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Preparation and Evaluation of Cross Linked Starch Urea-A New Polymer for Controlled Release of Aceclofenac

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The objective of the present investigation is to synthesize cross linked starch-urea, a new starch based polymer and to evaluate its application in controlled release and in the design of aceclofenac controlled release tablets. Starch-urea (carbamate) was prepared by gelatinizing potato starch in the presence of urea. The starch-urea was then cross linked by treatment with calcium chloride to result in cross-linked starch-urea. Matrix tablets each containing 100 mg of aceclofenac were formulated employing (i) starch-urea and (ii) cross-linked starch-urea in different proportions by wet granulation method and the tablets were evaluated. Cross-linked starch-urea was more suitable than starch-urea for controlled release application. Aceclofenac release from the matrix tablets formulated employing cross-linked starch-urea was slow, spread over 24 h and the release was diffusion controlled. Non-Fickian diffusion was the drug release mechanism from these matrix tablets. Aceclofenac release from matrix tablets (F3) formulated employing 50 % cross-linked starch-urea was similar to that from hifenac SR tablets, a commercial SR formulation of aceclofenac. Aceclofenac CR tablets for once-a-day (24 h) administration could be designed employing cross-linked starch-urea.

Key Words: Cross-linked starch-urea, Controlled release, Aceclofenac, 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 these systems should be at a desire 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. Starch is a natural, biodegradable polymer and modified starches are reported as fillers[1], disintegrants, dry binders and matrix formers for controlled release[2,3]. Starch reacts with urea to form starch-urea (carbamate), a hydrophilic water swellable polymer. In the present study starch-urea and

cross-linked starch-urea (a new starch based polymer) were prepared and evaluated for their application in the design of controlled release tablets of aceclofenac. Among the various approaches, preparation of drug-embedded matrix tablet is one of the least complicated approach for obtaining controlled release. Hence formulation of matrix tablets is aimed in the present study for obtaining controlled release. Aceclofenac containing matrix tablets were prepared employing (i) starch-urea and (ii) cross linked starch-urea and were evaluated for controlled release (CR) and to design aceclofenac CR tablets. Controlled release formulation is needed for aceclofenac because of its short biological half life of 4 h, low and variable oral bioavailability due to its poor aqueous solubility 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

Aceclofenac was a gift sample from M/s Suyaash Labs, Chennai. All other materials used were of pharmacopoeial grade.

Preparation of starch-urea: Potato starch (9 parts) was dispersed in purified water (10 parts) to form starch slurry. Urea (1 part) was 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 min to form starch-urea polymer. The mass formed was spread on to a stainless steel plate and dried at 85 ºC for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

Preparation of cross linked starch-urea polymer: Potato 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 min to form cross-linked starch-urea polymer. The mass formed was spread on to a stainless steel plate and dried at 85 ºC for 6-8 h. The dried polymer was powdered and passed through mesh No. 120.

Preparation of tablets: Matrix tablets each containing 100 mg of aceclofenac were prepared employing (i) starch-urea (ii) cross-linked starch-urea 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, water-alcohol (1:1) solution was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60 ºC for 4 h. The dried granules were passed through mesh No. 16 to break aggregates. The lubricants talc (2 %) and magnesium stearate (2 %) were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multi-station punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 8.0-9.5 kg/cm^2 using 9 mm round and flat punches.

Hardness of tablets was tested using 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, 0.1 N HCl and phosphate buffer of pH 6.8 as test fluids.

Estimation of aceclofenac: Aceclofenac content of the tablets was estimated by an UV spectrophotometric method based on the measurement of absorbance at 275 nm in phosphate buffer of pH 6.8. 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 0.45 %, 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 ± 0.5 ºC. Phosphate buffer of pH 6.8 (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 275 nm for aceclofenac using an Elico BL 198 double beam UV-spectrophotometer. For comparison, aceclofenac release from Hifenac 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

Starch-urea (carbamate) was prepared by gelatinizing potato starch in the presence of urea. The starch-urea was then cross linked by treatment with calcium chloride to result in cross-linked starch-urea. Both starch-urea and cross-linked starch-urea formed were found to be fine and free flowing powders upon drying and grinding. They are insoluble in water, aqueous fluids of acidic and alkaline pHs. When tested for melting point, the polymers charred at 220-230 ºC.

Matrix tablets each containing 100 mg of aceclofenac could be prepared employing (i) starch-urea (ii) cross-linked starch-urea in different proportions (33, 50 and 66 strengths in the formulae) by wet granulation method. Hardness of the tablets was in the range of 8.0-9.5 kg/cm^2. Weight loss in the friability test was less than 0.3 % in all the cases. All the matrix tablets prepared contained 100 ± 3 % of the labeled claim. All the tablets were found to be non-disintegrating in water, aqueous, acidic (pH 1.2) and alkaline (pH 6.8) fluids. As such, the prepared tablets were of good quality with regard to drug content, hardness and friability. As the tablets formulated employing starch-urea and cross-linked starch-urea were non-disintegrating in acidic and alkaline fluids, they are considered suitable for oral controlled release.

Release parameters of the matrix tablets prepared are summarized in Table-1. Aceclofenac release from the prepared tablets was slow and spread over 24 h and depended on the polymer type and concentration of cross linked starch-urea polymer in the tablets. Aceclofenac release was relatively rapid in the case of matrix tablets prepared employing starch-urea polymer at 50 % strength and the release was complete in 6 h. Whereas when cross-linked starch-urea polymer was used at the same strength of 50 % in the formula, the release was much slow and spread over 24 h. As the concentration of cross-linked starch-urea polymer in the matrix tablets was increased, the release rate was decreased. A good linear relationship was observed between per cent polymer (cross linked starch-urea) and release rate, K_0 (Fig. 1). Aceclofenac release from matrix tablets (F3) formulated employing 50 % cross-linked starch-urea polymer was spread over 24 h and was similar to that from Hifenac SR tablets, a commercial SR product of aceclofenac.

TABLE-1
ACECLOFENAC RELEASE CHARACTERISTICS OF MATRIX TABLETS FORMULATED EMPLOYING STARCH-UREA AND CROSS-LINKED STARCH-UREA

Formulation	Polymer (%)	Percent drug release at various times (h)						T_{50} (h)	T_{90} (h)	K_0 (mg/h)	'n' in Peppas eqn.
		1	4	6	8	12	24				
F1	SU (50)	26.0	93.3	100.0	–	–	–	2.5	3.7	17.770	0.8159
F2	CSU (33)	20.2	47.1	48.6	60.7	88.5	–	6.8	12.8	8.124	0.5659
F3	CSU (50)	12.4	25.2	32.1	39.2	49.3	100.0	12.2	21.7	3.696	0.6395
F4	CSU (66)	6.4	18.8	25.9	53.4	75.3	94.3	7.4	21.5	3.081	0.9924
Hifenac SR tablets	–	20.1	41.8	59.1	69.2	81.8	100.0	14.5	22.1	3.398	0.5213

SU: Starch-urea; CSU: Cross-linked starch-urea.

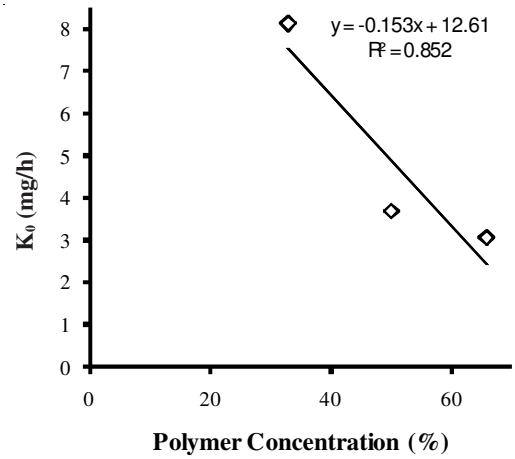

Fig. 1. Relationship between per cent polymer and release rate (K_0) of aceclofenac matrix ablets prepared employing cross linked starch-urea

Drug release data were analysed as per zero order, first order, Higuchi and Peppas equation kinetic models and the correlation coefficient (r) values in various models are given in Table-2. Analysis of release data as per zero order and first order kinetic models indicated that the aceclofenac release from the matrix tablets followed zero order kinetics. The correlation coefficient (r)-values were higher in the zero order model than in the first order model. Plots of per cent release *versus* square root of time were found to be linear with $r > 0.9581$ with all the tablets prepared indicating that the drug release from these tablets was diffusion controlled. When the release data were analyzed as per Peppas equation, the release exponent 'n' was in the range 0.5659-0.9924 indicating non-Fickian (anomalous) diffusion as the release mechanism from all the tablets prepared.

TABLE-2
CORRELATION COEFFICIENT (r) VALUES IN THE ANALYSIS OF RELEASE DATA AS PER ZERO, FIRST ORDER, HIGUCHI AND PEPPAS EQUATION MODELS

Formulation	'r' value			
	Zero order model	First order model	Higuchi model	Peppas equation
F1	0.9731	0.8903	0.9581	0.9766
F2	0.9766	0.9487	0.9831	0.9834
F3	0.9919	0.9564	0.9646	0.9874
F4	0.9422	0.9844	0.9581	0.9758
Hifenac SR	0.9722	0.8960	0.9276	0.9310

For comparison, aceclofenac release from one commercial SR brand (Hifenac SR tablets) studied. Drug release profiles of formulation F3 and Hifenac SR tablets were compared by calculating difference factor f_1 and similarity factor f_2. A value of $f_1 < 15$ and $f_2 > 50$ indicate similarity of the two drug release profiles. The values of f_1 and f_2 were found to be 12.27 and 62.7, respectively for the comparison of release profiles of formulation F3 and Hifenac SR tablets indicating that the release profiles of these two products are similar. Hence, matrix tablets formulated employing cross-linked starch-urea (F3) are considered suitable for controlled release of aceclofenac over 24 h (*i.e.*, once-a-day administration).

Conclusion

(i) Cross-linked starch-urea was more suitable than starch-urea for controlled release application. (ii) Aceclofenac release from the matrix tablets formulated employing cross-linked starch-urea was, slow, spread over 24 h and the release was diffusion controlled. (iii) Non-Fickian diffusion was the drug release mechanism from these matrix tablets. (iv) Aceclofenac release from the matrix tablets (F3) formulated employing 50 % cross-linked starch-urea was similar to that from Hifenac SR tablets, a commercial SR formulation of aceclofenac. (v) Aceclofenac CR tablets for once-a-day (24 h) administration could be designed employing cross-linked starch-urea.

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