Asian Journal of Chemistry Vol. 21, No. 6 (2009), 4173-4178

Synthesis and Evaluation of Starch-Urea-Borate for Controlled Release Application

K.P.R. CHOWDARY* and M.N. MURALI KRISHNA
University College of Pharmaceutical Sciences,
Andhra University, Visakhapatnam-530 003, India
E-mail: profkprc@rediffmail.com

The objective of the present investigation is to synthesize starch-urea-borate, a new starch based polymer and to evaluate its application in controlled release (CR) and in the design of controlled release tablets of diclofenac and gliclazide. The release retarding efficiency of starch-urea-borate was also compared with that of known polymers. Starch-urea-borate (SUB) polymer was synthesized by gelatinization of starch in the presence of urea and borax. Matrix tablets of diclofenac (100 mg) and gliclazide (60 mg) were formulated employing starch-urea-borate polymer in different proportions of drug and polymer and the tablets were evaluated. With both diclofenac and gliclazide, release from the formulated matrix tablets was slow and spread over 24 h and depended on per cent 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 formulated employing 33 % SUB (DF3) and gliclazide release from matrix tablets formulated employing 50 % SUB (GF4) was similar to that from the corresponding commercial SR tablets. Starch-urea-borate polymer was found suitable for the design of oral controlled release tablets of diclofenac and gliclazide. The order of increasing release retarding effect with various polymers was ethyl cellulose = guar gum > SUB > sodium CMC > HPMC. Starch-urea-borate is a better release retarding polymer than HPMC and sodium CMC for obtaining controlled release over 24 h.

Key Words: Starch-urea-borate, Controlled release, Diclofenac, Gliclazide, 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. 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, starch-urea-borate was synthesized and evaluated for its application in controlled release taking diclofenac and gliclazide as model drugs which require controlled release formulation. Among the various approaches, preparation of drug-embedded matrix tablet is one of the least complicated approach for obtaining controlled release. The release retarding efficiency of starch-urea-borate was also compared with that of known polymers. Controlled release formulation is needed for diclofenac because of its short biological half life[3] of 2.0 h and also to minimize the gastric intestine disturbances such as peptic ulceration with bleeding if present in larger concentration in gastric intestine tract[4]. Controlled release formulation is needed[5] for gliclazide for better control of blood glucose levels to prevent hypoglycemia and enhance clinical efficacy, to reduce gastric intestine disturbances and to enhance patient compliance.

EXPERIMENTAL

Diclofenac sodium is a gift sample from M/s Micro Labs Ltd., Pondicherry. Gliclazide is a gift sample from M/s. Ranbaxy Research Labs., Gurgaon, Haryana. Hydroxy propyl methyl cellulose (50 cps), sodium carboxy methyl cellulose (sodium CMC with a viscosity of 1500-3000 cps of a 1 % w/v solution at 25 °C), guar gum (Loba chemie) and ethyl cellulose (viscosity of 5 % w/w solution in 80:20 toluene:ethanol by weight at 25 °C is 18 cps, containing not less than 46.5 % ethoxyl groups) were procured from commercial sources. All other materials used were of Pharmacopoeial grade.

Methods

Preparation of starch-urea-borate polymer: Potato starch (50 g) was dispersed in 100 mL of purified water to form starch slurry. Borax (12.5 g) and urea (12.5 g) were dissolved separately in 400 mL of purified water and the solution was heated to boiling. While boiling, the starch slurry was added and mixed. Mixing while heating was continued for 10 min to gelatinize starch to form starch-urea-borate polymer. The mass formed was spread on to a stainless steel plate and dried at 80 ºC for 6-8 h. The dried polymer was powdered and passed through mess no. 120.

Preparation of tablets: Matrix tablets of diclofenac (100 mg) and gliclazide (60 mg) were prepared employing starch-urea-borate 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.

Matrix tablets were also prepared employing starch-urea-borate, HPMC, sodium CMC, guar gum and ethyl cellulose at 1:1 ratio of drug: polymer in each case for a comparative evaluation of their release-retarding efficiency.

Hardness of tablets were tested using a monsanto hardness tester. Friability of tablets were 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 drug content in tablets: Drug content of the prepared tablets was estimated by UV spectrophotometric method based on the measurement of absorbance at 276 nm in the case of diclofenac tablets and at 229 nm in the case of gliclazide tablets in phosphate buffer of pH 7.4. The methods were validated for linearity, precision and accuracy. The methods obeyed Beer's law in the concentration range 1-10 µg/mL. The mean error (accuracy) and relative standard deviation (precision) of the methods were in the range 0.5-0.8 %. No interference from the excipients used was observed.

Drug release study: Drug release from 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 in the case of diclofenac and at 229 nm in the case of gliclazide using a Shimadzu UV-150 double beam UV-spectrophotometer. For comparison, drug release from commercial SR tablets in each case 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

Starch-urea-borate was synthesized by gelatinizing potato starch in the presence of borax and urea. The starch-urea-borate 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 210 ºC.

Matrix tablets of diclofenac (100 mg) and gliclazide (60 mg) could be prepared employing different proportions (10, 20, 33 and 50 % concentrations in the formulae) of starch-urea-borate polymer by conventional 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 the drug 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 starch-urea-borate were non-disintegrating with acidic and alkaline fluids, they are considered suitable for oral controlled release.

Release parameters of the diclofenac and gliclazide tablets are summarized in Tables 1 and 2, respectively. With both diclofenac and gliclazide the release from the prepared tablets was slow and spread over 24 h and depended on the concentration of starch-urea-borate polymer. When the release data were analyzed as per zero and first order kinetic models, the best fit with higher correlation ($r > 0.93$) was observed with zero order model indicating that the drug release from all the tablets followed zero order kinetics. As the polymer concentration was increased, release rate was decreased. Good linear relationships was observed between per cent polymer and release rate (K_0) in both the cases. 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 STARCH-UREA-BORATE POLYMER

Formulation	Polymer conc. (%)	% Drug released at various time (h)					T_{50} (h)	T_{90} (h)	K_0 (mg/h)	'n' in peppas eqn.
		1	4	8	12	24				
DF1	10	19.35	52.920	95.60	97.50	97.50	3.50	6.30	12.700	0.732
DF2	20	21.30	49.620	81.87	97.71	97.71	4.05	8.25	9.260	0.635
DF3	33	16.76	36.490	59.08	78.79	99.61	6.15	15.00	5.708	0.588
DF4	50	9.50	24.990	45.75	70.81	99.01	9.00	20.15	4.580	0.736
Reaction SR tablets	–	16.62	37.115	62.65	73.81	99.00	6.00	16.80	4.018	0.573

TABLE-2
GLICLAZIDE RELEASE CHARACTERISTICS OF MATRIX TABLETS FORMULATED EMPLOYING STARCH-UREA-BORATE POLYMER

Formulation	Polymer conc. (%)	% Drug released at various time (h)					T_{50} (h)	T_{90} (h)	K_0 (mg/h)	'n' in peppas eqn.
		1	4	8	12	24				
GF1	10	14.23	34.12	78.65	98.40	–	5.1	11.5	4.70	0.6756
GF2	20	11.16	32.76	67.36	94.63	99.20	5.2	14.0	3.17	0.7123
GF3	33	13.33	29.63	60.70	87.80	96.50	5.6	18.5	2.80	0.6470
GF4	50	13.20	22.56	46.56	71.70	92.00	9.5	22.0	2.23	0.6226
Diamicron MR tablets	–	9.91	19.63	52.31	79.90	96.26	7.6	22.2	2.53	0.6996

When the release data were analyzed as per peppas equation, the release exponent 'n' was found in the range 0.5888-0.7363 indicating non-fickian (anomalous) diffusion as the release mechanism from all the tablets prepared. Plots of per cent released *vs.* square root of time was found to be linear ($r > 0.9523$) with all tablets prepared indicating that the drug release from the tablets was diffusion controlled.

TABLE-3
DRUG RELEASE CHARACTERISTICS OF MATRIX TABLETS
FORMULATED EMPLOYING VARIOUS POLYMERS

Formulation	Polymer	Release parameter			
		T_{50} (h)	T_{90} (h)	K_0 (mg/h)	'n' in Peppas equation
DF4	SUB	9.0	20.15	4.58	0.7360
DF5	HPMC	4.8	9.0	9.54	0.7980
DF6	Sodium CMC	6.2	10.0	8.15	0.8750
DF7	Guar gum	11.4	> 24	2.622	0.5930
GF4	SUB	9.5	22.4	2.23	0.6223
GF5	HPMC	5.2	9.8	4.97	0.6553
GF6	Sodium CMC	9.3	15.4	3.12	0.7731
GF7	Ethyl cellulose	22.4	–	1.20	0.5079

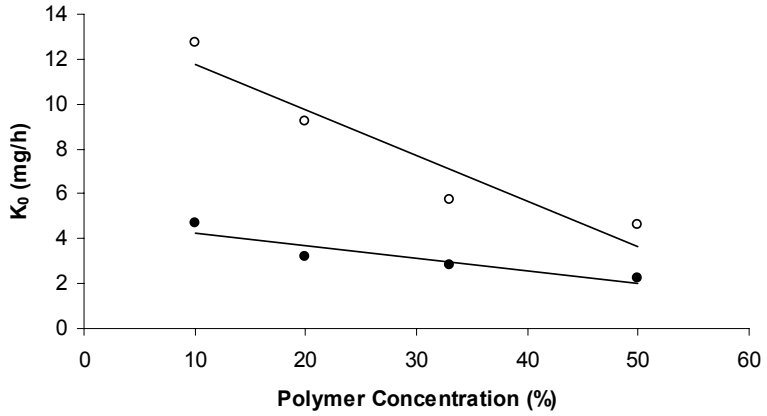

Fig. 1. Relationship between percent polymer and release rate of matrix tablets of diclofenac (**o**) and gliclazide (•) formulated employing starch-urea-borate

Much variations or differences in drug release from the tablets formulated with different polymers were observed in both the cases though all the polymers were used at the same strength *i.e.*, 50 % in the formula. The drug release was relatively rapid in the case of HPMC and sodium CMC and guar gum and ethyl cellulose gave very slow release. Whereas in the case of starch-urea-borate the release was slow, gradual and spread over 24 h. The order of increasing release-retarding effect observed with various polymers was ethyl cellulose = guar gum > starch-urea-borate > sodium CMC > HPMC. Thus starch-urea-borate was found to be a better release-retarding polymer than HPMC and sodium CMC with both diclofenac and gliclazide.

Diclofenac release from matrix tablets DF3 formulated employing 33 % starch-urea-borate was similar to that from Reactin SR tablets, a commercial sustained release formulation of diclofenac. Similarly gliclazide release from matrix tablets

GF4 formulated employing 50 % starch-urea-borate was similar to that from Diamicron MR tablets, a commercial sustained release formulation of gliclazide.

Conclusion

(i) Matrix tablets formulated employing starch-urea-borate, a new starch based polymer are suitable for oral controlled release of diclofenac and gliclazide. (ii) Drug release from the formulated tablets was slow and spread over 24 h and depended on per cent polymer in the tablet. Release was diffusion controlled and followed zero order kinetics. (iii) Non-fickian diffusion was the drug release mechanism from the matrix tablets formulated employing starch-urea-borate. (iv) The order of increasing release retarding effect with various polymers was ethyl cellulose = guar gum > starch-urea-borate > sodium CMC > HPMC. (v) Starch-urea-borate is a better release retarding polymer than HPMC and sodium CMC for obtaining controlled release over 24 h.

REFERENCES

1. M.K. Kottke, H.R. Chuech and C.T. Rhodes, *Drug Dev. Ind. Pharm.*, **18**, 2207 (1992).
2. J. Herman and J.P. Remon, *Int. J. Pharm.*, **63**, 201 (1990).
3. K.A. Kobayashi, L.A. Bauer, J.R. Horn, K. Opheim, F. Jr. Wood and W.A. Kradjan, *Clin. Pharm.*, **7**, 224 (1988).
4. H.P. Rang, M.M. Dale and J.M. Ritter, Pharmacology, Churchill Living Stone, London, edn. 4, p. 230 (1999).
5. C. Kilo, J. Dudley and B. Kalb, *Diabetes Res. Clin. Pract.*, **14**, S79 (1991).
6. T. Higuchi, *J. Pharm. Sci.*, **52**, 1145 (1963).
7. P.L. Ritger and N.A. Peppas, *J. Control. Rel.*, **5**, 37 (1987).

(*Received*: 7 January 2008; *Accepted*: 2 March 2009) AJC-7308