

## Design and Evaluation of Diltiazem Controlled Release Tablets Employing Calcium Starch

K.P.R. CHOWDARY\*, P. TRIPURA SUNDARI and N. NEELIMA

*University College of Pharmaceutical Sciences,  
Andhra University, Visakhapatnam-530 003, India  
Fax: (91)(891)2525611; Tel: (91)(891)2844925  
E-mail: profkprc@rediffmail.com*

The objective of the present investigation is to synthesize calcium starch, a new starch based polymer and to evaluate its application in controlled release and in the design of diltiazem 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 90 mg of diltiazem hydrochloride were formulated employing calcium starch polymer in different proportions of drug and polymer and the tablets were evaluated. Diltiazem release from the formulated tablets was slow and spread over 24 h and depended on per cent polymer in the tablet. Fickian diffusion was the drug release mechanism from the formulated tablets. Diltiazem release from matrix tablets F3 formulated employing 15 % calcium starch and F4 formulated employing 20 % calcium starch were similar to that from diltiazem SR and DTM 90 SR tablets respectively. Calcium starch polymer was found suitable for the design of oral controlled release tablets of diltiazem.

**Key Words:** Calcium starch, Controlled release, Diltiazem, 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, 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<sup>1,2</sup>, 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. Matrix tablets of diltiazem were formulated

employing calcium starch and evaluated for controlled release and to design diltiazem controlled release tablets. Diltiazem is an orally active calcium channel blocking agent effective in angina and in the management of hypertension. Diltiazem has a relatively short biological half life<sup>3</sup> of 3-4 h. Because of this and rather high frequency of administration, it is necessary to develop controlled release preparations with extended clinical effect. A few controlled release formulations of diltiazem are available commercially. The high solubility of diltiazem is a major challenge in designing its controlled drug delivery systems. The extreme release retarding ability of calcium starch is utilized to overcome this problem.

### EXPERIMENTAL

Diltiazem hydrochloride is a gift sample from M/S Micro Labs., Pondicherry, India. All other materials used were of Pharmacopoeial grade.

**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 and mixing was continued for 0.5 h 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 h to precipitate calcium starch formed. The calcium starch formed was collected by vacuum filtration, washed repeatedly with water and dried at 80 °C. The dried polymer was powdered and passed through mesh no. 100.

**Preparation of tablets:** Matrix tablets each containing 90 mg of diltiazem hydrochloride 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 dough mass. The mass was passed through mesh no. 12 to obtain wet granules. The wet granules were dried at 60 °C for 2 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 thermionic tablet disintegration test machine using water, 0.1 N HCl and phosphate buffer of pH 7.4 as test fluids.

**Estimation of diltiazem:** Diltiazem content of the tablets was estimated by UV spectrophotometric method based on the measurement of absorbance at 240 nm in distilled water. The method was validated for linearity, precision and accuracy.

The method obeyed Beer's Law in the concentration range 1-10 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  $37 \pm 1$  °C. Distilled water (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 240 nm for diltiazem using a Shimadzu UV-150 double beam UV-spectrophotometer. For comparison, diltiazem release from Dilzem SR and DTM 90 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<sup>4</sup> and Peppas<sup>5</sup> models to assess the drug release kinetics and mechanism from the tablets prepared.

## 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 °C.

Matrix tablets each containing 90 mg of diltiazem hydrochloride could be prepared employing different proportions (5, 10, 15, 20 and 40 % 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/cm<sup>2</sup>. Weight loss in the friability test was less than 0.4 % in all the cases. All the matrix tablets prepared contained diltiazem within  $100 \pm 3$  % 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 prepared are summarized in Table-1. Diltiazem release from the prepared tablets was slow and spread over 24 h and depended on the concentration of calcium starch polymer in the tablets. Analysis of the release data as per zero and first order kinetic models indicated that the drug release from the matrix tablets formulated employing calcium starch followed first order kinetics. The correlation coefficient ( $r$ ) values were higher in the first order model than in the zero order model. When the release data were analyzed as per Peppas equation, the release exponent 'n' was found in the range 0.291-0.482 indicating fickian

TABLE-1  
DILTIAZEM RELEASE CHARACTERISTICS OF MATRIX TABLETS  
FORMULATED EMPLOYING CALCIUM STARCH POLYMER

Formulation	Polymer conc. (%)	% Drug released at various times (h)					T <sub>50</sub> (h)	T <sub>90</sub> (h)	K <sub>1</sub> (h <sup>-1</sup> )	'n' in peppas equation
		1	4	8	12	24				
F1	5	47.91	88.22	100.0	100.0	100.0	1.12	4.24	0.539	0.386
F2	10	38.45	78.55	87.38	92.75	100.0	1.36	10.00	0.225	0.349
F3	15	30.91	64.75	80.05	87.25	100.0	2.24	14.36	0.163	0.371
F4	20	19.85	56.88	74.48	82.32	100.0	3.00	17.00	0.133	0.453
F5	40	14.75	18.23	21.90	26.85	35.2	> 24	> 24	0.014	0.291
DTM 90 SR	–	23.09	49.75	67.99	87.08	100.0	4.06	13.00	0.153	0.482
Dilzem SR	–	25.98	55.74	80.90	90.05	95.02	3.12	12.00	0.192	0.426

diffusion as the release mechanism from all the matrix tablets prepared and commercial. Plots of per cent released *versus* square root of time were found to be linear ( $r > 0.919$ ) with all tablets prepared indicating that the drug release from these tablets was diffusion controlled.

As the polymer concentration was increased, release rate was decreased. Good linear relationships were observed between percent polymer in the tablets and release rate K<sub>1</sub> (Fig. 1). Thus drug release from the matrix tablets could be controlled by varying the proportion of drug and polymer in the matrix.

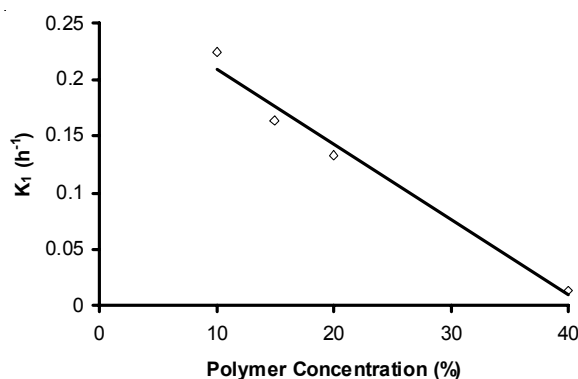


Fig. 1. Relationship between per cent polymer and release rate (K<sub>1</sub>) of diltiazem matrix tablets formulated employing calcium starch

For comparison, diltiazem release from two commercial controlled release tablets was also studied. Drug release profiles of formulated and commercial controlled release 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 two drug release profiles. The results indicated that the release profiles of the two commercial controlled release products tested were similar with  $f_1$  value of 9.16 and  $f_2$  value of 142.6. The

release profiles of formulation F3 and dilzem SR were similar with  $f_1$  value of 6.49 and  $f_2$  value of 136.4. Similarly the release profiles of formulation F4 and DTM 90 SR were similar with  $f_1$  value of 6.69 and  $f_2$  value of 135.8. Matrix tablets formulated employing calcium starch (F3 & F4) are comparable to the commercial controlled release products and hence these tablets are considered suitable for oral controlled release of diltiazem over 24 h.

### Conclusion

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

(2) Diltiazem release from the formulated tablets was slow and spread over 24 h and depended on percent polymer in the tablet. Fickian diffusion was the drug release mechanism from the formulated tablets.

(3) Diltiazem release from formulations F3 and F4 formulated employing 15 and 20 % calcium starch was similar to that from dilzem SR and DTM 90 SR tablets, two commercial controlled release products of diltiazem, respectively.

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

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*Contact:*

Dr. Kumi Yoshida Graduate School of Information Science,  
Nagoya University, Chikusa Nagoya, 464-8601, Japan.

Tel&Fax:+81-52-789-5638,

e-mail:yoshidak@is.nagoya-u.ac.jp,

web site <http://www.is.nagoya-u.ac.jp/IWA2009/>