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Preparation and Evaluation of Sustained Release Matrix Tablet of Diclofenac Sodium using Natural Polymer

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Abstract:

Sustained release tablets of Diclofenac Sodium were fabricated using Cashew nut tree gum, HPMC and Carbopol . The tablets were evaluated for preformulation studies like angle of repose, bluk density, compressibility index and physical characteristics like hardness, weight variation, fraibilty and drug content. *In-vitro* release of drug was performed in PBS pH 7.2 for twelve hours. All the physical characters of the fabricated tablet were within acceptablelimits. The tablet with HPMC(Batch B-I) and Carbopol(Batch C-I) exhibited greater drug content than those with cashew nut tree gum and other batches of HPMC and carbopol. A better sustained drug release (50.65%) was obtained with the matrix tablet (Batch C-III) made-up of the carbopol than with the cashew nut tree gum and HPMC. It is cleared through the dissolution profile of Diclofenac sodium from matrix tablets prepared using different polymers were indicated an increase in the polymer ratio retarded the drug release to a greater extent.

Key words: *Diclofenac sodium, Cashew nut tree gum, HPMC, Carbopol, Sustained release matrix tablets.*

Introduction:

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Regular research is going on infield of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration. The advantages of natural plant based excipients include low cost, natural origin, free from side effects, biocompatible, bioacceptable, renewable source; environmental friendly processing, local availability, better patient tolerance as well as public acceptance. They improve the national economy by providing inexpensive formulations to people, using locally available materials.

Cashew nut tree gum is a polysaccharide comprising galactose, arabinose, rhamnose, glucose, glucurine acid and other sugar residues. It has been used as matrix former for controlled release tablet. Primarily cashew gum is used in industrial application for binding books, as adhesives for envelopes, label, stamps and posters. HPMC is used as matrix former represents nondigestible material which forms gel in situ. The release of drug from these systems is controlled by penetration of water through a gel layer produced by hydration of polymer and diffusion of drug through the swollen, hydrated matrix, in addition to the erosion of gelled layer. The extent to which the erosion or diffusion controls the release depends on polymer selection as well as on the drug-polymer ratio used in the formulation. High drug polymer ratios result in formulations from which drug release is controlled by attrition.

Diclofenac Sodium [2-[(2, 6-dichlorophenyl) amino] benzene acetic acid monosodium salt] is a drug which is sparingly soluble in water and freely soluble in organic solvent like methanol. By using it is classified pharmacologically NSAID and therapeutically Antiarthritic and Anti-inflammatory. Anti-inflammatory and antipyretic action is through an unknown mechanism that may involve inhibition of prostaglandin synthesis. Pharmacokinetic profile of Diclofenac sodium is after oral administration, diclofenac is rapidly and almost completely absorbed. Absorption is delayed by food. It is highly protein bound. Diclofenac undergoes first-pass metabolism, with 60% of unchanged drug reaching systemic circulation. About 40% to 60% is excreted in the urine; the balance is excreted in the bile. Diclofenac sodium is used as analgesic, antipyretic, anti-inflammatory and approved in the United States for the long-term symptomatic treatment of rheumatoid

arthritis, osteoarthritis and ankylosing spondylitis. Oral form of diclofenac sodium is contraindicated in the patients having hypersensitivity, hepaticporphyria, history of asthma, utricaria, late pregnancy, breast feeding and cautious in case of peptic ulcer. Diclofenac sodium have many side effects like anxiety, depression, dizziness, insomnia, hypertension, edema, taste disorder, transient stinging, abdominal pain or cramps, bleeding, colitis, acute renal failure, nephritic syndrome, heart failure. The present invastigation is aimed to formulate the matrix tablet of diclofenac sodium with cashew nut tree gum, HPMC and carbopol.

Materials and Methods:

*Materials:*Diclofenac sodium was purchased from all fine chemicals, Chennai. Cashew nut tree gum was collected from various parts of Andhra Pradesh. HPMC (Methocel-k-100 CR) was purchased from DOW, USA. Carbopol (934) was purchased from Loba chemie pvt. Ltd. Microcrystalline cellulose was purchased from Signet chemicals, Mumbai. Magnesium stearate, Talc and Potassium hydrogen phthalate were purchased from S.D Fine chemicals Ltd, Mumbai. Sodium hydroxide pellets were purchased from Merck chemicals, Mumbai. Other materials used were of analytical grade, and procured from commercial sources.

Preformulation studies

Development of calibration curve for Diclofenac Sodium: A stock solution of diclofenac sodium was prepared by dissolving 100mg of drug in 100ml of phosphate buffer of pH 6.8 (1 mg/ml) . From this stock solution, 0,5,10,15,20 µg/ml dilutions were prepared . The λ_{max} of the drug was determined by scanning one of the dilutions between 400 to 200 nm using a UV- visible spectrophotometer.

Compatibility Studies

A physical mixture (1:1) of drug and polymers was prepared and mixed with suitable quantity of IR grade potassium bromide and prepared transparent pellets. They were scanned from 4000 to 400 cm^{-1} in a Perkin Elmer FTIR spectrophotometer.

Preparation of sustained release matrix tablets

Tablet formulation was prepared by wet granulation technique. All the powders were passed through BSS-80 mesh. Required quantities of Diclofenac sodium and other polymers (Cashew nut tree gum, HPMC and Carbopol) were mixed separately and thoroughly and a sufficient volume of granulating agent (water) was added slowly. After enough cohesiveness was obtained, the mass was sieved through NO: 10 mesh. The granules were dried at 40°c for 30 mins and then were passed through 16/22 mesh. Talc and magnesium stearate were finally added as glidant and lubricant for each batch of granules. The tablets were compressed (8 mm diameter, standard concave punches) using a Rotary tablet compression machine (10 station, Rimek, Ahmedabad, India).

Batch details for the formulations of Diclofenac sodium sustained release matrix tablets

Table 1: Diclofenac sodium SR matrix tablets with Cashew nut tree gum

S. No	Name of the Ingredient	Category	Batch code		
			A-I	A-II	A-III
1	Diclofenac sodium (in mg)	NASID	100.00	100.00	100.00
2	Cashew nut tree gum (in mg)	Polymer	40.00	60.00	80.00
3	Microcrystalline cellulose (in mg)	Diluent	54.00	34.00	14.00
4	Distilled water (in ml)	Granulating agent	q. s	q. s	q. s
5	Magnesium stearate (in mg)	Lubricant	4.0	4.0	4.0
6	Talc (in mg)	Glidant	2.0	2.0	2.0

Table 2: Diclofenac sodium SR matrix tablets with HPMC

S. No	Name of the Ingredient	Category	Batch code		
			B-I	B-II	B-III
1	Diclofenac sodium (in mg)	NASID	100.00	100.00	100.00
2	HPMC (in mg)	Polymer	40.00	60.00	80.00
3	Microcrystalline cellulose (in mg)	Diluent	54.00	34.00	14.00
4	Distilled water (in ml)	Granulating agent	q. s	q. s	q. s
5	Magnesium stearate (in mg)	Lubricant	4.0	4.0	4.0
6	Talc (in mg)	Glidant	2.0	2.0	2.0

Table 3: Diclofenac sodium SR matrix tablets with Carbopol

S. No	Name of the Ingredient	Category	Batch code		
			C-I	C-II	C-III
1	Diclofenac sodium (in mg)	NASID	100.00	100.00	100.00
2	Carbopol (in mg)	Polymer	40.00	60.00	80.00
3	Microcrystalline cellulose (in mg)	Diluent	54.00	34.00	14.00
4	Distilled water (in ml)	Granulating agent	q. s	q. s	q. s
5	Magnesium stearate (in mg)	Lubricant	4.0	4.0	4.0
6	Talc (in mg)	Glidant	2.0	2.0	2.0

Evaluation of Diclofenac sodium SR matrix tablets:

Evaluation of granules

Angle of repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Where h and r are the height and radius of the powder cone.

Bulk Density

Both loose bulk density and tapped bulk density were determined and calculated by using the following formulas.

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [TBD-LBD] X 100 / TBD

Evaluation of tablets:

Average weight

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Sartorius India, limited), and the test was carried according to the Indian Pharmacopoeia.

Drug Content

Five tablets were weighed individually, and the drug was extracted in pH 6.8 phosphate buffer. The drug content was determined according to the IP.

Hardness and Friability

The hardness and friability were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the

friability testing apparatus (Indian equipments, Mumbai, India), respectively.

In Vitro release studies

The ***in vitro*** dissolution studies of the developed formulation (SR) were carried out using USP apparatus type II (Electro lab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900 ml of phosphate buffer pH 7.2 from 0 to 12 hours for the developed sustained release formulation maintained at $37^{o}c \pm 0.5^{o}c$. The drug release at different time intervals was measured by UV-visible spectrophotometer (Shimadzu) at specific $\lambda_{max.}$

Results and Discussion:

Pre formulation studies

Development of calibration curve for Diclofenac sodium

The scanning of the drug solution in the UV range showed maximum absorbance at 275.4 nm and hence , the calibration curve was developed at this wavelength.The values are given in Table 4.

Table 4: Calibration curve readings for Diclofenac sodium

Concentration (µg/ml)	Absorbance at 275.5 nm
5	0.164
10	0.318
15	0.446
20	0.617

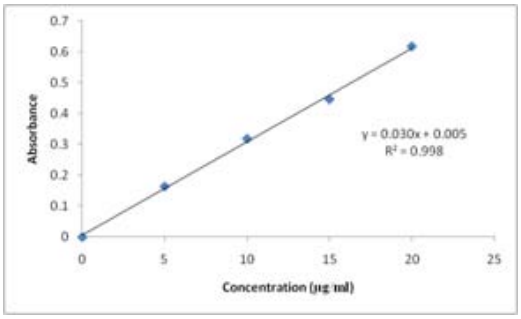

Figure 1: Calibration curve of Diclofenac sodium

Compatibility Studies

The compatibility between the drug and the selected polymers was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the polymer-drug mixture, which confirmed the absence of any chemical interaction between the drug and the polymers.

Effect of polymer concentration:

Granular characteristics

The results of evaluation of granules are shown in Table no: 4. Angle of repose, bulk density and compressibility index was found for batches A-I, A-II and A-III respectively, which indicates good flow properties. The granules evaluation indicates good physicochemical properties. This results also applicable to batches of HPMC (B-I, B-II and B-III) and Carbopol (C-I, C-II and C-III) respectively and results are shown in Table no: 5 & 6.

Tablet characteristics

The results of the physicochemical evaluation of tablets are given in Table no : 7, 8 & 9 for all batches of tablets. The average weight of tablets was found to be within 197.3 – 202.0 mg. Drug content was found to be between 95.7 – 101.7 %. The hardness of tablets was found to be from 5-6 (kg/cm^2). Friability was found to be less than 1%.

In vitro drug release profile

The ***in vitro*** drug release profile of the batches with different polymer level is given in table no: 10, 11 & 12 and figure no: 1, 2 & 3. The rate of ***in vitro*** drug release was found to be decrease as the polymers level was increased. The batches formulated with 40% of the polymer exhibited slower release when compared to other batches. Therefore, 40% of polymer level was found to be ideal concentration for the formulation of sustained release matrix tablets.

Table 5: Formulation batches with cashew nut tree gum

S. No	Parameter	Batch Code		
		A-I	A-II	A-III
1	Angle of repose (^{o})	22.5	26.4	20.4
2	Loose bulk density (g/cm^3)	0.5142	0.538	0.583
3	Tapped bulk density(g/cm^3)	0.6	0.636	0.7
4	Compressibility index (%)	14.3	15.408	16.714

Table 6: Formulation batches with HPMC

S. No	Parameter	Batch Code		
		B-I	B-II	B-III
1	Angle of repose (^{o})	23.2	24.6	25.36
2	Loose bulk density (g/cm^3)	0.538	0.546	0.522
3	Tapped bulk density(g/cm^3)	0.648	0.639	0.636
4	Compressibility index (%)	16.975	14.55	17.924

Table 7: Formulation batches with Carbopol

S. No	Parameter	Batch Code		
		C-I	C-II	C-III
1	Angle of repose (^{o})	23.5	24.1	25.16
2	Loose bulk density (g/cm^3)	0.528	0.534	0.543
3	Tapped bulk density(g/cm^3)	0.640	0.632	0.672
4	Compressibility index (%)	17.5	15.506	19.196

Table 8: Formulation batches with cashew nut tree gum

S. No	Parameter	Batch Code		
		A-I	A-II	A-III
1	Average weight	199.8mg	197.3mg	200.5mg
2	Drug content (%)	95.7	97.43	99.78
3	Hardness (kg/cm^2)	5	5	5
4	Friability (%)	0.47	0.29	0.36

Table 9: Formulation batches with HPMC

S. No	Parameter	Batch Code		
		B-I	B-II	B-III
1	Average weight	199.48mg	200.5mg	201.4mg
2	Drug content (%)	101.7	99.43	98.78
3	Hardness (kg/cm^2)	5.5	5	5.5
4	Friability (%)	0.35	0.43	0.57

Table 10: Formulation batches with Carbopol

S. No	Parameter	Batch Code		
		C-I	C-II	C-III
1	Average weight	198.42mg	200.1mg	202.0mg
2	Drug content (%)	101.7	99.3	99.78
3	Hardness (kg/cm^2)	6	5	5
4	Friability (%)	0.32	0.38	0.65

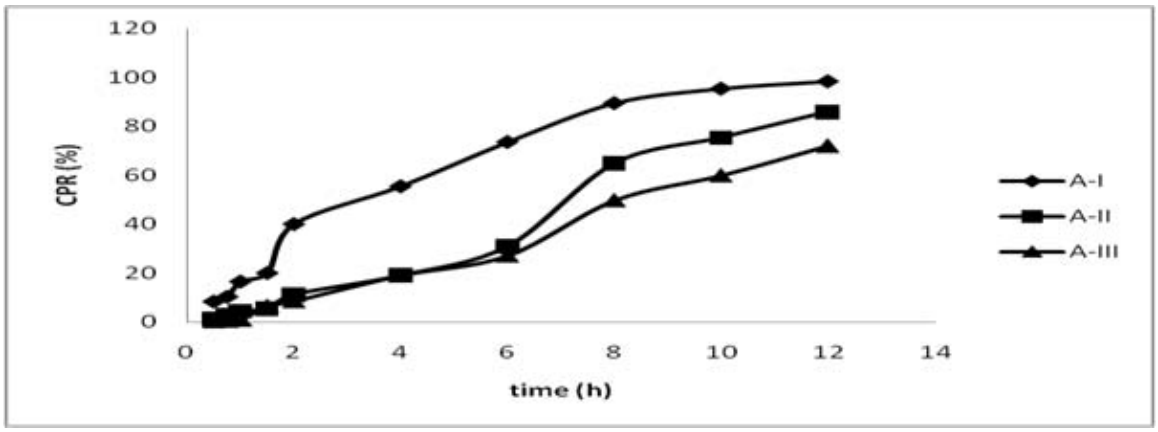

Figure 2: Effect of cashew nut tree gum concentrations: A-I(20%), A-II(30%)&A-III(40%)

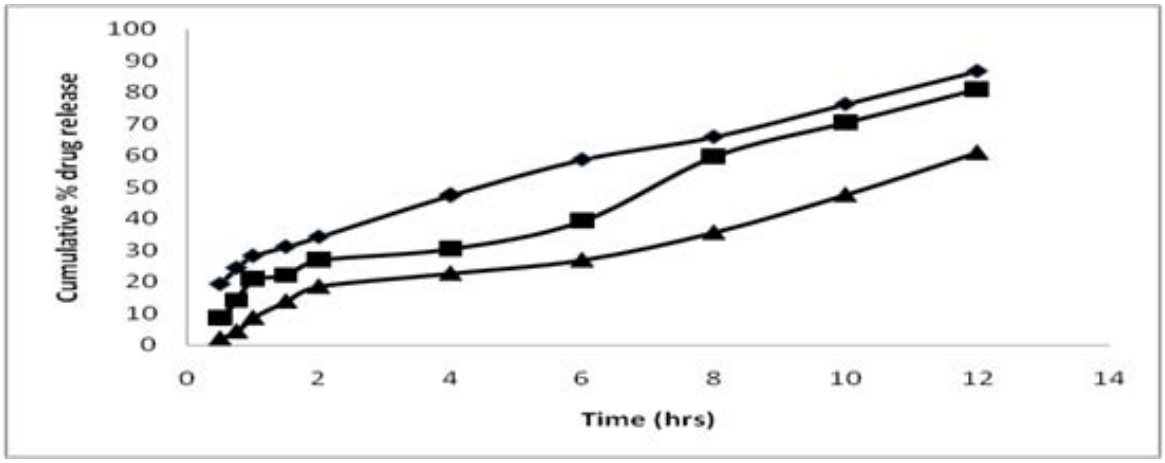

Figure 3: Effect of HPMC concentrations: B-I (20%), B-II (30%) &B-III (40%)

Table 11: In vitro drug release behavior of formulation batches with cashew nut tree gum

Time (hrs)	Cumulative % drug release		
	A-I	A-II	A-III
0.5	8.305	1.261	0.235
0.75	10.272	2.775	0.477
1.0	16.48	4.528	0.901
1.5	19.957	5.582	6.447
2.0	39.963	11.339	8.489
4.0	55.428	19.135	18.968
6.0	73.541	31.106	27.105
8.0	89.421	64.895	49.702
10.0	95.347	75.372	59.889
12.0	98.324	85.92	72.048

Table 12: In vitro drug release behavior of formulation batches with HPMC

Time (hrs)	Cumulative % drug release		
	B-I	B-II	B-III
0.5	19.263	8.472	2.114
0.75	24.401	14.171	4.357
1.0	28.224	20.884	8.689
1.5	31.112	22.047	13.869
2.0	34.254	26.932	18.590
4.0	47.429	30.548	22.716
6.0	58.749	39.399	26.954
8.0	65.944	59.805	35.697
10.0	76.327	70.613	47.625
12.0	86.767	81.173	61.011

Table 13: In vitro drug release behavior of formulation batches with carbopol

Time (hrs)	Cumulative % drug release		
	C-I	C-II	C-III
0.5	2.020	0.929	0.054
0.75	5.497	2.020	0.175
1.0	8.625	5.407	0.720
1.5	23.261	11.749	2.475
2.0	31.004	19.972	8.347
4.0	39.267	30.221	17.222
6.0	52.074	39.261	27.103
8.0	60.140	45.152	35.886
10.0	64.939	53.193	41.47
12.0	72.170	60.026	50.654

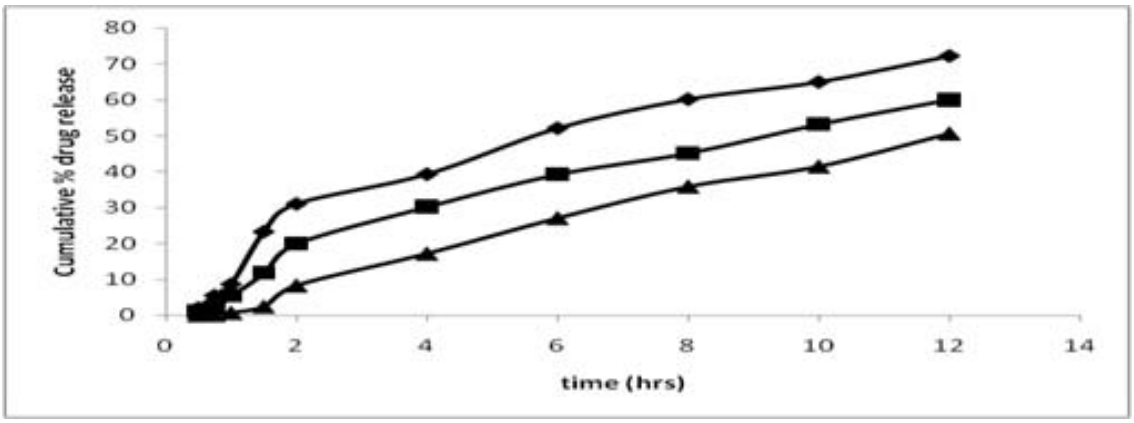

Figure 4: Effect of Carbopol concentrations: C-I (20%), C-II (30%) &C-III (40%)

Discussion:

There must be sufficient polymer content in a matrix system to form a uniform barrier. The barrier protects the drug from immediately releasing into the dissolution medium. If the polymer level is too low, a complete gel layer may not form,. In most studies, increased polymer level in the formulation results in decreased drug-release rates. Because hydrophilic matrix tablets containing hydrophilic polymers absorb water and swell, the polymer level in the outermost hydrated layers decreases with time. The outermost layer of the matrix eventually becomes diluted to the point where individual chains detach from the matrix and diffuse into the bulk solution. The polymer chains break away from the matrix when the surface concentration passes a critical polymer concentration of macromolecular disentanglement or surface erosion. The polymer concentration at the matrix surface is defined as the polymer disentanglement concentration. It was observed that higher polymer levels result in slower release rates as evident from the *in vitro* drug release profile of batches A-III, B-III & C-III. Therefore, 40% polymer level was found to be ideal for the matrix system.

Conclusion:

This study deals with the investigations carried out with the objective of developing oral sustained release formulations through matrix tablets for the widely used nonsteroidal anti-inflammatory drug Diclofenac sodium using natural polymer cashew nut tree gum and polymers Hydroxy propyl methyl cellulose, Carbopol and evaluation of their sustained release potential. Based on above results and discussion, it is concluded that the formulated matrix tablets of Diclofenac sodium using natural polymer Cashew nut tree gum, HPMC and Carbopol were capable of exhibiting sustained release properties They are thus capable of reducing the dose intake, minimize the blood level oscillations, dose-related adverse effects and cost thus ultimately improve the patient compliance in the therapeutic management of pain and inflammation.

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