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Research Article

FORMULATION OF CONTROLLED RELEASE MATRIX TABLET OF DICLOFENAC SODIUM USING CROSS LINKED STARCH UREA

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ABSTRACT
The présent works aims to develop controlled release matrix tablet of diclofenac sodium with modified starch cross linked starch urea as an sustained release polymer and to evaluate the prepared dosage form for physical parameters like weight variation, hardness, friability and drug content. Cross linked starch urea is modified starch introducing desirable alterations in the starch structure so that its behavior is predictable and controllable. In the current study, the influence of different concentration of polymer on erosion of matrix system was studied with a view to develop controlled release formulation of diclofenac sodium. The Diclofenac sodium tablet was prepared by wet granulation method. The result from in vitro drug release study indicated that formulation F1 to F6 were with different polymer concentration and F5 found to release the drug at a steady state over an extended period of time up to 24 h.

Keywords: Modified starch, Matrix tablets, Control release, Diclofenac sodium, Cross linked starch urea**.**

INTRODUCTION

Oral drug delivery is one of the most common and most patients – convenient means of drug administration. It is one of the largest and the oldest segments of the total drug delivery market. The popularity of the oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improved shelf life of the product. Consequently, much effort is directed during drug discovery to identify orally active candidates that will provide reproducible and effective plasma concentration *in vivo*. The reality is that many compounds are either incompletely or ineffectively absorbed after oral administration (i.e., bioavailability is an issue) or that the required dosing frequency is too short to enable once or twice daily administration (i.e., pharmacokinetic half – life is an issue). Lead optimization typically addresses such short comings during a discovery program; however, in many cases it is not possible to identify an appropriate clinical candidate with the requisite "ideal" physicochemical and/or pharmacokinetic properties. For clinical research phase drug candidate, or drug already marketed, the opportunity for enhancing their clinical pharmacology profile after oral administration through attainment of more optimal blood drug concentration – time profiles should always be considered. Modified release formulation technologies offer an effective means to optimize the bioavailability and resulting blood concentration – time profiles of drugs that otherwise suffer from such limitations.[1]

Modification of starch

Starch is one of the most important but flexible food ingredients possessing attributes for innumerable industrial applications.[2] It is widely distributed in the form of tiny granules as the major reserve carbohydrate in stems, roots, grains, and fruits of all forms of green leafed plants. Cereal grains, such as corn, wheat, sorghum and tubers, and roots, such as potato, tapioca, arrowroot, etc., are some of the commercial sources of starch for industrial exploitation. Starch contributes significantly to the texture and sensory properties of processed foods. It exhibits a wide range of functional properties and it is probably the most commonly used hydrocolloid. One third of total starch produced is utilized for a variety of industrial applications that take advantage of its unique properties. Starch is a carbohydrate of high natural abundance next to cellulose and chitin.[3]

Starch-value addition by modification

To meet the demanding technological needs of today, the properties of starch are modified by a variety of modification methods. Starch modification is aimed at correcting one or some of the above mentioned shortcomings which will enhance its versatility and satisfy consumer demand. Thus, the various chemically or otherwise modified starch derivatives offer significant value addition and give scope to develop a variety of fabricated food products having varied texture and mouth feel.[4] These modifications are aimed at introducing desirable alterations in the starch structure so that its behavior is predictable and controllable. Therefore, the modified starch derivatives are the products of either glycoside bond cleavage (acid modification to dextrin) or forming new functional groups (carbonyl group formation during oxidation) or substitution of free available hydroxyl groups (by etherification or esterification) or bridging of molecular chains by cross-linking reactions. Functional property modification is better exemplified by ionic hydrophilic substitution than by non-ionic hydrophobic substitution. In such functionalizations, the distribution of the introduced chemical substituent's and of the remaining free hydroxyl groups within the anhydroglucose residue and along the polymer chain can exert a strong influence on the product properties. Some of the newly developed starch derivatives have been designed for nonfood uses because of escalating costs for safety studies necessary to clear them for food use.[5]

METHODS AND MATERIALS

Diclofenac sodium, Corn Starch, Calcium Chloride, Urea, Magnesium Stearate, Talc were taken from B.R. Nahata College of Pharmacy, Mandsaur. All other materials were used of analytical grade and procured from commercial sources.

Preparation of Crosslinked Starch – Urea

Corn starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part), calcium chloride (1 part) were dissolved in purified water (40 parts) and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was continued for 20 minutes to form cross-linked starch-urea polymer. The mass formed was spread on to a stainless steel plate and dried at 85^{0}C for 6-8 h. The dried polymer was powdered and passed through mesh No. 100.[6]

Raw form

Powder form

Figure 1: Raw and Powdered forms of Crosslinked Starch – Urea

Preparation of controlled release matrix tablet

Matrix tablets each containing 100mg of Diclofenac sodium were prepared by wet granulation method using cross linked starch. The tablets prepared were as per the formulae given in the Table 1. Diclofenac sodium and polymer cross linked starch and corn starch in various ratios like were taken accurately and blended thoroughly. The blend was moistened with distilled water to get damp mass. The damp mass was then passed through sieve no 12 and the granular mass obtained were dried in hot air oven at 60º c for 1hr.The dried granules were passed through sieve no 16 to get free flowing and uniform sized granules. The granules were lubricated with 2% talc and 2% magnesium stearate were added which is previously passed through sieve no 100. The tablets were compressed (9 mm diameter, standard flat punches) using 8 station double rotary compression machine.[7,8]

Figure 2: Final product using Crosslinked starch urea

Evaluation of Tablet[7,9,10]

A. Pre-compression parameter

Angle of repose

Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is determined by using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone heighty (h) was obtained. The radius of the heap (r) was measured as angle of repose (θ) was calculated using the formula:

$$\theta = \tan^{-1} (h/r)$$

Bulk Density

Apparent bulk density (P_b) was determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula:

$$P_b = M/V_b$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (P_t) was calculated by using formula:

$$P_t = M/V_t$$

Compressibility index

The simplest way for measuring of free flow of powder was compressibility, an indication of the ease with which a material can be induced to flow was given by compressibility index

$$I = (V_o - V_t/V_o) \times 100$$

Where, V_o is the bulk volume and V_t is tapped volume.

Hausner's ratio

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by:

$$\text{Hausner ratio} = P_t/P_d$$

Where, P_t is tapped density and P_d is bulk density lower hausner's ratio (1.25)

B. Post-compression parameters

Weight variation

Twenty tablets were selected random and weighed individually. The individual weights were compared with average weight for determination of weight variation.

Friability

Twenty tablets from each batch were selected randomly and weighed. These preweighted tablets were subjected to friability testing using Roche friabilator for 100 revolutions. The tablets in the fibrilator undergo both abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability.

$$F = (1 - W_0 - W)\ 100$$

Where, W_0 is weight of the tablets before and W is weight of the tablets after test.

Hardness
Five tablets from each batch were selected and hardness was measured using Monesanto hardness tester to find the average tablet hardness or crushing strength.

Content uniformity
Five tablets were selected randomly and powdered. A quantity of this powder corresponding to 100 mg of Diclofenac sodium was dissolved in 100 mL of pH 6.8 phosphate buffer stirred for 60 min and filtered. 1mL of the filtrate was diluted to 100 mL with pH 6.8 phosphate buffer. Absorbance of this solution was measured at 276 nm using pH 6.8 phosphate buffer as blank and content of Diclofenac sodium was estimated.

***In vitro* drug release/Dissolution studies**
The tablet samples were subjected to in-vitro dissolution studies using USP Type 2 dissolution apparatus at 37±2°C and 50 rpm speed. As per the official recommendation of USFDA, 900 ml of 0.1 N HCl (2h) and pH 6.8 Phosphate buffer (next 8h) was used as dissolution medium. Aliquot equal to 5 ml was withdrawn at specific time intervals and. The dissolution media volume was complimented with fresh and equal volume of blank media (0.1 N HCl). The aliquots were filtered and scanned with appropriate dilution and amount of Diclofenac sodium released from the tablet samples was determined spectrophotometrically at a wavelength of 276 nm by comparing with the standard calibration curve.

RESULT AND DISCUSSION

The compositions of all the formulations were prepared by wet granulation method being tabulated in Table 1. Different proportions of cross linked starch urea and corn starch were taken for the formulations F_1 to F_6. 100 mg Diclofenac sodium was incorporated in all the formulations and final weight was made up to 300 mg. The granules obtained in different formulations were evaluated for different pre-compression parameters as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio were tabulated in Table 2. Further the post compression parameters were also evaluated which being shown in Table 3 and release kinetics results shown in Table 4.

Table 1: Formulation of Controlled Release Matrix Tablets of Diclofenac Sodium Using Crosslinked Starch Urea.

Name of Ingredients	Quantity (mg)					
	F_1	F_2	F_3	F_4	F_5	F_6
Diclofenac Sodium	100	100	100	100	100	100
Crosslinked Starch Urea	30	60	90	120	150	180
Corn Starch	158	128	98	68	38	8
Talc	6	6	6	6	6	6
Magnésium Stearate	6	6	6	6	6	6

Table 2: Pre-compression parameter

F	Angle of repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility (%)	Hausner's Ratio
F_1	33.56°	0.724	1.12	35.350	1.546
F_2	31.68°	0.787	1.15	31.565	1.461
F_3	29.26°	0.812	1.13	28.142	1.391
F_4	26.42°	0.849	1.14	25.981	1.351
F_5	25.19°	0.885	1.17	24.745	1.328
F_6	23.47°	0.884	1.15	23.986	1.315

Table 3 : Post-compression Parameter

F	Thickness	Weight Variation (mg) 300 mg ± 30 %	Hardness (kg/cm^2)	Friability (%)	Content uniformity (%)
F_1	4.83333	299.40	7.50	0.14799	98.42
F_2	4.86667	298.60	8.333	0.15654	99.07
F_3	4.63333	301.95	8.00	0.13898	97.89
F_4	4.53333	302.60	8.333	0.12955	98.58
F_5	4.66667	300.23	8.333	0.12057	98.76
F_6	4.86667	303.25	7.833	0.10415	9823

Table 4 : *In Vitro* Drug Release Study for Crosslinked Starch Urea Based Tablets

Time (h)	Cumulative percentage of Diclofenac sodium release					
	F_1	F_2	F_3	F_4	F_5	F_6
0.5	10.2±1.2	9.5±1.1	9.1±1.0	8.8±1.0	7.8±0.5	7.1±0.4
1	14.1±1.5	13.2±1.3	12.1±1.2	12.2±1.5	10.7±1.5	9.9±1.4
2	25.5±1.9	22.1±1.7	19.2±1.6	18±1.7	17.6±1.8	15.9±1.6
3	39.4±2.3	35.6±2.1	30.4±2	28.4±1.8	26.4±1.9	22.3±1.5
4	56.2±3.9	50.4±3.5	45.3±3	44.3±3.0	40.3±3.2	35.6±2.1
5	75.7±3.7	70.3±3.5	64.9±1.6	60.6±3.7	57.6±3.9	47.6±3.6
6	89.6±2.7	82.7±2.2	76.5±3.8	72.1±1.9	69.1±1.9	56.4±3.9
7	100	94.1±2.1	84.6±2.4	80.4±2.1	80.4±2	65.2±1.5
8.		100	94.2±2.2	84.6±2.4	80.6±2.6	74.3±3.6
9.			100	92.7±2	96.7±2	80.4±2
10				100	99.8±2.9	86.5±2.6

CONCLUSION

Matrix tablets of Diclofenac sodium can be effectively prepared by wet granulation techniques using cross linked starch selected for the better patient compliance and controlled release therapy. From the present study, it can be concluded that among all the formulations F5 containing crosslinked starch and corn starch (5:1) was found to release the drug in a controlled manner with maximum drug release of 99.8% following zero order release kinetics

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