Int. J. Chem. Sci.: 6(3), 2008, 1189-1195

EVALUATION OF CALCIUM STARCH : A NEW STARCH BASED POLYMER FOR CONTROLLED RELEASE OF DICLOFENAC

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ABSTRACT

The objective of the present investigation is to synthesize calcium starch, a new starch based polymer and to evaluate its application in controlled release (CR) and in the design of diclofenac controlled release tablets. Calcium starch polymer was synthesized by gelatinization of starch in the presence of sodium hydroxide and cross linking by treatment with calcium chloride. Matrix tablets each containing 100 mg of diclofenac sodium were formulated employing calcium starch polymer in different proportions of drug and polymer and the tablets were evaluated. Diclofenac release from the formulated tablets was slow and spread over 24 h and depended on percent polymer in the tablet. Release was diffusion controlled and followed zero order kinetics. Non – Fickian diffusion was the drug release mechanism from the formulated tablets. Diclofenac release from matrix tablets F3 formulated employing 15 % calcium starch was similar to that from Reactin SR tablets, a commercial sustained release formulation of diclofenac. Calcium starch polymer was found suitable for the design of oral controlled release tablets of diclofenac.

Key words: Calcium starch, Controlled release, Diclofenac, Matrix tablets.

INTRODUCTION

In the last two decades, controlled – release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Drug release from the systems should be at a desired rate, predictable and reproducible. Polymers, which are used as release – retarding materials in the design of controlled – release dosage forms play a vital role in controlling the delivery of drug from these dosage forms. Though a wide range of polymers and other release – retarding materials are available, there is a continued need to develop new, safe and effective release – retarding polymers for controlled release.

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Starch is a natural, biodegradable polymer and modified starches are reported as fillers[1,2] disintegrants and dry binders. In the present study, a new starch – based polymer, calcium starch was synthesized and evaluated for its application in controlled release. Among the various approaches, preparation of drug – embedded matrix tablet is one of the least complicated approach for obtaining controlled release. Diclofenac containing matrix tablets were prepared employing calcium starch and evaluated for controlled release (CR) and to design diclofenac CR tablets. Controlled release formulation is needed for diclofenac because of its short biological half life[3] of 2.0 h and also to minimize the g.i. disturbances such as peptic ulceration with bleeding, if present in larger concentration in g.i. tract[4].

EXPERIMENTAL

Materials and methods

Materials

Diclofenac sodium is a gift sample from M/s. Micro Labs Ltd., Pondicherry. All other materials used were of Pharmacopoeial grade.

Methods

Preparation of calcium starch polymer

Potato starch (5 parts) was dispersed in purified water (50 parts) to form starch slurry. Sodium hydroxide (3 parts) was dissolved in water (30 parts) and the solution was added to starch slurry, while mixing. Mixing was continued for 30 minutes to form a thick gelatinized mass. The mass formed was added to 300 mL of calcium chloride (20 % w/v) solution contained in a vessel while stirring at 1000 rpm with a medium duty stirrer. The stirring was continued for 1 hour to precipitate calcium starch formed. The calcium starch formed was collected by vacuum filtration, washed repeatedly with water and dried at 80ºC. The dried polymer was powdered and passed through mesh No. 100.

Preparation of tablets

Matrix tablets each containing 100 mg of diclofenac sodium were prepared employing calcium starch in different proportions of drug and polymer. The required quantities of medicament and matrix materials were mixed thoroughly in a mortar by following geometric dilution technique. The binder solution (mixture of alcohol and purified water at 1 : 1 ratio) was added and mixed thoroughly to form a dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried

at 60° for 4 h. The dried granules were passed through mesh No. 16 to break the aggregates. The lubricants, talc (2%) and magnesium stearate (2%) were passed through mesh No. 100 onto dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multi-station tablet punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 8 - 10 kg/sq.cm. using 9 mm round and flat punches.

Hardness of tablets was tested using a Monsanto hardness tester. Friability of tablets was determined in a Roche friabilator. Disintegration time was determined in a Thermonic tablet disintegration test machine using water, 0.1N HCl and phosphate buffer of pH 7.4 as test fluids.

Estimation of diclofenac

Diclofenac content of the tablets was estimated by UV spectrophotometric method based on the measurement of absorbance at 276 nm in phosphate buffer of pH 7.4. The method was validated for linearity, precision and accuracy. The method obeyed Beer's law in the concentration range 0-10 μg/mL. When a standard drug solution was assayed repeatedly (n = 6), the mean error (accuracy) and relative standard deviation (precision) were found to be 0.6 and 0.8 %, respectively. No interference from the excipients used was observed.

Drug release study

Drug release from matrix tablets was studied using 8 station dissolution rate test apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at 37±1°C. Phosphate buffer of pH 7.4 (900 mL) was used as dissolution fluid. Samples of 5 mL of each were withdrawn at different time intervals over a period of 24 h. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and assayed at 276 nm for diclofenac using a Shimadzu UV-150 double beam UV-spectrophotometer. For comparison, diclofenac release from Reactin SR tablets was also studied. The drug release experiments were conducted in triplicate.

Data analysis

Release data were analyzed as per zero order, first order, Higuchi[5] and Peppas[6] models to assess the drug release kinetics and mechanism from tablets.

RESULTS AND DISCUSSION

Calcium starch was synthesized by gelatinizing potato starch in the presence of sodium hydroxide and cross linking by treatment with calcium chloride. The calcium starch polymer formed was found to be fine and free flowing powder upon drying. It was insoluble in water, aqueous fluids of acidic and alkaline pHs. When tested for melting point, the polymer charred at 220^0C.

Matrix tablets each containing 100 mg of diclofenac could be prepared employing different proportions (5, 10, 15 and 20 % concentrations in the formulae) of calcium starch polymer by conventional wet granulation method. Hardness of the tablets was in the range of 8 – 10 kg/ sq. cm. Weight loss in the friability test was less than 0.4% in all the cases. All the matrix tablets prepared contained diclofenac within 100 ± 3% of the labeled claim. All the tablets were found to be non – disintegrating in water and aqueous, acidic (pH 1.2) and alkaline (pH 7.4) fluids. As such, the prepared tablets were of good quality with regard to drug content, hardness and friability. As the tablets formulated employing calcium starch were non – disintegrating in acidic and alkaline fluids, they are considered suitable for oral controlled release.

Release parameters of the tablets are summarized in Table 1. Diclofenac release from the prepared tablets was slow and spread over 24 h and depended on the concentration of calcium starch polymer. When the release date were analyzed as per zero and first order kinetic models, the best fit with higher correlation ($r > 0.96$) was observed with zero order model indicating that the drug release from all the tablets followed zero order kinetics. When the release data were analyzed as per Peppas equation, the release exponent 'n' was found in the range 0.587 – 0.686 indicating non – Fickian (anomalous) diffusion as the release mechanism from all the tablets prepared. Plots of percent released versus square root of time were found to be linear ($r > 0.948$) with all tablets prepared indicating that the drug release from the tablets was diffusion controlled.

As the polymer concentration was increased, release rate was decreased. Good linear relationship was observed (Fig. 1) between percent polymer and release rate (K_0). Thus drug release from the matrix tablets could be controlled by varying the proportion of drug : polymer in the matrix.

Table 1: Diclofenac release characteristics of matrix tablets formulated employing calcium starch polymer

Formulation	Polymer concentration (%)	Percent drug released at various times (h)					T_{50} (h)	T_{90} (h)	K_0 (mg/h)	'n' in Peppas equation
		1	4	8	12	24				
F1	5	21.53	50.58	95.96	100	100	3.6	7.2	9.83	0.686
F2	10	20.35	53.65	72.12	95.36	100	3.6	10.8	7.232	0.598
F3	15	15.79	41.41	58.59	73.95	100	6	17.5	4.622	0.587
F4	20	12.5	33.37	49.55	65.91	85	8.2	> 24	3.44	0.616
Reactin SR tablets	--	16.62	37.11	58.65	78.3	100	5.8	15.5	4.832	0.64

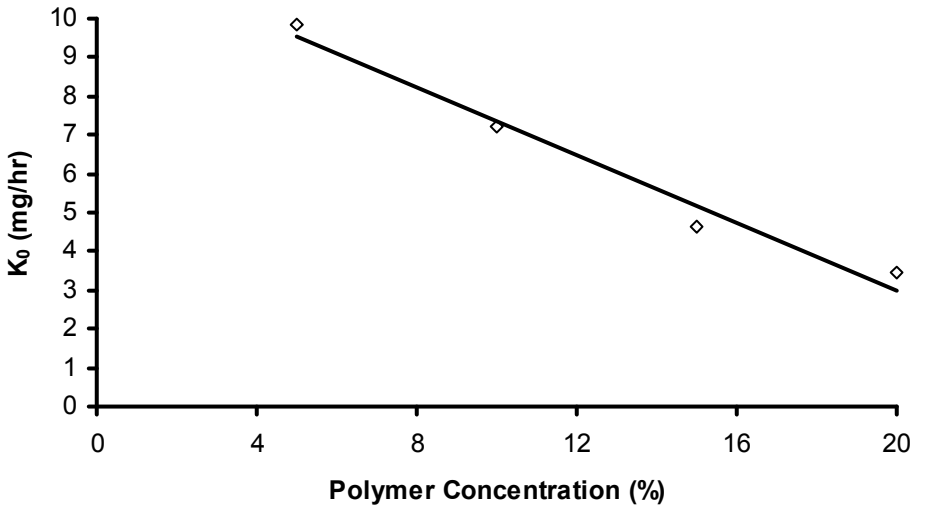

Fig. 1: Relationship between percent polymer and release rate (K_0) of diclofenac matrix tablets formulated employing calcium starch.

For comparison, diclofenac release from one commercial brand (Reactin SR) was also studied. Drug release profiles of formulation F3 and Reactin SR tablets were compared by calculating difference factor f_1 and similarity factor f_2. A value of $f_1 < 15$ and $f_2 > 50$ indicates similarity of the two drug release profiles. The values of f_1 and f_2 were found to be 13.15 and 123.38, respectively for the comparison of release profiles of formulation F3 and Reactin SR tablets indicating that the release profiles of these two products are similar. Hence, matrix tablets formulated employing calcium starch (F3) is considered suitable for controlled release of diclofenac over 24 h.

CONCLUSIONS

(i) Matrix tablets formulated employing calcium starch, a new starch based polymer, are suitable for oral controlled release of diclofenac.

(ii) Diclofenac release from the tablets formulated employing calcium starch was slow and spread over 24 h and depended on percent polymer in the tablet. Release was diffusion controlled and followed zero order kinetics.

(iii) Non – Fickian diffusion was the drug release mechanism from the formulated tablets.

(iv) Diclofenac release from matrix tablets F3 formulated employing 15 % calcium starch was similar to that from Reactin SR tablets, a commercial sustained release formulation of diclofenac.

(v) Calcium starch polymer is suitable for the design of oral controlled release tablets.

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Accepted : 26.06.2008