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

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The objective of the present investigation is to synthesize cross-linked starch-urea, a new starch based polymer and to evalate its application for controlled release of glipizide. The release retarding and rate controlling efficiency of cross-linked starch-urea was also compared with that of other known polymers. Starch-urea (carbamate) was prepared by gelatinizing potato starch in the presence of urea. The starch-urea was then cross linked treatment with calcium chloride to result in cross-linked starch-urea. Matrix tablets each containing 10 mg of glipizide 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. Glipizide 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-Fickain diffusion was the drug release mechanism from these matrix tablets. Matrix tablets (F2) formulated employing 50 % cross-linked starch-urea > sodium CMC > sodium alginate > methyl cellulose. Cross-linked starch-urea was found to be a better release-retarding polymer than sodium alginate, sodium CMC and methyl cellulose. Cross linked starch-urea and HPMC, K15M were found more suitable for controlled release application. Glipizide 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, Glipizide, 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 desired rate, predicatable and reproducible. Polymers, which are used as release-retarding materials in the design of controlled-release dosage forms play a vital role in controlled 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 starch based polymer) was prepared and evaluated for its application in the design of controlled release tablets of glipizide. 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. Glipizide 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 glipizide because of its short biological half life[4] of 3.4 ± 0.7 h and also to minimize the g.i. disturbances, for better control of glucose levels, to enhance patient compliance and clinical efficiency.

EXPERIMENTAL

Glipizide 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 (IP) 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. 120.

Preparation of tablets: Matrix tablets each containing 10 mg of glipizide 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 of matrix materials were mixed thoroughly in a mortar by following geometric dilution technique. The binder (alcohol-water 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 8-9 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, glipizide (10 mg) matrix tablets were also prepared employing MC, HPMC, sodium CMC 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 Mansanto 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 glipizide: Glipizide 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 0.8 and 1.6 %, respectively. No interference from the excipients used was observed.

Drug release study: Durg 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 at 37 ± 0.5 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 glipizide using an Elico BL 198 double beam UV-spectrophotometer. For comparison, glipizide release from glynase XL SR tablets was also studied. The drug release experiments were conducted intriplicate.

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 n 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 220-230 ºC.

Matrix tablets each containing 10 mg of glipizide could be prepared employing corss-linked starch-urea in different proportions (33, 50 and 66 % strengths in the formulae) and other polymers at 50 % strength by wet granulation method. Hardness of the tablets was in the range of 8-9 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 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. Glipizide release from the prepared matrix tablets was slow and spread over 24 h and depended on the concentration of cross linked starch-urea and the polymer used in the tablets. As the concentration of cross-linked starch-urea polymer in the matrix tablets was increase, the release rate was decreased. For comparison, glipizide release from one commericial SR brand (glynase XL SR tablets) was also studied. Glipizide release from the commercial SR tablets was relatively rapid in the initial times upto 12 h and later the release was very slow and incomplete in 24 h. Whereas glipizide release from the matrix tablets F2 formulated employing 50 % cross-linked starch-urea polymer was slow and spread over and complete in 24 h. As such these matrix tablets (F2) formulated employing 50 % corss linked starch-urea are considered suitable for controlled release of glipizide for once-a-day (24 h) administration.

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

Formulation	Polymer (%)	Per cent drug release at various time (h)						T_{50} (h)	T_{90} (h)	K_0 (mg/h)	'n' in Peppas eqn.
		1	4	6	8	12	24				
F1	CSU (33)	10.1	20.7	30.8	34.7	55.5	100	10.50	20.50	0.5482	0.6489
F2	CSU (50)	16.3	22.6	38.5	49.0	70.4	100	7.00	14.00	0.4951	0.5220
F3	CSU (66)	10.2	14.7	16.5	16.9	29.2	94.3	16.00	22.50	0.2463	0.5158
F4	HPMC (50)	19.2	23.36	35.04	38.33	51.92	94.29	11.50	23.00	0.3204	0.4470
F5	CMC (50)	19.3	60.62	83.45	92.58	100	–	3.25	7.25	1.112	0.6105
F6	SA (50)	58.39	100	–	–	–	–	0.75	1.75	2.790	0.5966
F7	MC (50)	64.98	100	–	–	–	–	0.75	2.0	3.1609	0.6165
Glynase XL SR tablets	–	22.7	48.4	58.9	69.7	75.6	89.0	5.00	> 24	0.3230	0.4321

CSU: Cross-linked starch-urea, MC: Methyl cellulose, HPMC: Hydroxy propyl methyl cellulose, 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 (F2), HPMC (F4), sodium. CMC (F5). In the case of tablets formulated employing sodium alginate (F6), methyl cellulose (F7) and glynase XL SR tablets the release followed first order kinetics. Plots of per cent release *versus* square root of time were found to be linear with 4 > 0.9295 with all the tablets prepared except formuation F3, indicating that the drug release from these matrix tablets was diffusion controlled.

When the release data were analyzed as per Peppas equation, the release exponent 'n' was in the range 0.5158-0.6489 in the case of all the matrix tablets prepared except F4 and commercial SR formulation indicating non-Fickian (anomalous) diffusion as the release mechanism from these matrix tablets prepared. Whereas in the case of F4 and glynase XL SR tablets, the 'n' value was 0.4470 and 0.4231, respectively indicating that the release from these tablets was by fickian diffusion mechanism.

All the release parameters indicated variations or differences in drug release from the tablets formualted with different polymers though al the polymers was used at same strength *i.e.*, 50 % in the formula. The drug (glipizide) release was relatively rapid in the case of methyl cellulose and sodium alginate. Hydroxy propyl ethyl cellulose (HPMC) and cross linked starch-urea gave slow and gradual release over 24 h. The order of increasing release retarding effect observed with various polymers was HPMC (K15M) > cross-linked starch-urea > sodium CMC > sodijm alginate > MC. Thus, cross-lined starch-urea and HPMC were found to be better release-retarding polymers when compared to all other polymers tested. Overall cross-linked starch-urea and HPMC (K15M) were more suitable for controlled release application.

Conclusion

- Glipizide release from the matrix tablets formulated employing cross-linked starch-urea and various other polymers was slow, spread over 24 h and depended on the concentration of cross linked starch-urea and the polymer used.
- Non-Fickian diffusion was the drug release mechanism from all the matrix tablets prepared except those prepared with HPMC.
- The order of increasing release retarding effect observed with various polymers was HPMC (K15M) > cross-linked starch-urea > sodium CMC > sodium alginate > MC.
- Cross-linked starch-urea and HPMC were found to be better release-retarding polymers when compared to the other polymers tested.
- Overall cross-linked starch-urea and HPMC (K15M) were found more suitable for controlled release application.
- Glipizide CR tablets for once-a-day (24 h) administration could be designed employing cross linked strach-urea.

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