Suzhou Ausun, China), HPMC (Methocel K4M, DOW Chemical Company USA), PVP K30 (Jiaozuo Yuanhai, China) and Magnesium Stearate (Fine Chemicals, Taiwan), Lactose monohydrate (Seagal Company) and PVP all were the kind gifts from USAWA Pharmaceuticals, Risalpur, Pakistan. Sunflower stems were purchase from local former of District Mardan, Pakistan. NaOH and Phosphate Buffer (pH 7.5) used were of analytical grade.

Preparation of Sunflower Stem Residue

Sunflower stems were cut into small pieces (about 2 inches) and then crushed into powder form by grinding machine (General Machinery, Peshawar). The crushed materials were then passed through Tests Sieve No.60 (Estecotte Limited, London, England). The leaker ratio was determined by socking it in water[10]. The powder materials were treated with 3% NaOH, 6%NaOH, 3% Urea, 6% Urea, 3% Urea & 6% NaOH (1:1), 6% Urea & 3% NaOH (1:1) separately and were kept in open air for one week. The materials were then washed with distilled water till turned neutral. The neutral materials were placed in open air for drying to obtain treated sunflower stem residues.

Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) for the treated sunflower stem residues were done at Centralized Resource Laboratory, University of Peshawar. The samples were first dried by keeping in oven for about 1 hour. Sample stubs (0.5inch) were used to hold the samples. The samples were mounted in gold-palladium glue, which gave adequate time to dry before imaging. The mounted samples were placed in Bakelite and epoxy followed by polishing for optical examination before SEM analysis.

Preparation of Tablets

Matrix tablets were prepared by wet granulation method. The composition of different formulations is given in Table 1. DS, HPMC (Methocel K4M), Sunflower Stem Residue (Treated with NaOH 3%, NaOH 6%, Urea 3%, Urea 6%, Urea 3% &NaOH 6%(1:1), 6% Urea & 3% NaOH (1:1) separately) and Lactose Monohydrate were mixed in a poly bag and the mixtures were passed through mesh No. 40. The mixtures were turned into wet mass by using the

solution of PVP K30. The wet masses were passed through mesh (No.8) to prepare the granules. The granules so formed were placed in oven at 55 ^{0}C for about 4 hours. The dry granules were then sized by mesh (No. 16) and mixed with Talc and Magnesium Stearate. Tablets (200mg) were then prepared on a compression machine (ZP-19, Germany) with 8 mm oval shaped punches.

Table 1.Different formulations/ compositions of DS tablets*

Name of Component	**Quantity (grams) per 100 tablets****					
	Standard	**B-1**	**B-2**	**B-3**	**B-4**	**B-5**
Diclofenac Sodium	10	10	10	10	10	10
HPMC (Methocel K4M)	5.5	4.4	3.3	2.2	1.1	00
Sunflower Stem Residue (Treated with 6% NaOH)	00	1.1	2.2	3.3	4.4	5.5
Lactose Monohydrate	3.2	3.2	3.2	3.2	3.2	3.2
Talc	0.4	0.4	0.4	0.4	0.4	0.4
PVP K30	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	0.4	0.4	0.4	0.4	0.4	0.4
Total	**20**	**20**	**20**	**20**	**20**	**20**

HPMC indicates Hydroxypropylmethylcellulose. PVP, Polyvinylpyrrolidone

**Batches, B-1,20% Sunflower stem residue; B-2,40% Sunflower stem residue; B-3,60% Sunflower stem residue; B-4,80% Sunflower stem residue; B-5,100% Sunflower stem residue;

Evaluation of Tablets

The prepared tablets were tested as per standard procedures (USP) for weight variation (n=20), hardness (n=6), drug content, thickness, and friability, swelling characteristics. Weight variation was conducted by using Analytical Balance (Ax 200, Shimadzu Kyoto, Japan). Hardness and thickness of tablets were determined by using Digital Pharma Tester (Germany). Friability test were conducted using Roshefriabilator (Switzerland). Drug content of DS were analyzed by measuring the absorbance of standard and sample at λ=276nm using UV/Visible spectrophotometer (Ce Cell, England).

Swelling behavior of formulations.

The swelling behavior of standard formulation (Fenbar SR) and B-1to B-5 (modified formulations) were studied. One tablet from each formulation was kept in a Petri dish containing phosphate buffer (pH 7.5). After 2 h, the tablet was kept on tissue paper and weighed. The weighing was continued for every 2 h, till the end of 10 h. The % weight gain by the tablet was calculated by formula.

$$S.I = \{(Mt-M0) / M0\} X 100$$

Where, S.I = swelling index, Mt = weight of tablet at the time (t) and Mo = weight of tablet at time 0.

Characteristics of In-Vitro Drug Release

Drug release from matrix tablets(Fenbar SR and modified formulations) were assessed by dissolution test under the following conditions: n=6, USP type II dissolution apparatus at 50rpm in 900mL of Phosphate buffer at pH7.5 maintained at 37^{o}C ± 0.5^{o}C. Sample (10 ml) was withdrawn at regular interval and replaced with the same volume of pre-warmed fresh dissolution medium (37^{o}C ± 0.5^{o}C). The sample withdrawn was filtered through Whattman filter paper (No.1). The sample was then diluted to 100mL with phosphate buffer solution (pH7.5). Drug content in each sample was analyzed at λ=276nm using UV/Visible spectrophotometer (Ce cell England)

RESULTS AND DISCUSSION

A sustained-release dosage form is one for which the drug release characteristics of time course and location are chosen to obtain the desire therapeutic or convenience objectives which cannot be achieved by conventional dosage forms [11].

The results obtained from different parameters are

Scanning Electron Microscopy (SEM):

Scanning electron microscopy of both treated and untreated sunflower stem residue [Figure1 (a-c)] revealed that they possess a rough and rugged surface. The pores were created in the size range 2-7 µm after treatment with different concentrations of NaOH and Urea.

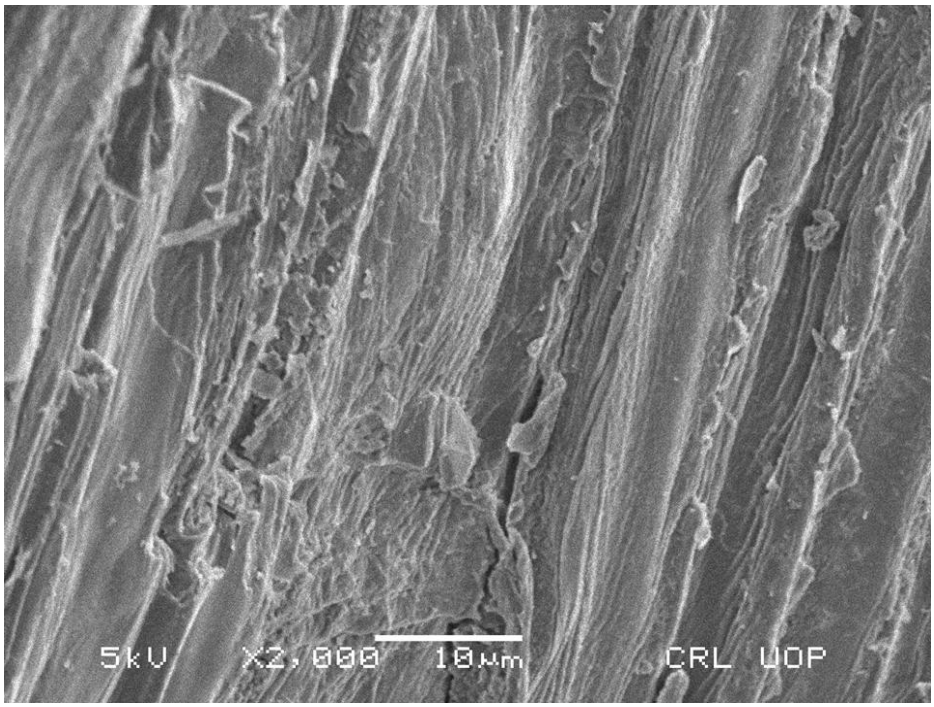

Figure.1 (a) Blank sunflower stem at 2000 micron

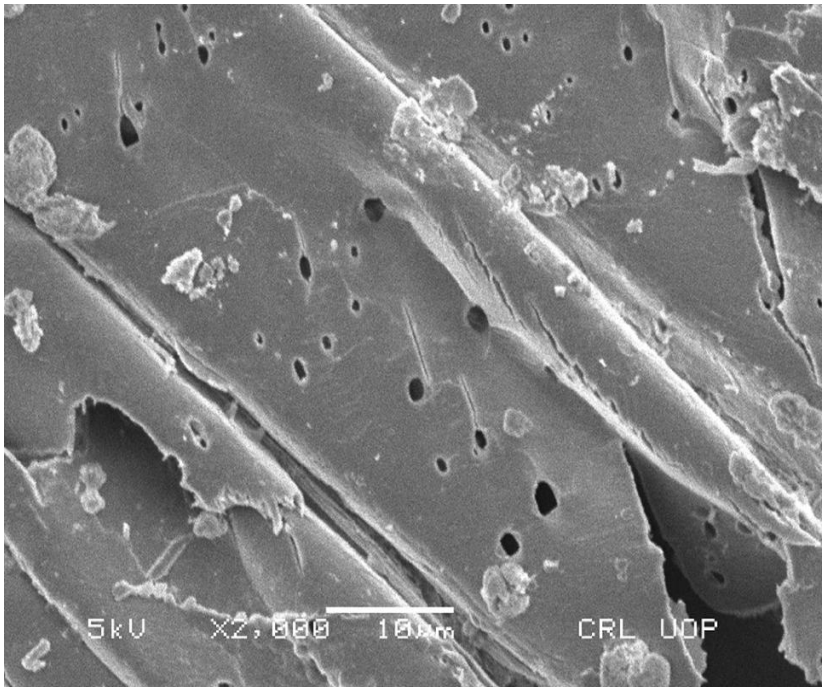

Figure. 1 (b) Treated with NaOH 6% sunflower stem at 2000 micron

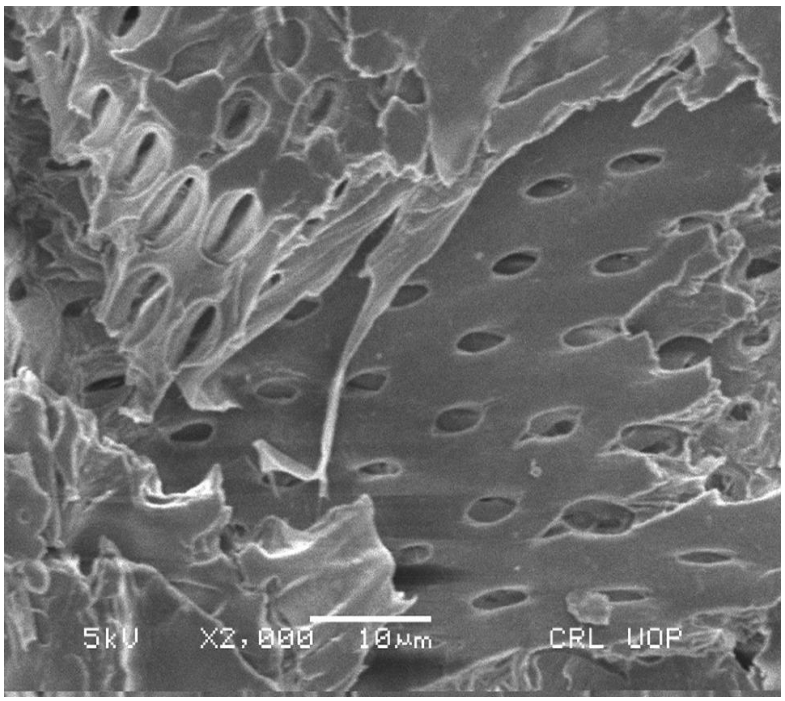

Figure. 1 (c) Treated with NaOH 6% and 6% Urea sunflower stem at 2000 micron

PHYSICAL PROPERTIES:

Weight variation:

Weight variation tests were conducted for both Standard and modified formulations (Table.2). All these results showed that all the five batches containing different concentration of HPMC & treated sunflower stem residue were in conformity of the USP criteria for weight variation.

Table 2: Physical properties different formulations/ compositions of DS tablets*

Analysis	Results						
	Standard	**B-1**	**B-2**	**B-3**	**B-4**	**B-5**	***p-Value***
Weight (mg) ± SD	200 ±3.231	197±2.341	205±3.451	201±4.345	199±4.678	203±4.451	0.526
Hardness in Kg ± SD	9.3±0.707	8.1±0.893	8.6±0.761	9.3±0.673	9.5±0.672	8.0±0.871	0.506
Drug Content % ± SD	99.3±0.353	98.2±0.278	99.6±0.345	98.3±0.276	99.1±0.734	99.5±0.456	0.940
Thickness in mm ± SD	6.3±0.141	5.9±0.234	6.3±0.435	6.3 ±0.125	6.3±0.432	6.3 ±0.157	0.509
Friability % ± SD	0.14±7.095	0.16±5.321	0.15±3.456	0.14±3.239	0.15±2.783	0.13±6.765	0.707

***Hardness test**:*

Hardness test was conducted by using Digital Pharma Tester. The hardness ranged from 12 – 17 Kg.(Table.2). The hardness of all batches were not only similar to the standard tablets but also obey the USP Criteria.

Content uniformity:

Different batches under observation fulfilled the USP content uniformity criteria. The percent content uniformity for all batches was from 98.3-99.5%, which was under the USP limits. This content uniformity was also comparable with standard marketed drug i.e 99.3%.(Table.2)

Friability:

According to USP friability limit for all tablets is less than 1%. All the batches containing different concentrations of HPMC and Sunflower stem residue were under USP limit i.e. 0.17-0.36 %. These limits were also similar to the friability of Standard Tablets (FENBAR SR) i.e.0.14%.(Table.2)

Similarly the thickness of all tablets under observation was similar and according to the specifications.

Swelling Determination of Tablets:

From the swelling studies of the optimized batches performed at an interval of 10, 20, 40 and 60 minutes respectively it was found that HPMC K4M and treated sunflower stem residue were also similar.(Table.3) & (Figure.2)

Table 3: Percent swelling of different formulations/ compositions of DS tablets

Batch	Percent Swelling			
	After 10 Minutes	**After 20 Minutes**	**After 40 Minutes**	**After 60 Minutes**
Standard	10.4	21.6	45.9	80.4
B-1	10.9	22.4	45.9	78.9
B-2	11.8	23.7	47.3	83.1
B-3	11.2	21.5	47.9	81.5
B-4	10.4	23.00	43.5	82.4
B-5	10.6	22.1	44.9	80.7

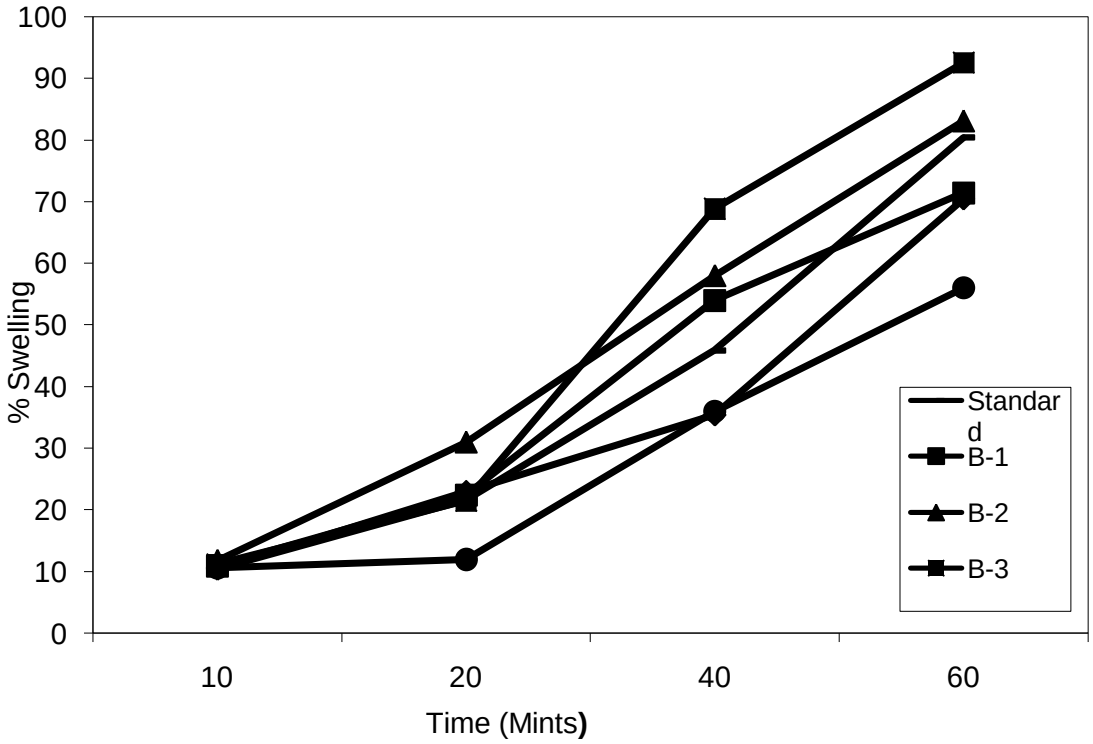

Figure.2. Swelling of different formulations/ compositions of DS tablets

In Vitro Release Studies

The cumulative percentage drug release data obtained were fitted to zero order, first order, Higuchi's and Korsmeyer-Peppas equation to understand the mechanism of drug release from the matrix tablet. The slopes and the regression co-efficient of determinations r^2 were listed in Table 5.[10,13]. The drug release kinetics of all formulations having 20% , 40% and 60% modified sunflower stem residue instead of HPMC, predominantly follows Higuchi pattern of drug release followed by first order, Korsmeyer-Peppas and then zero order. According to Peppas model, the 'n'value for B-1, B-2 and B-3 was found to be 0.8556, 0.7882 and 0.9755 respectively, which are more than 0.5, indicates that the release approximates non-Fickian diffusion mechanism.

The drug release profiles of all these three formulations were compared with the release profiles of standard marketed product Fenbar SR (Fig.1). The drug release profiles of B-1, B-2 and B-3 were closely approximates the release profiles of the standard Fenbar-SR-100. The drug release from the Fenbar- SR-100 tablets at the end of 10th hour is 98.43%, which is comparable to B-1, B-2 and B-3 resulting 96.38%, 97.07% and 99.26 for B-1, B-2 and B-3 respectively of the drug release at the same hour.

The drug release pattern was different in these five formulations. In B-1, B-2, & B-3 where HPMC was replaced by the sunflower stem residue with 20%, 40% and 60% respectively all

these formulation were in conformity with USP dissolution test but the remaining two formulations i.e. B-4 & B-5 where sunflower stem residue replaced HPMC by 80% & 100% respectively, didn't obey the USP dissolution test. (Table 4 &Figure 3).

Table 4: Percent Release of different formulations/ compositions of DS tablets

Time (hrs)	Percent release *					
	Standard/Reference	B-1	B-2	B-3	B-4	B-5
0	00	00	00	00	00	00
1	18.63	14.67	16.56	19.66	28.66	36.53
2	29.23	27.31	29.41	31.09	39.99	56.67
4	47.24	42.49	46.02	51.26	61.53	100
6	65.55	63.21	66.43	67.69	75.88	---
10	98.44	96.39	97.06	99.23	100	----

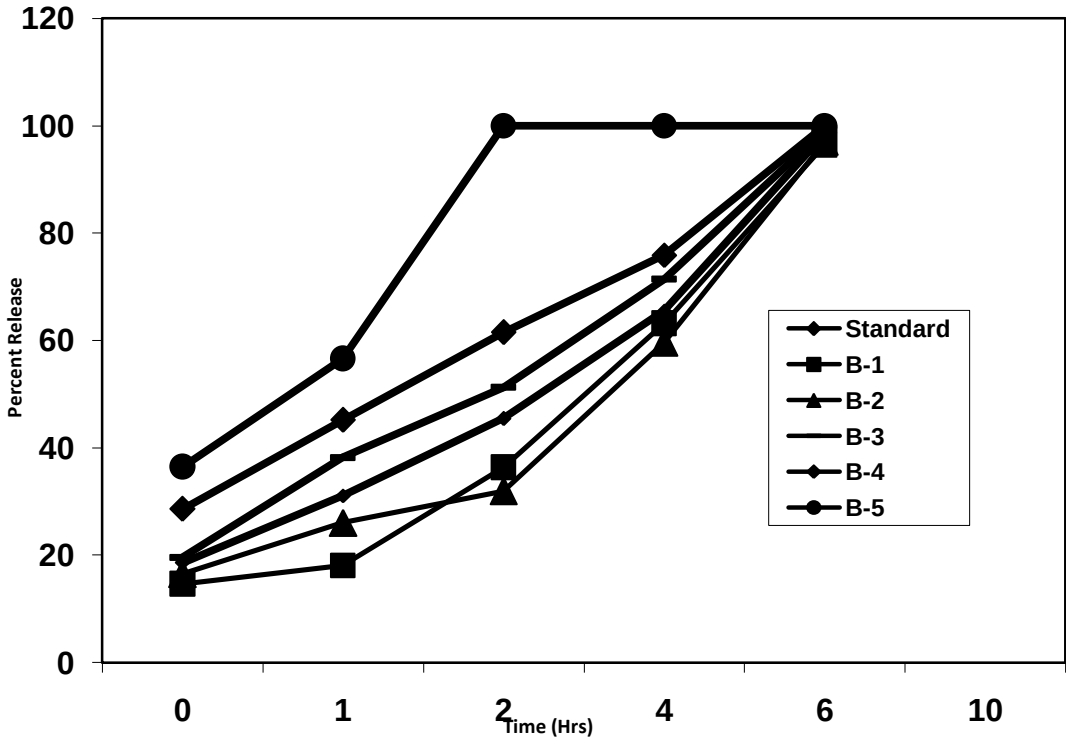

Figure.3 Release of different formulations/ compositions of DS tablets

The replacement of HPMC in specific ratio by treated Sunflower stems residue in matrix tablets of Diclofenac Sodium SR showed that drug releases from these tablets is comparable with to standard tablets.

Scanning electron microscopy of both treated and untreated sunflower stem residue [Figure1 (a-c)] revealed that they possess a rough and rugged surface. The SEM study shows that creation of pores is responsible for the release of drug.

When sunflower stem residues treated with different chemical i.e. NaOH 3%, NaOH 6%, Urea 3%, Urea 6%, Urea 3% &NaOH 6%(1:1), 6% Urea & 3% NaOH (1:1) separately and each time

the HPMC was replaced by these materials individually in the preparation of tablets. The physical properties as well as the release pattern of all these tablets were studied and compared to USP standard. From these results it was observed that the tablets prepared from sunflower stem residues treated with NaOH 6% gave the best result according to the standard and selected for further study.

HPMC was replaced by NaOH 6% treated sunflower stem residues with different concentrations and tablets were prepared. These tablets were investigated for different studies like physical tests, swelling behavior, dissolution (In-vitro release).

Physical properties, tests like friability, weight variation, hardness, drug content, thickness and the dynamic of water uptake and erosion studies are comparable with the standard.

The resemblance in the swelling behavior of both standard and modified formulations is expected due to similar cross linking in polymer, which accounts for comparatively same penetration of water inside the polymer matrix and thus results in similar swelling behavior in all five batches

Dissolution testing study was performed to predict bioavailability, to ensure uniformity and to measure any change in an existing formulation[12,13,16]. For comparison of two dissolution profiles similarity factor study was performed[17]. Similarity factor analysis between the new formulations and marketed tablets Fenbar SR (USAWA pharmaceuticals) tablets for the release of DS clearly showed that the release of DS from the prepared tablets i.e. B-1, B-2 & B-3 were similar to that of commercially available tablets. So, it is clear from this study that HPMC can be replaced up to 60% by treated sunflower stem residue in Diclofenac sodium matrix tablets to obtain the comparable controlled release tablets.

Table 5. Release parameters of DS sustained release tablets

Formulation	Zero Order		First order		Higuchi		Korsmeyer-Peppas		
	r^2	K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	k_H ($h^{-1/}$)^2	r^2	*n value*	K_{KP} (h^{-n})
Standard	0.9672	4.0042	0.9933	0.1414	0.9994	17.569	0.9942	0.8556	0.4265
B-1	0.9562	4.1672	0.9928	0.1421	0.9995	16.982	0.9932	0.7982	0.4313
B-2	0.9682	4.2310	0.9918	0.1417	0.9991	17.822	0.9931	0.8755	0.4231
B-3	0.9462	4.2381	0.9921	0.1458	0.9992	16.993	0.9931	0.8735	0.4314
B-4	1.4534	6.4525	0.5431	0.1349	0.7539	19.461	0.5629	0.4329	0.2912
B-5	1.4536	6.4210	0.5612	0.1239	0.7653	19.643	0.5894	0.3871	0.2811

CONCLUSION:

The present investigational study tries to design and evaluate sustained release tablets of Diclofenac sodium using treated sunflower stem residue as a release retarding polymer to replace HPMC. The results of the present study clearly indicates that the replacement of treated

sunflower stem residue with HPMC up to 60% in DS controlled released tablets gives the comparable results with commercially available Fenbar SR tablets. So sustained releases tablets were formulated which may have the potential to increase patient compliance and decreased signs of adverse effects.

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