Drug Development and Industrial Pharmacy, 23(6), 567–574 (1997)

RESEARCH PAPER

Development and Evaluation of Controlled-Release Diltiazem HCl Microparticles Using Cross-Linked Poly(Vinyl Alcohol)

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ABSTRACT

Hydrogels of cross-linked poly(vinyl alcohol) (PVA) were developed and their properties were evaluated as a controlled-release oral solid dosage form. The concentration of glutaraldehyde involved in cross-linking is directly proportional to the compactness of the three-dimensional networks of the cross-linked PVA. The theoretical calculations reveal that the release of diltiazem HCl from PVA could be described by the combination of Fickian and diffusion-controlled models. The confirmation of cross-linking was done by differential scanning calorimetry and infrared spectroscopy. The microparticles show lower percentage compressibility but good flowability, hence a capsule dosage form was thought to be suitable. The toxicity level of PVA was confirmed to be 10 g/kg body weight. The microparticle formulation was optimized with respect to size distribution and increased drug loading. The microparticles were physically evaluated with respect to bulk density, angle of repose, and percent compressibility. The microparticles released a drug for 12 hr. The microparticles had a drug loading of 61% to 67%.

Key Words: *Cross-linking density; Diltiazem; Glutaraldehyde; Microparticles; Poly(vinyl alcohol).*

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INTRODUCTION

Diltiazem has gained acceptance in the treatment of various cardiovascular diseases such as angina pectoris, cardiac arrhythmias and hypertension (1). The usual dose of diltiazem in adults is 30 mg 4 times a day. The maximum dose that can be consumed daily is 360 mg (2).

None of the conventional formulations are able to keep the plasma concentration of diltiazem in the therapeutic range for a long time duration owing to the drug's short biological half-life, and repeated administration of conventional formulations will produce too many peaks and valleys in the plasma concentration versus time profile (3). Hence, to maintain plasma concentration in the therapeutic range, many attempts have been made to sustain the therapeutic concentration of diltiazem. The sustained-release formulations have advantages of patient compliance, and the release is less variable and less dependent on gastric transit time. The use of sustained-release formulations will improve the efficiency of treatment.

This paper reports the development and evaluation of controlled-release diltiazem microparticles. The method of preparation of diltiazem microparticles involves in situ cross-linking of poly(vinyl alcohol) using glutaraldehyde as cross-linking agent. Various batches were made to optimize the release pattern and the best ones were chosen. The release pattern of drug from microparticles is inversely proportional to cross-linking density of PVA, and concentration of glutaraldehyde is directly proportional to cross-linking density of PVA; hence effect of glutaraldehyde is observed on various parameters. The parameters considered are: (i) drug loading in microparticles, (ii) particle size, (iii) swelling kinetics, (iv) bulk density, (v) compressibility, (vi) angle of repose, and (vii) in vitro release pattern.

MATERIALS AND METHODS

Materials used were:

Diltiazem HCl: acquired from Intas Pharmaceuticals Ltd., Ahmedabad, India.

Poly(vinyl alcohol): Vam Organic Chemicals Ltd., Ahmedabad; MW = 60,000–80,000, n = 1700, 88% hydrolyzed.

Glutaraldehyde: S. D. Fine Chemicals, Boisar, India.

Preparation of Microparticles

The preparation of diltiazem microparticles involves cross-linking of PVA with glutaraldehyde 25% w/v as cross-linking agent.

A 15% w/v solution of PVA was prepared in distilled water. To the solution (10 g), 2 ml of methanol was added with stirring followed by 1 ml of 1% w/v solution of sulfuric acid. To this solution, 5.2 g of diltiazem HCl was added with stirring. Stirring was continued until all drug was dissolved. Adequate quantity of glutaraldehyde was then added to this mixture. The beaker was kept at room temperature for 12 hr to allow cross-linking of poly(vinyl alcohol) to take place. The contents of the beaker were then subjected to 60°C temperature in an oven for 6 hr to promote cross-linking. The resulting hydrogel was then ground and washed with water for seven to eight times to remove unreacted glutaraldehyde and sulfate ions. The ground particles were then dried to constant weight at 40° to 50°C, and particle size fractions of 0.105–0.25, 0.25–0.35, and 0.35–0.71 mm were separated by sieving.

Determination of Drug Content

To determine the yield and efficiency of drug loading, microparticles were analyzed for drug content. Microparticles, 100 mg, were crushed to give fine powder, distilled water was added, and the solution kept for 12 hr. After 12 hr, the solution was sonicated for 30 min. The solution was then filtered through Whatmann filter paper No. 1. Two milliliters of clear filtrate was diluted to 100 ml with distilled water. The absorbance of the solution was measured on a Hitachi U 2000 double-beam UV–VIS spectrophotometer at 237 nm using distilled water as blank. The standard curve of diltiazem HCl was recorded in distilled water for the exact concentration.

Physical Evaluation of Microparticles

1. *Particle size distribution studies of microparticles*: The particle size distribution studies were carried out by the sieving technique and three fractions of particle size ranges 105–250 μm, 250–350 μm, 350–710 μm were separated.
2. *Bulk density*: The term "bulk density" refers to a measure used to describe a packing of particles or granules. Both loose and tapped bulk densities were determined (4).

a. Loose bulk density = mass of powder/volume of packing
b. Tapped bulk density = mass of powder/tapped volume of packing
c. Weighed amounts of microparticles were taken in a 10-ml measuring cylinder after shaking lightly to break any agglomerates. After observing the initial volume of microparticles the cylinder was allowed to fall under its own weight on a hard surface from the height of 2–5 cm. The tapping was continued at a rate of 120 taps/min until no further change in volume was noted.

3. *Compressibility*: This is the value useful in prediction of flowability. The % compressibility of microparticles was calculated using the following formula (5):

$$C = \frac{pb - pu}{pb} \times 100$$

where pb = tapped bulk density; pu = loose bulk density.

4. *Angle of repose*: Angle of repose for microparticles was calculated using the formula:

$$\Theta = \tan^{-1}(h/r)$$

where h = mean height; r = mean radius. The coefficient of friction (α) value was calculated from the angle of repose value using the formula: $\alpha = \tan \Theta$.

5. *Swelling studies*: Swelling studies of microparticles having different cross-linking densities were carried out in simulated conditions of gastrointestinal tract. The microparticles (100 mg) were first kept in 0.1 N HCl pH 1.2 for 2 hr. Then the fluid was replaced by 50 ml phosphate buffer pH 7.6 and the microparticles were kept for 24 hr at 37°C. The fluid content (%) and equilibrium fluid content (%) of microparticles were calculated (7).

In Vitro Drug Release Studies of Diltiazem HCl Microparticles

In vitro release studies for diltiazem microparticles were carried out with the USP XXI dissolution test apparatus using the rotating basket method (8,9). Volume of dissolution media used was 900 ml. For the first 2 hr a 0.1 N HCl pH 1.2 solution was used as dissolution medium to simulate the gastric pH. From 2 hr onwards phosphate buffer pH 7.6 was used as dissolution medium to simulate the intestinal pH. The basket speed was kept at 50 ± 1 rpm. Aliquots of 5 ml of dissolution media were withdrawn from the dissolution vessel at interval of 15 min for 1 hr and hourly thereafter. After withdrawal of a sample, an equal volume of fresh dissolution medium was added to maintain a constant volume of 900 ml. The samples were analyzed spectrophotometrically at 237 nm.

RESULTS AND DISCUSSION

Preparation of Diltiazem Microparticles

A concentration higher than 15% poly(vinyl alcohol) solution was found to hinder the ease of mixing of drug, the cross-linking agent, and the catalyst. Two milliliters of methanol was found to be optimum in preventing the formation of hydrogel for about 10 min after mixing all the ingredients. The amount of glutaraldehyde was kept as low as possible without compromising the cross-linking density at a maximum level of 8.1% of the formulation ingredients since further increase in glutaraldehyde content led to higher proportion of unreacted glutaraldehyde in the final hydrogel without significant increase in the substance of the drug release. Slow and complete cross-linking of the PVA was found to give a more uniform and denser network where the drug was tightly held in the hydrogel network. Various batches were prepared with varying percentages of glutaraldehyde (Table 1).

Confirmation of Cross-Linking in Poly(Vinyl Alcohol) Using DSC and IR Spectroscopy

The cross-linking of PVA macromolecular chains using glutaraldehyde is proven by using differential scanning calorimetry (DSC). The DSC thermogram of pure PVA shows that

1. The T_g of the polymer at 43.86°C has an enthalpy of 0.17 J/g degree.
2. The decomposition endotherms occur at 120°–150°C and at 180°–200°C.

The DSC thermograms of PVA with varying degrees cross-linking were studied and the endotherms and enthalpies were:

Table 1

Various Batches with Drug Loading Data

Sr. No.	Batch No.	Drug (g)	PVA (g)	Glutaraldehyde (g)	Content (%)		Loading Efficiency (%)
					Theoretical	Actual	
1	B1	5.2	1.5	0.1	76.47	65.0	85
2	B2	5.2	1.5	0.2	75.36	64.8	85.98
3	B3	5.2	1.5	0.3	74.28	66.2	89.12
4	B4	5.2	1.5	0.4	73.24	61.9	84.51
5	B5	5.2	1.5	0.5	72.22	60.9	84.32
6	B6	5.2	1.5	0.6	71.23	61.3	86.06

Endotherm (°C)	Enthalpy (J/g)	Sample No.
151.01	147	1
130.8	184.94	2
131.73	200.56	3
134.56	203.71	4

The absence of the broad decomposition peaks present in pure polymer indicate that PVA is not present in the samples in the free form. On the other hand, the presence of a sharp peak in the 130°–150°C region indicates the melting of a highly ordered structure that has an enthalpy of 147 to 203 J/g (Fig. 1 shows only one thermogram of polymer and sample 1). This means that there is a cross-linked structure present in the sample which requires increasing energy to break as the cross-linking density increases. In other words, the sample having a higher cross-link network and a more stable structure requires more energy to break itself; hence the increase in the enthalpy as we go from sample 1 to sample 4.

Cross-linking was confirmed using IR spectroscopy. It has been reported that PVA undergoes cross-linking at the hydroxyl groups on reaction with glutaraldehyde (10). Hence cross-linked PVA is expected to show considerable decrease in its hydroxyl content. This reduction in hydroxyl content is reflected in the IR spectro-

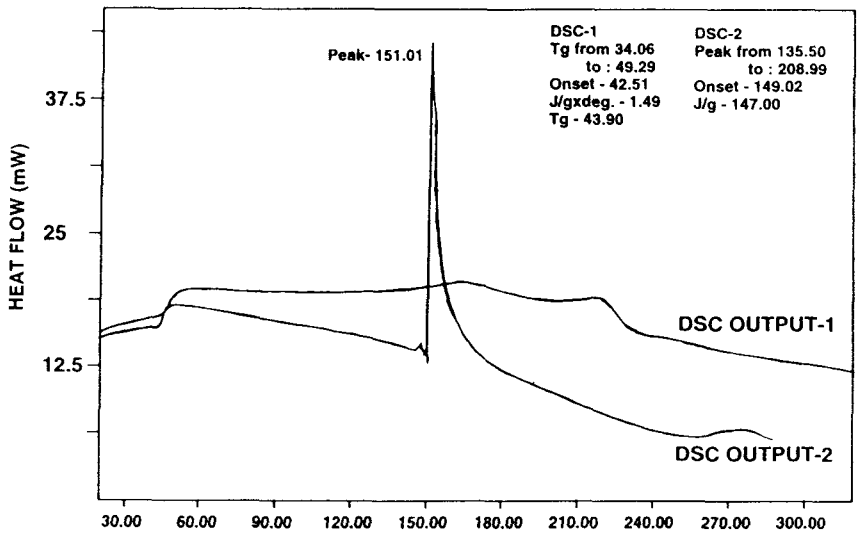

Figure 1. DSC output for confirming cross-linking of poly(vinyl alcohol).

Figure 2. Comparative IR spectra for cross-linking confirmation.

scopic studies on pure polymer, which show a broad peak characteristic of the hydroxyl group stretching vibration in the 3000–3600 nm region of the IR spectrum; this is significantly reduced in sample spectra (Fig. 2).

Unreacted glutaraldehyde was detected by high-performance liquid chromatography (HPLC). The glutaraldehyde shows 2 peaks at retention times of 2.44 min and 4.067 min. These peaks were found to be absent in washed microparticles but seen in unwashed microparticles (Fig. 3).

Drug Content of Microparticles

The main objective of the study is to prolong the release of drug from microparticles, which was made possible by use of the cross-linking agent glutaraldehyde; and hence concentration of glutaraldehyde has an effect on drug content or drug loading of microparticles. Concentration of glutaraldehyde is directly proportional to cross-linking density of PVA, and drug loading is inversely proportional to cross-linking density of PVA.

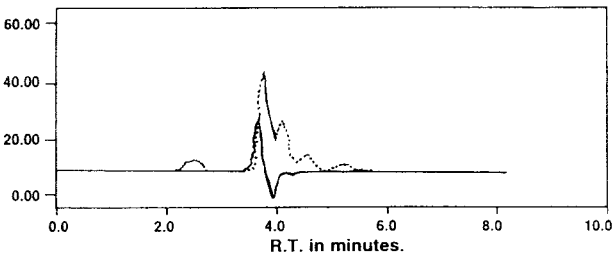

Figure 3. HPLC chromatograms indicating absence of glutaraldehyde in cross-linked polymer.

From Table 1 it is clear that as % glutaraldehyde increases, the drug loading of the batch decreases.

Compressibility, Bulk Density, and Angle of Repose

The results of compressibility and bulk density are given in Table 2. The microparticles show lower % compressibility, with a maximum of 19% compressibility. Since powders having % compressibility less than 20–21 have good flowability, the microparticles can be said to have good flowability.

For most pharmaceutical powders, the angle of repose values ranges from 25 to 45 (10), with decrease in values indicating better flowability. The angle of repose of batches B1 to B6 is in the range of 20.78 to 36.48; hence they can be said to have acceptable flow characteristics. Results are tabulated in Table 2.

Swelling Kinetics

The rate of fluid uptake is significantly different from batch B1 to B6. The observed difference in swelling kinetics of various batches seems to be due to a decrease in the free hydroxyl groups of polymer at higher crosslinking densities, which makes the hydrogel less hydrophilic and consequently there is less swelling. The swelling kinetics of PVA hydrogels can therefore also be used to characterize the extent of cross-linking and may prove useful in predicting the drug release since there is a direct correlation between the decrease in the drug release with decrease in the swelling kinetics of microparticles on increase in the crosslinking density (Table 3) and (Fig. 4).

Table 2

Physical Evaluation of Microparticles

Batch	Fraction Size (μm)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Angle of Repose (tan Θ)	Percent Compressibility
B1	105–250	0.34	0.41	32.39	18.46
	250–350	0.32	0.39	30.48	18.53
	350–710	0.31	0.37	23.52	14.15
B2	105–250	0.4	0.49	31.27	18.8
	250–350	0.31	0.4	32.15	18.24
	350–710	0.35	0.42	21.6	16.49
B3	105–250	0.3	0.39	31.4	19.21
	250–350	0.33	0.4	24.22	15.67
	350–710	0.38	0.47	20.78	19.01
B4	105–250	0.37	0.45	36.48	17.41
	250–350	0.32	0.39	31.53	17.21
	350–710	0.35	0.42	24.38	16.67
B5	105–250	0.35	0.43	33.61	16.96
	250–350	0.36	0.43	28.3	17.27
	350–710	0.33	0.38	22.75	13.77
B6	105–250	0.33	0.4	33.75	18.15
	250–350	0.36	0.44	26.28	17.09
	350–710	0.31	0.38	22.33	17.96

Table 3

Swelling Kinetics Studies of Drug-Loaded Microparticles (Fluid Uptake % for Batches B1 to B6)[a]

Sr. No.	Time (min)	B1	B2	B3	B4	B5	B6
1	30	14.7	16.2	10.1	7.14	8.2	4.2
2	60	31.3	27.1	12.7	9.6	10.7	6.3
3	120	42.1	31.9	14.4	11.4	13.4	10.4
4	180	49.9	35.9	17.5	16.0	19.6	15.1
5	240	54.1	41.4	19.0	23.1	20.4	21.3
6	300	59.1	44.6	24.6	26.5	22.1	22.1
7	360	63.6	57.1	31.3	31.9	25.2	26.2
8	420	66.4	61.5	39.1	38.7	34.4	31.4
9	480	71.2	65.6	42.4	41.1	36.0	34.1
10	540		66.8	46.1	44.5	39.7	36.4
11	600			52.6	45.1	42.0	39.9
12	660						41.7
13	720						43.1

[a]The last value for each batch indicates equilibrium fluid content % (EFC%).

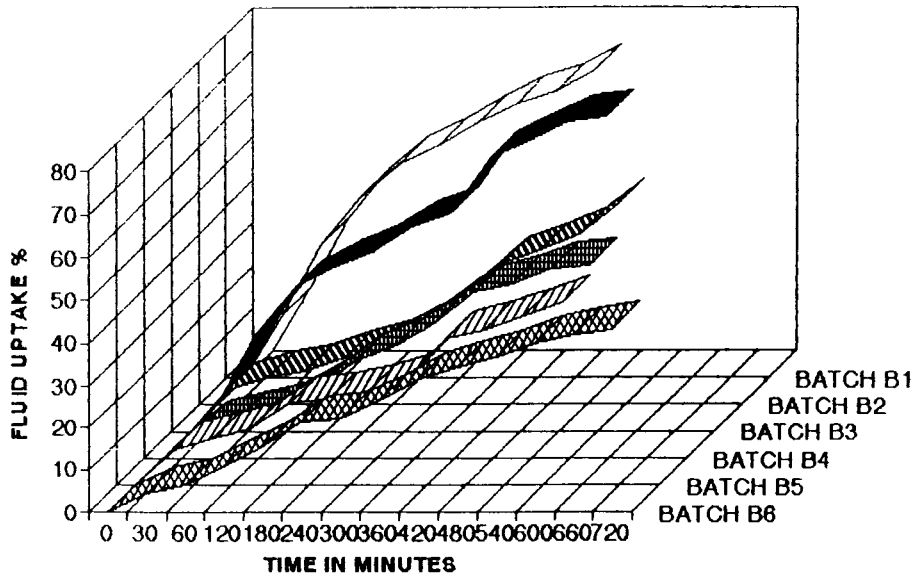

Figure 4. Swelling kinetics of microparticles.

Table 4

T_{30}, T_{50}, and T_{90} Values for Various Batches of Microparticles

Sr. No.	Batch No.	Fraction Size (μm)	T_{30} (min)	T_{50} (min)	T_{90} (min)
1	B1	105–250	99	157	305
2		250–350	99	165	330
3		350–710	118	186	354
4	B2	105–250	125	187	400
5		250–350	128	245	448
6		350–710	135	256	503
7	B3	105–250	153	236	421
8		250–350	182	257	480
9		350–710	201	281	537
10	B4	105–250	174	255	471
11		250–350	205	276	495
12		350–710	208	295	545
13	B5	105–250	174	315	570
14		250–350	220	320	591
15		350–710	223	370	597
16	B6	105–250	162	300	647
17		250–350	209	401	672
18		350–710	264	415	686

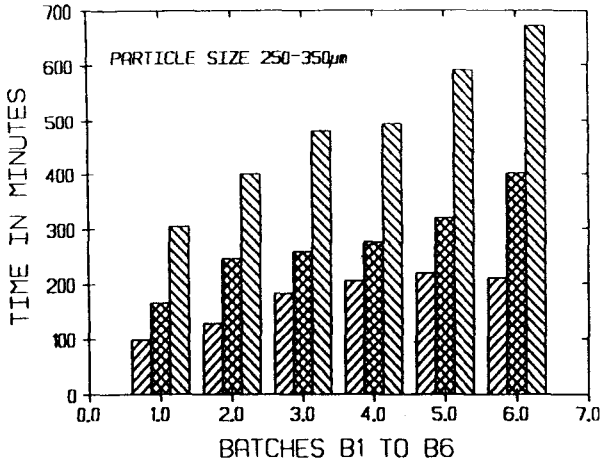

Figure 5. Comparison of drug release at T_{30}, T_{50}, and T_{90}.

In Vitro Release from Microparticles

The in vitro drug release showed that as amount of glutaraldehyde went on increasing, there was a further prolongation in drug release. For batch B1 (fraction 0.25–0.35 mm), the T_{30} is 99 min; T_{50} is 165 min; T_{90} is 330 min. In the case of batch B6, T_{30} was 209 min, T_{50} was 401 min, and T_{90} was 672 min. See Table 4 and Figs. 5 and 6.

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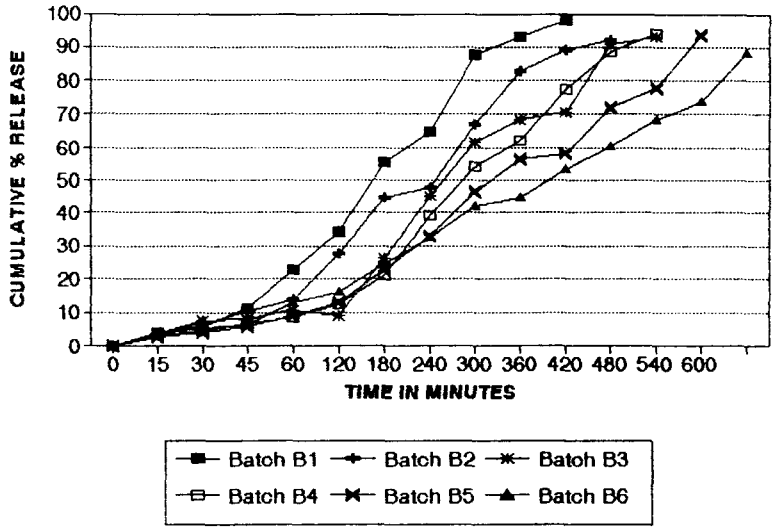

Figure 6. Drug release: comparison of batches B1 through B6.