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Formulation and Release Characteristics of Sustained Release Diltiazem Hydrochloride Tablet

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Diltiazem hydrochloride was tried to be formulated as sustained release tablet using hydroxy propyl methyl cellulose (methocel), ethyl cellulose and Eudragit as sustaining materials in various proportions. Thus ten formulations were prepared and some of them had same amount of ingredients but they differed in hardness. One commercial sustained release tablet was compared with fabricated sustained release tablets. One fabricated tablet was found close to theoretical sustained release and commercial sustained release tablet during *in vitro* release characteristics. Study indicated that higher hardness slowed the release pattern in dissolution study. Hydroxy propyl methyl cellulose in the drug:polymer ratio 1:0.6 at 7.5 kg/cm² hardness showed almost required result in present study. Successful formulation was found stable in release profile for 45 d stability study at 40±1°.

Diltiazem hydrochloride is a calcium channel blocker with peripheral and coronary vasodilator properties[1]. Studies revealed that diltiazem uncouples the excitation-contraction coupling in the cardiac cell and this is because of its ability to reduce intracellular concentrations of free calcium ions[2]. The plasma half-life following a single oral dose is approximately 3.5 h[3]. Diltiazem hydrochloride is available as 30, 60 and 90 mg tablets. The success of a therapy depends on selection of the appropriate delivery system as much as it depends on the drug itself[4]. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action[5]. Thus the present drug is chosen as suitable candidate for formulation of sustained release drug delivery system.

In the present investigation, an attempt was made to formulate diltiazem hydrochloride as a sustained release tablet using hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC) and Eudragit separately in various ratios. While formulating, alteration in hardness was made and studied for *in vitro* study in demineralised (DM) water and at buffer pH 1.2 and 7.2. A commercial sustained release tablet (MDSR) along with one (DSR3) from fabricated sustained release tablets were studied for dissolution profile at the buffer pH 1.2,4.5 and 7.2.

Theoretical sustained release profile needed for diltiazem hydrochloride was worked out based on its pharmacokinetics parameters as suggested by Wagner[6]. Thus the sustained release tablet of diltiazem hydrochloride should contain a total dose of 90 mg and the drug should be released at the rate of 5.94 mg/h. The most suitable found fabricated sustained release formulation DSR3 was studied for release profile after storage of 15, 30 and 45 d at 40±1°.

MATERIALS AND METHODS

Diltiazem hydrochloride was procured from Sumitra Pharmaceuticals and Chemicals Limited, Hyderabad. Hydroxy propyl methyl cellulose (Methocel-K4M, The Dow Chemical Company, U.S.A), Ethylcellulose (Asha Cellulose (I) Pvt. Ltd., Abrama, Valsad-390 001) and Eudragit S100 (TTK Pharma, Chennai) were obtained from commercial

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sources. All other chemical reagents were of analytical grade. All materials were used as received.

Formulation of fabricated tablets DSR 1-DSR 10:

All the formulations were prepared according to Table 1. The drug and polymer (Methocel/Eudragit S 100) were mixed uniformly. Lactose was added to the drug and polymer mixture or drug alone and blended for 5 min. Polyvinyl pyrrolidone (PVP) was dissolved in isopropyl alcohol (IPA) and EC in acetone. PVP solution in IPA was added to drug, methocel and lactose mixture to form granules. The blend of drug and lactose was granuled with EC solution in acetone and the mass was forced manually through sieve number 10. IPA in sufficient quantity was incorporated to mixture of drug, Eudragit S 100 and lactose to form granules and the mass was forced manually through sieve number 16. The granules were dried at 40° for 2 h. The dried granules were passed through the sieve number 16. The portion, which was retained on sieve number 16 was collected and fines were rejected. The resulting granules were mixed with magnesium stearate in a polythene bag for 5 min. The lubricated granules were compressed into tablets using 9/32 DC punch in 16 station single rotary Cadmach machine. Hardness in kg/cm^2 was kept at 4 for DSR 1, 7.5 for DSR 2 and DSR 3, 5 for DSR 4, DSR 5 and DSR 9, 7 for DSR 6, DSR 7 and DSR 8 and 6 for DSR 10.

Interference study:

Interference study was carried out for any interference of drug-polymer, drug-diluents and drug-lubricant used in the formulations. The solution was made in water and absorbance was observed at 236 nm in an UV/vis spectrophotometer.

Physical characteristics of fabricated tablets:

The dimensional specifications were measured using digital micrometer calipers. Weight variation test was conducted as per specifications of IP[7]. Hardness test was performed by using Monsanto hardness tester. The friability test was performed by using Roche friability testing machine and content uniformity test was performed as per description given for assay of diltiazem hydrochloride in IP[8].

***In vitro* dissolution profile[9]:**

The dissolution profiles of tablets of diltiazem hydrochloride were determined by using USP XXII apparatus-2 dissolution apparatus taking DM water and various physiological buffer solutions of pH 1.2, 4.5 and 7.2 as dissolution medium. The dissolution medium of 900 ml was maintained at a temperature of 37±1°. The speed of rotation of paddle was 100 rpm. The sample dilution was made for about 10 μg/ml and the absorbance was noted at 236 nm in a Shimadzu UV spectrophotometer. The dissolution test was carried out for 12 h.

Stability study:

The fabricated diltiazem hydrochloride sustained release tablet DSR 3 containing 90 mg of drug was packed in

TABLE 1: FORMULAE OF FABRICATED TABLETS.

Ingredient (mg/tablet)	DSR 1	DSR 2	DSR 3	DSR 4	DSR 5	DSR 6	DSR 7	DSR 8	DSR 9	DSR 10
Drug: Polymer	**1:0.2**	**1:0.4**	**1:0.6**	**1:0.5**	**1:0.6**	**1:0.3**	**1:0.5**	**1:0.6**	**1:0.6**	**1:0.6**
Diltiazem HCL	90	90	90	90	90	90	90	90	90	90
Methocel	18	40	60	-	-	-	-	-	60	60
Ethycellulose	-	-	-	45	60	-	-	60	-	-
Eudragit	-	-	-	-	-	30	45	-	-	-
Lactose	47	47	30	50	30	60	45	30	30	30
PVP	4	10	10	-	-	-	-	-	10	10
Acetone	-	-	-	q.s	q.s	-	-	q.s	-	-
Mag. stearate	3	3	3	5	5	5	5	5	3	3
IPA	q.s	q.s	q.s	-	-	q.s	q.s	-	q.s	q.s

a screw capped bottles and stored at temperature of 40±1°. The product was analysed at 15, 30 and 45 d of storage and drug release profile was found out using buffer pH 1.2, 4.5 and 7.2 as dissolution medium.

RESULTS AND DISCUSSION

The present investigation was undertaken to fabricate and evaluate the sustained release formulation of diltiazem hydrochloride using matrix technique and compare with theoretical and commercial product. It was found that there was no interference to the drug with excipients and polymers in the present study. The prepared tablets and commercial SR tablet showed a fair uniformity of drug content of 99 to 101%. Physical parameters were observed fairly good in the present study conforming to requirements. Weight variation was found within the specification of IP for all ten fabricated tablet formulations (DSR 1 to DSR 10) and one commercial formulation (MDSR). Average weight of one tablet of all the ten fabricated tablet formulations (DSR 1 - DSR 10) and one commercial sustained release tablet (MDSR) was found in the range of 162 mg to 193 mg. In the present study hardness of all the tablet formulations was observed in the range of 4 to 7.5 kg/cm². Thickness and diameter of all ten fabricated tablet formulations and one commercial sustained release tablet were found in the range of 3.53-4.16 mm and 7.16-8.00 mm, respectively. Friability for all the formulations in the study was in the range of 0.103 to 0.310%.

In vitro dissolution release profile showed that MDSR was released more rapidly in DM water than other media (fig. 1 and fig. 2). *In vitro* release profile in DM water for fabricated tablets and commercial sustained release is shown in fig. 1. *In vitro* release profile in buffer solutions pH 1.2 and 7.2 is shown in fig. 2 for fabricated tablets and buffer

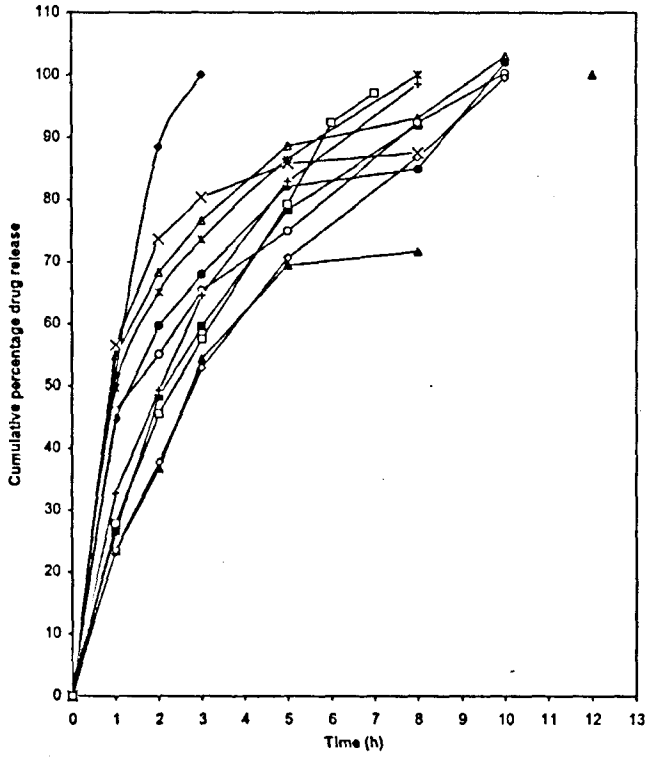

Fig. 1: Cumulative percent release of diltiazem hydrochloride in DM water.

The various formulations prepared were DSR 1(-◆-), DSR 2 (-▪-), DSR 3 (-▲-), DSR 4 (-×-), DSR 5 (-✳-), DSR 6 (-●-), DSR 7 (-△-), DSR 8 (-○-), DSR 9 (-I-), DSR 10 (-◇-) and commercial MDSR (-□-) was taken.

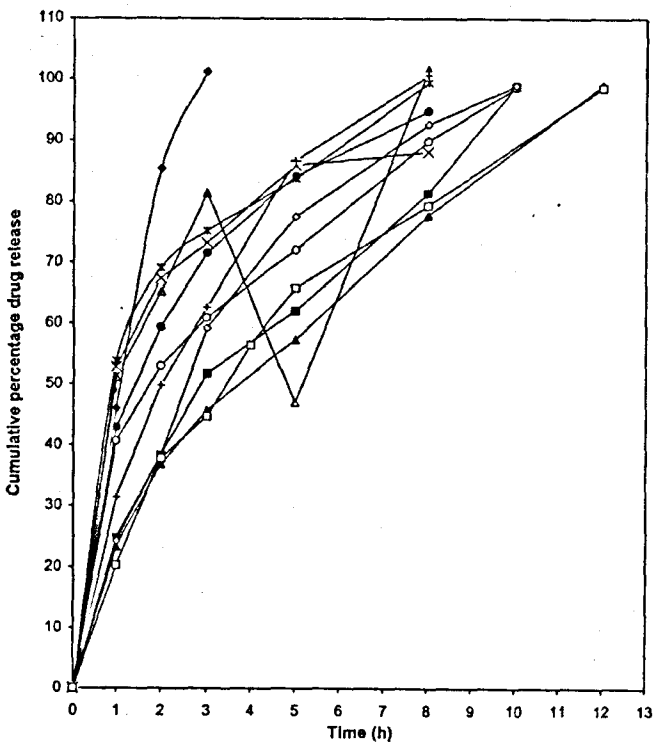

Fig. 2: Cumulative percent release of diltiazem hydrochloride in buffers.

***In virtro* dissolution study was carried out in buffer pH 1.2 for 2 h and in buffer pH 7.2 further up to 12 h for fabricated tablet formulations DSR 1(-◆-), DSR 2 (-▪-), DSR 3 (-▲-), DSR 4 (-×-), DSR 5 (-✳-), DSR 6 (-●-), DSR 7 (-△-), DSR 8 (-○-), DSR 9 (-I-), DSR 10 (-◇-) and commercial MDSR (-□-) tablet was carried out in buffer pH 1.2 for first 2 h, buffer pH 4.5 for next 2 h (3rd and 4th h) and buffer pH 7.2 for next 8 h (5th- 12th h).**

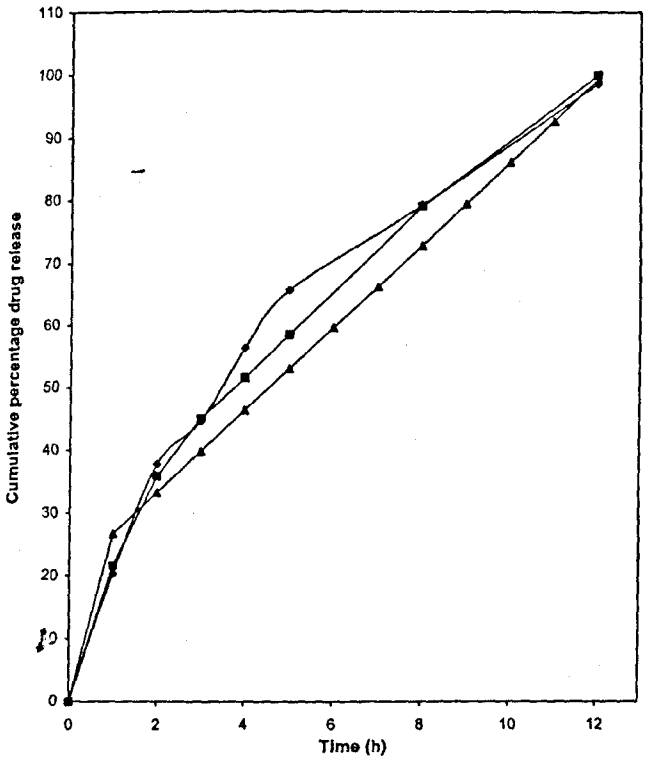

Fig. 3: Cumulative release profile of diltiazem hydrochloride.

Cumulative percent release of diltiazem hydrochloride in buffer pH 1.2 for 2 h, buffer pH 4.5 for next up to 4 h and buffer pH 7.2 next up to 12 h was studied for *in vitro* dissolution of MDSR (-●-), DSR 3 (-▫-) and TSR (-▲-).

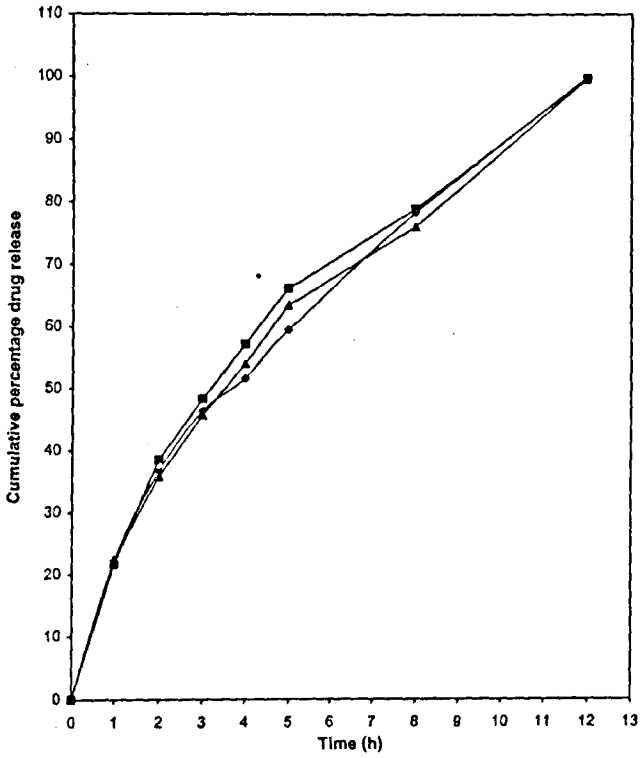

Fig. 4: Stability study of DSR 3.

***In vitro* dissolution study was carried out after storage of DSR 3 for 15 d (-◆-), 30 d (-▫-) and 45 d (-▲-) at 40±1° using buffer pH 1.2 for first 2 h, buffer pH 4.5 for next 2 h (3rd and 4th h) and buffer pH 7.2 for next 8 h (5th to 12th h).**

pH 1.2, 4.5 and 7.2 for MDSR. Fig. 3 shows cumulative percent release of drug at buffer pH 1.2, 4.5 and 7.2 from MDSR, DSR 3 and calculated theoretical sustained release (TSR). From these observations DSR 3 is more close to the release pattern of MDSR and TSR. DSR 3 may be taken as suitable sustained release fabricated tablet formulation.

DSR 3, DSR 9 and DSR 10 are similar in all ingredients but they differ in manufacturing in only hardness. The same is the case with DSR 5 and DSR 8. These formulations in *in vitro* release pattern differ from each other being having the same amount of all ingredients. Hence higher hardness had slowed the release patten. DSR 3 among DSR 9 and DSR 10 showed almost suitable release profile and close to MDSR and TSR just because of a little higher hardness of 7.5 kg/cm^2. This may be explained on the basis that higher hardness makes polymer and drug particles more intact. Therefore maintenance of a suitable hardness is an important factor of sustained release pattern of matrix tablet.

Release profiles at 15, 30 and 45 d of drug from fabricated DSR 3 kept at 40±1° are depicted in fig. 4 in various physiological buffer pH. The formulation DSR 3 is found well stable for 45 d at 40±1°. Thus the present study warrants further *in vivo* study of DSR 3. From the present study it may be concluded that diltiazem hydrochloride may be formulated as sustained release tablet drug delivery system with HPMC (drug:polymer ratio; 1:0.6) for maintaining hardness of tablets of 7.5 kg/cm^2. Apart from polymer ratio, hardness should be also taken into consideration for manufacture of sustained release drug delivery system.

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