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A Comparative Evaluation of Cross Linked Starch Urea-A New Polymer and Other Known Polymers for Controlled Release of Diclofenac

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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 for controlled release of diclofenac. The release retarding and rate controlling efficiency of cross-linked starch-urea was also compared with that of other known polymers. Cross-linked starch-urea polymer was synthesized by gelatinization of starch in the presence of urea and calcium chloride. Matrix tablets each containing 100 mg of diclofenac were formulated employing cross-linked starch-urea in different concentrations in the formula and other polymers such as methyl cellulose (MC), hydroxy propyl methyl cellulose (HPMC, K15M), sodium carboxy methyl cellulose (sodium CMC) and sodium alginate (SA) at 1:1 ratio of drug:polymer by wet granulation method and the tablets were evaluated. Diclofenac release from the matrix tablets formulated employing cross-linked starch-urea was slow, spread over 24 h and depended on the concentration of cross-linked starch-urea polymer in the tablets. Non-Fickian diffusion was the drug release mechanism from these matrix tablets. Diclofenac release from the matrix tablets (F3) formulated employing 66 % cross-linked starch-urea was similar to that from voveran SR tablets, a commercial SR formulation of diclofenac. The order of increasing release retarding effect observed with various polymers was HPMC, K15M > cross-linked starch-urea > MC > sodium CMC > sodium alginate. Cross-linked starch-urea was found to be a better release-retarding polymer than sodium alginate, sodium carboxy methyl cellulose and methyl cellulose. Cross-linked starch-urea and hydroxy propyl methyl cellulose were found more suitable for controlled release application. Diclofenac 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, 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 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]. In the present study cross-linked starch-urea (a new modified starch) was prepared and evaluated for its application in the design of controlled release tablets of diclofenac. The release retarding and rate controlling efficiency of cross-linked starch-urea was also compared with that of other known polymers. 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. Diclofenac containing matrix tablets were prepared employing cross-linked starch-urea in different concentrations in the formula and other polymers such as methyl cellulose (MC), hydroxy propyl methyl cellulose (HPMC, K15M), sodium carboxy methyl cellulose (sodium CMC) and sodium alginate (SA) at 1:1 ratio of drug:polymer. All the matrix tablets prepared were evaluated for drug release kinetics and suitability for controlled release. Controlled release formulation is needed for diclofenac because of its short biological half life[4] of 2 h and also to minimize the g.i. disturbances such as peptic ulceration with bleeding, if present in larger concentration in g.i. tract[5].

EXPERIMENTAL

Diclofenac sodium was a gift sample from M/s. Micro Labs Ltd., Pondicherry. Methyl cellulose (100 cps), hydroxy propyl methyl cellulose (K15M), sodium carboxy methyl cellulose (high viscosity grade) and sodium alginate (I.P.) were procured from commercial sources. All other materials used were of pharmacopoeial grade.

Methods

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. 100.

Preparation of tablets: Matrix tablets each containing 100 mg of diclofenac sodium were prepared employing cross-linked starch-urea in different proportions of drug and polymer and other polymers at 1:1 ratio of drug:polymer. The required quantities of medicament and matrix materials were mixed thoroughly in a mortar by following geometric dilution technique. The binder (1 % PVP 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 8-10 kg/cm^2. using 9 mm round and flat punches. For comparing the release retarding and rate controlling efficiency of cross-linked starch-urea with that of other known polymers, diclofenac (100 mg) matrix tablets were also prepared employing methyl cellulose, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose and sodium alginate at a drug: polymer ratio of 1:1 (*i.e.*, 50 % polymer concentration in the tablets). All the prepared matrix tablets were evaluated for drug content, friability, hardness, disintegration and dissolution characteristics.

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 7.4 as test fluids.

Estimation of diclofenac: Diclofenac content of the tablets was estimated by an 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 the matrix tablets prepared was studied using 8 station dissolution rate test apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at 37 ± 1 ºC. 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 an Elico BL 198 double beam UV-spectrophotometer. For comparison, diclofenac release from Voveran 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[6] and Peppas[7] models to assess the drug release kinetics and mechanism from tablets.

RESULTS AND DISCUSSION

Cross-linked starch-urea was prepared by gelatinizing potato starch in the presence of urea and calcium chloride to result in cross-linked starch-urea. Cross-linked starch-urea formed was found to be fine and free flowing powder upon drying and grinding. It is insoluble in water, aqueous fluids of acidic and alkaline pHs. When tested for melting point, the polymer charred at 230 ºC.

Matrix tablets each containing 100 mg of diclofenac could be prepared employing cross-linked starch-urea in different proportions (33, 50, 66 and 75 % strengths in the formulae) and other polymers at 50 % strength by wet granulation method. Hardness of the tablets was in the range of 8-10 kg/cm^2. Weight loss in the friability test was less than 0.4 % 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 7.4) fluids. As such, all the prepared matrix tablets were of good quality with regard to drug content, hardness and friability. As the tablets formulated employing cross-linked starch-urea and other polymers were non-disintegrating in acidic and alkaline fluids, they are all considered suitable for oral controlled release.

Release parameters of the matrix tablets prepared are summarized in Table-1. Diclofenac release from the prepared tablets was slow and spread over 24 h and depended on the concentration of cross linked starch-urea polymer in the tablets. As the concentration of cross-linked starch-urea polymer in the matrix tablets was increased, the release rate was decreased. Diclofenac release from matrix tablets (F3) formulated employing 66 % cross-linked starch-urea polymer was spread over 24 h and was similar to that from Voveran SR tablets, a commercial SR product of diclofenac.

TABLE-1
DICLOFENAC RELEASE CHARACTERISTICS OF MATRIX TABLETS FORMULATED EMPLOYING CROSS-LINKED STARCH-UREA AND VARIOUS OTHER POLYMERS

Formu.	Polymer (%)	Percent drug release at various times (h)						T_{50} (h)	T_{90} (h)	K_0 (mg/h)	K_1 (h^{-1})	'n' in Peppas equation
		1	4	6	8	12	24					
F1	CSU (33)	43.50	72.40	100	–	–	–	1.3	4.7	18.51	0.3193	0.379
F2	CSU (50)	12.30	35.20	51.4	70.5	91.0	100	5.8	11.8	07.28	0.1968	0.942
F3	CSU (66)	20.60	46.60	60.4	72.8	90.7	100	4.4	12.0	04.42	0.2179	0.618
F4	CSU (75)	19.20	93.60	100	–	–	–	1.8	3.6	13.05	0.7787	0.916
F5	MC (50)	15.10	37.80	46.5	70.8	100	–	6.2	10.2	8.10	0.1973	0.804
F6	HPMC (50)	19.60	44.80	57.7	68.5	92.6	100	4.8	11.2	6.75	0.1349	0.625
F7	Sodium CMC (50)	17.06	72.20	97.5	–	–	–	3.1	4.8	17.78	0.6372	1.120
F8	SA (50)	79.70	91.07	100	–	–	–	0.8	3.8	59.16	1.4010	1.071
Voveran SR tablets	–	20.10	41.80	59.1	69.2	81.8	100	4.8	15.0	03.95	0.1723	0.545

CSU: Cross-linked starch-urea; MC: methyl cellulose; HPMC: hydroxy propyl methyl cellulose; sodium CMC: sodium carboxy methyl-cellulose; and SA: sodium alginate.

Analysis of release data as per zero order and first order kinetic models indicated that both the models are equally applicable to describe the release data of matrix tablets formulated employing cross-linked starch-urea. Plots of per cent release *versus* square root of time were found to be linear with $r > 0.9626$ 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 0.618-0.942 indicating non-Fickian (anomalous) diffusion as the release mechanism from all the tablets prepared except formulation F1. In the case of formulation F1, which gave rapid release of diclofenac, the 'n' was found to be 0.379 indicating Fickian diffusion as the release mechanism from these tablets.

For comparison, diclofenac release from one commercial SR brand (Voveran SR tablets) studied. Drug release profiles of formulation F3 and voveran 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 4.62 and 132.16, respectively for the comparison of release profiles of formulation F3 and Voveran 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 diclofenac over 24 h (*i.e.*, once-a-day administration).

All the release parameters indicated variations or differences in drug release from the tablets formulated with different polymers though all the polymers were used at same strength *i.e.*, 50 % in the formula. The drug (diclofenac) release was relatively rapid in the case of sodium alginate and sodium carboxy methyl cellulose and hydroxy propyl methyl cellulose and cross-linked starch-urea gave slow and gradual release spread over 24 h. The order of increasing release retarding effect observed with various polymers was HPMC, K15M > cross-linked starch-urea > MC > sodium CMC > sodium alginate. Thus, cross-linked starch-urea was found to be a better release-retarding polymer than sodium alginate, sodium carboxy methyl cellulose and methyl cellulose. Cross-linked starch-urea and HPMC, K15M were found more suitable for controlled release application.

Conclusion

Diclofenac release from the matrix tablets formulated employing cross-linked starch-urea was slow, spread over 24 h and depended on the concentration of cross-linked starch-urea polymer in the tablets. Non-Fickian diffusion was the drug release mechanism from these matrix tablets. Diclofenac release from the matrix tablets (F3) formulated employing 66 % cross-linked starch-urea was similar to that from Voveran SR tablets, a commercial SR formulation of diclofenac. The order of increasing release retarding effect observed with various polymers was HPMC, K15M > cross-linked starch-urea > MC > sodium CMC > sodium alginate. Cross-linked starch-urea was found to be a better release-retarding polymer than sodium alginate, sodium carboxy methyl cellulose and methyl cellulose. Cross-linked starch-urea and HPMC, K15M were found more suitable for controlled release application. Diclofenac CR tablets for once-a-day (24 h) administration could be designed employing cross-linked starch-urea.

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