Development and *in vitro* Assessment of Multiparticulate sustained release formulation of Diltiazem Hydrochloride

BIJAYA GHOSH**, C. MALLIKARJUN SETTY[1] AND JASMINA KHANAM[2]*
[1]Department of Pharmaceutics, V.L. College of Pharmacy, Raichur, Karnataka - 584 101
[2]Department of Pharmaceutical Technology, Jadavpur University, Calcutta-700 032

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Diltiazem sustained release pellets were prepared by pan-coating process using nonpareil sugar cores of appropriate size. The drug was dispersed in melted stearic acid (1:1), and the mixture was loaded on the basic sugar cores using polyvinylpyrrolidone (PVP, 10% w/v in water) as the binder. The drug-loaded beads were then coated with ethylcellulose coating solution. Dissolution test was carried out in hydrochloric acid media of pH 1.2 (0.085 M) for the first two hours and then the media was replaced by phosphate buffer of pH 7.2 (0.05 M). The release pattern was diffusion controlled for the formulations having lesser amount of ethylcellulose (SA I, ethylcellulose content 9.09% of the total wt) but shifted towards zero order with the increase in the proportion of ethylcellulose in the formulations. A near zero-order release profile was obtained in formulations having higher amount of ethylcellulose (SA IV, 28.57% w/w) which was able to sustain the drug-release upto 12 h.

Diltiazem hydrochloride, an effective drug in the treatment of ischaemic heart diseases is also used in the treatment of hypertension[1,2]. Among the calcium channel blockers, diltiazem occupies a superior position because of its highly favourable side effect profile [3]. Apart from its role in hypertension, diltiazem is also reported to reduce the cost of treatment in organ transplantation by its potentiating effect of cyclosporine activity[4-6]. However, due to short half life of the drug (3.7±1.2 h) high frequency dosing is necessary to satisfy the requirements of persistent medication. Sustained release formulations of diltiazem are considered to be more effective in comparison to its conventional dosage forms, because of the maintenance of plasma level and improved patient compliance, significant factors in the management of hypertension[7]. The present study describes the development and *in vitro* evaluation of a multiparticulate sustained release formulation of diltiazem hydrochloride using the pan-coating process.

***For Correspondence**
****Present Address : S.B.S. (P.G) Institute of Biomedical Science & Research, Balawala, Dehradun-248 161**

Diltiazem hydrochloride (USP) was received as a gift sample from Torrent Laboratories Ltd. Ahmedabad, India. The other ingredients purchased were ethylcellulose (14 cp) and diethylphthalate from Central Drug House, Bombay; Stearic acid from S.D. Fine Chemicals, Boisar; Chloroform and acetone from Qualigens Fine Chemicals, Bombay. The sugar used for making the nonpareil cores were purchased from local market and estimated for conformity with IP grade. Hydrochloric acid and phosphate buffers were prepared by using the prescribed procedure of Indian Pharmacopoeia[8]. All other chemicals used were of analytical grade. Nonpareil sugar cores were prepared by spraying super-saturated hot syrup over finely powdered sucrose particles rotating in a coating pan to yield very hard sugar cores[9]. The size fraction 450-500 μm was chosen as the core material for drug loading. The drug was dispersed in melted stearic acid (1:1,80°) and the mixture after cooling was passed through a sieve (#44) to get free flowing particles. Sucrose cores (20 g) were taken in a coating pan (diameter 26.4 cm) rotating at 32 rpm and adhesiveness was developed by spraying polyvinylpyrrolidone solution (PVP, 10% w/v water). Strearic acid-coated drug particles were then sprinkled

Table I - Physical parameters of the sustained release pellets

Formulation	Core:Coat	Particle size (μm)	Mean bulk density (g/ml)	Angle of repose (Degress)	Friability (%)
SA I	10.0 : 1	740 ± 36.5	0.694	21.37	0.02
SA II	5.0 : 1	769 ± 23.7	0.672	21.38	0.02
SA III	3.3 : 1	833 ± 130.0	0.655	21.16	0.01
SA IV	2.5 : 1	909 ± 52.7	0.649	20.69	0.01

Particle size represents mean ± S.D of 50 observations.
All other values are average of three determinations.

Table II - Content uniformity of sustained release pellets

Formulation	Expected drug content in 100 mg of pellets (mg)	Actual drug content in 100 mg of pellets (mg)	Yield in terms of drug (%)	Coefficient of variation
SA I	17.045	13.265 ± 0.151	77.82	1.138
SA II	15.625	12.302 ± 0.179	78.73	1.382
SA III	14.423	11.666 ± 0.129	80.90	1.106
SA IV	13.392	10.651 ± 0.079	79.53	0.742

Each value represent the mean ± S.D. of five determinations.

over the cascading pellets and the process of alternate application of drug and binder was continued till the predetermined amount of the drug mixture had been loaded. Finally ethycellulose (5% w/v in chloroform) plasticized with diethylphthalate (5% w/w of the polymer) was sprayed over the cascading pellets until the predetermined weight gain in the pellets was achieved. Best coating was produced when the spraying was done for every 20 sec followed by a rest period of 2 min dry off the pellets. Initially drying was rapid and SA I fraction could be prepared within 2 h with the increment in the particle size, increased number of spraying was required to deposit the same amount of coating material and longer rest periods (2.5-5 min) allowed to dry off the solvent. No extra heating facility was provided to assist the vaporisation of chloroform but the drying was facilitated by the high room temperature which varied between 28-33°. Pellets of different core:coat ratio's were prepared from the same starting batch as described by Cartensen[10]. For the determination of the moisture content the standard IP procedure was followed[11].

Spectrophotometric analysis was performed using a scanning ultraviolate-visible-stectrophotemeter (U-2000, Hitachi, Japan) Beers law calibration curves were obtained in hydrochloric acid of pH 1.2 (0.085 M) as well as phosphate buffer of pH 7.2 (0.05 M) for the dissolution studies. Drug content and homogeneity of the different formulations were determined by spectrophotometric assay, after removal of five 100 mg samples from each formulations and extracting the same in phosphate buffer by crushing the pellets. Dissolution study was carried out in a USP XXI Dissolution apparatus (M/S Cambell electronics). the Paddle rotation was adjusted to 100 rpm and temperature was maintained at 37±1° throughout the span of the experiment. Hydrochloric acid buffer of pH 1.2 (0.085 M) was used for the first two hours of drug release. At the end of second hour, the dissolution fluid was replaced by phosphate buffer pH 7.2 (0.05 M) and the study was continued upto 12 h or till completion of drug release.

Physical parameters of the various fractions, presented in the Table-1, clearly indicate that the pellets have

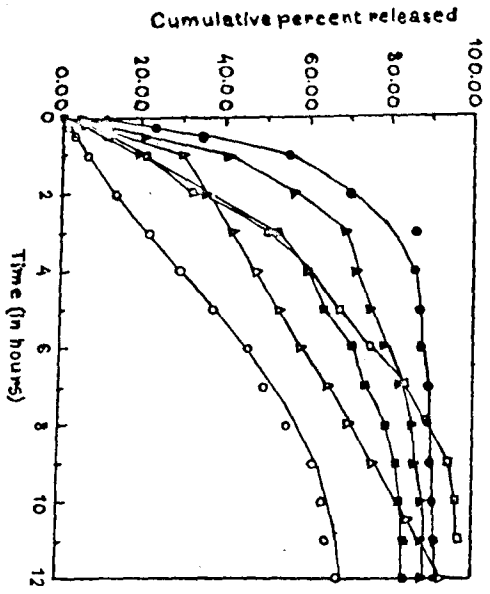

Fig. 1 : Comparison of drug release from various experimental formulation with that of marketed product and the theoretical release profile

Key : •,SA I; ◇, SA II; □, SA III;○, SA IV; □, Dilzem SR-90 (marketed product), Δ, Theoretical release profile

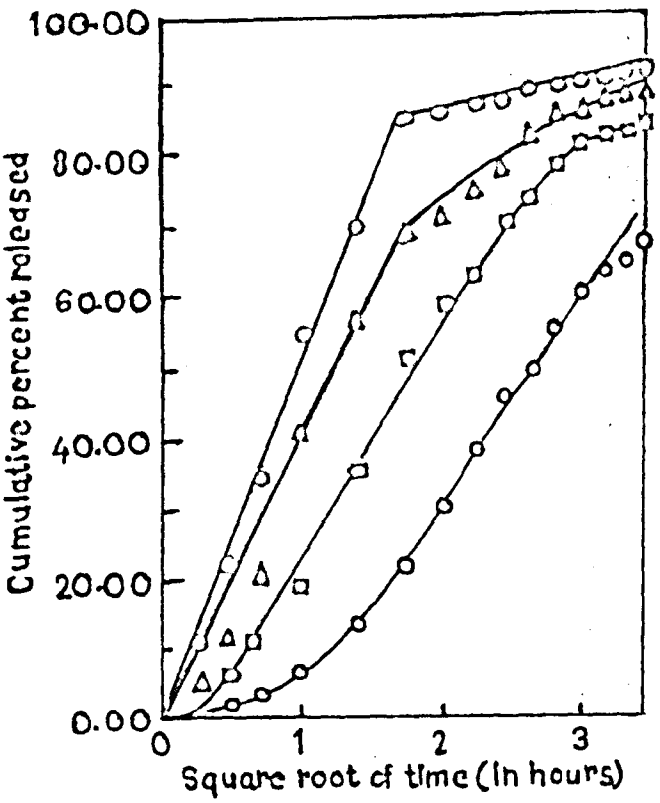

Fig. 2 : Higuchi plot for the release profile of diltiazem hydrochloride.

Key : ·, SA I; Δ, SA II; □ SA III; O, SA IV.

good flowability and can be easily encapsulated in hard gelatin capsule. It is evident from Table-2 that there is good reproducibility between the batches and the drug content was nearly 80% of the theoretical value. Since the drug loading was done with PVP and coating procedure involves the use of chloroform, moisture content determination was carried out on the drug loaded pellets only. These values, when converted in terms of total weight of the pellets, were found to vary between 3.5 to 4.5% of the final preparation, with SA IV containing the least amount of moisture (3.5%). The results of the *in vitro* dissolution study was summarised as the cumulative release versus time graph in Figure 1, which clearly shows that the rate of drug release decreases with the increase of coating thickness. All the formulations except SA IV showed high rate of drug release in the initial phase of dissolution. However, the rate declined drastically after 70-75% of total content had been released. Of the formulations Sa IV was found to give the most sustained effect and was closest of the zero order pattern. In none of the formulations, complete release was obtained and the tendency of incomplete release increased with the increase in the proportion of ethylcellulose used in the system. In case of SA IV only 67% of the total drug was released upto 12 h.

Fig. 2 To investigate the mechanism of drug release the *in vitro* data were plotted as cumulative release versus square root of time (Figure 2) as described by Higuchi[12]. Since linearity was observed in these graphs, diffusion controlled release is the logical inference. However, with the increase in the proportion of ethylcellulose in the formulation the release profile showed a shift towards the zero order pattern. SA IV formulation showed the highest zero order correlation coefficient of 0.9874 and could sustain the drug release upto 12 h. The release profile of the experimental formulations were also compared to that of the marketed product Dilzem SR-90 as well as theoretical release profile (Figure 1). The theoretical release profile was worked out by using the available pharmacokinetic data (Vd = 3.1±1.2 L/kg, $t^1/_2$ = 3.7+1.2, bioavailability 40-44%) [13,14]. The calculated total dose was 90 mg for a period of 12 h including the loading dose of 30 mg. As expected there were deviations from the theoretical release profile but SA II formulation showed close resemblance to the marketed product and its

cumulative release was always on the plus side of the theoretical requirement. SA IV formulations showed the most sustaining effect but its release constant (k=6.09 per h) is slightly lesser than the theoretical requirement (k = 8.19 per h). However, there is scope for correction by making allowance for extra drug (30 mg) or by modification of the formulation parameters.

We conclude that stearic acid and ethylcellulose can be used in combination to produce oral sustained release dosage form of diltiazem hydrochloride.

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Visible Spectrophotometric Method for the Determination of Salmeterol Xinafoate

K.P.R. CHOWDARY* AND G. DEVALA RAO
Sidddartha College of Pharmaceutical Sciences,
Vijayawada - 520 010, A.P.

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A simple and sensitive visible spectrophotometric method based on the reaction of salmeterol xinafoate with diazotised dapsone under alkaline conditions to form a stable orange colored chromogen, which can be quantitatively measured at 465 nm, is reported.

Salmeterol xinafoate[1,2] chemically (RS-5-{1-Hydroxy-2-[6(4-phenyl butoxy) hexylamino] ethyl} salicyl alcohol 1-hydroxy-2-naphthoate, is a relatively new long acting antiasthmatic drug. HPLC[3-6] and few spectrophotometric method[7,8] have been reported earlier for the determination of salmeterol in human plasma and in pharmaceutical dosage forms. In the present investigation, the authors have developed a simple, sensitive spectrophotometric method.

* For Correspondence

A 1.0 mg/ml solution of salmeterol xinafoate in methanol was prepared. Working standard solution (100 µg/ml) was prepared by further dilution with distilled water. Aqueous solutions of sodium nitrite (3% w/v), sodium hydroxide (1N) and solution of dapsone (0.5% w/v) in 10% hydrochloric acid were prepared in the usual way. An ELICO UV-VIS spectrophotometer model SL-150 with 1 cm matched quartz cells was employed for spectral measurements.

One ml of dapsone solution was pipetted out into a series of 10 ml volumetric flasks, 1 ml of sodium nitrite