

IN-VITRO EVALUATION OF COMMERCIALY AVAILABLE SUSTAINED RELEASE CAPSULE CONTAINING DILTIAZEM HYDROCHLORIDE

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ABSTRACT

Diltiazem hydrochloride (Diltiazem HCl) is a calcium channel blocker widely used for its peripheral and vasodilator properties. It is also used for lowering blood pressure and has some effect on cardiac induction. It is given as oral dosage form in the treatment of angina pectoris and in the management of hypertension. The purpose of this study was to determine the pharmaceutical quality of the sustained release Diltiazem HCl capsules dispensed in India. Three different brands of Diltiazem HCl capsules were purchased from pharmacies. The organoleptic and physicochemical properties of these Diltiazem HCl capsules were assessed according to established methods. The results of weight variation, swelling study, drug content and drug release of all marketed products comply with established limit.

Keywords: Diltiazem HCl capsules, Hypertension, Pharmaceutical quality, Drug content.

INTRODUCTION

Hypertension is a very common disorder in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. It is not a disease itself, but is an important risk factor for cardiovascular mortality and morbidity.¹ Since high blood pressure is the leading cause of strokes and a major risk factor for heart attacks, the most important aspects of preventive cardiology should be identify as many people who have the disease as possible and to take steps to lower the blood pressure before it causes damage to the blood vessels, heart, kidneys, eyes and other organs. Fortunately, the last 30 to 35 years have seen remarkable advances in the treatment of high blood pressure, with major payoffs. Diltiazem HCl is a calcium channel blocker, which has been used in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension.² It has a short biological half-life of about 3.5 hours³ and is rapidly eliminated. Chemically Diltiazem HCl is 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5-[2(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis (Figure 1).

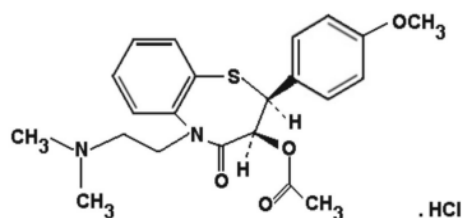


Fig. 1: Structure of Diltiazem hydrochloride

Diltiazem HCl produces its antihypertensive effects primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives. Diltiazem HCl

has been shown to produce increase in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal workloads. Diltiazem HCl has been shown to be a potent dilator of coronary arteries, both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasms are inhibited by diltiazem HCl⁴. The drug is completely absorbed throughout the intestinal tract, but it is extensively metabolized in the liver by deacetylation, resulting in incomplete bioavailability (about 35–40%).⁵

The usual dose of diltiazem HCl is 180-240 mg/day. The conventional tablet and capsule is administered 3 or 4 times a day due to its short biological half-life of 3.5 hours⁶. The problems of frequent administration and variable low bioavailability (40-60%) after oral administration of conventional tablet or capsules have been attenuated by designing diltiazem in the form of sustained release tablet or capsules. The sustained release forms are administered two times a day due to its limited residence time in the gastrointestinal tract.^{7,8,9}

In vitro testing or quality control of drugs is set of studies or experiments undertaken during production in process and occasionally ought to be undertaken post production by regulatory agencies and researchers. Routine laboratory testing of drugs in market is a crucial to protect public health especially in developing countries where counterfeit and substandard drugs have become a major challenge to health care services. The objective of this work was therefore to evaluate the pharmaceutical quality of some Diltiazem hydrochloride sustained release capsules dispensed in India.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride brands having label strength of 90mg (Table 1) were purchased from a retail pharmacy. All tests were performed with in product expiry dates. The reagents potassium dihydrogen phosphate and sodium hydroxide were obtained commercially and used as received.

Table 1: Brands of Diltiazem HCl capsules used in the study

Code	Brands name	Batch no.	Mfg. date	Exp. date	Label strength	Manufacturer
A	Dilzem CD 90	CA251009	Mar.2011	Feb. 2013	90 mg	Torrent Pharmaceutical LTD.
B	Angizem CD 90	BSK 0289	Feb.2011	Jan. 2014	90 mg	Sun Pharma Sikkim
C	Channel CD 90	CHXK07	Nov.2010	Oct. 2012	90 mg	Srushli Pharmaceutical Pvt. LTD

Methods

Weight variation

Ten capsules from each batch were collected randomly and weight of individual capsules was determined. The average weight of the twenty capsules was calculated. Percentage deviation in weight of each capsule from the average weight was determined.¹⁰ The test requirements are met if none of the individual weight are less than 90%, or more than 110% of the average.

Swelling study

The swelling behaviors of capsule beads were studied in pH6.8 phosphate buffer solution.^{11,12,13} Samples of known weight were exposed to 50 ml of the swelling medium and allowed to swell for four hours. The swollen beads were periodically removed, blotted

with tissue paper and weighed. The swelling ratios were calculated as follows:

$$\text{Swelling ratio} = (\text{Final weight} - \text{Initial weight}) / \text{Initial weight}$$

Preparation of standard calibration curve for Diltiazem HCl in phosphate buffer

10mg of Diltiazem HCl was taken in a 100ml volumetric flask and volume was made up to the mark by adding the phosphate buffer solution (pH 6.8). The solution was used as a stock solution having a concentration of 0.1mg/ml. Different concentration of drug solution were prepared from stock solution. Absorbances of the samples were taken at 236nm in a spectrophotometer (UV- 1800, Shimadzu Japan). Using phosphate buffer solution (pH6.8) as blank. The average values of absorbance were plotted against respective concentrations. (Figure 2)

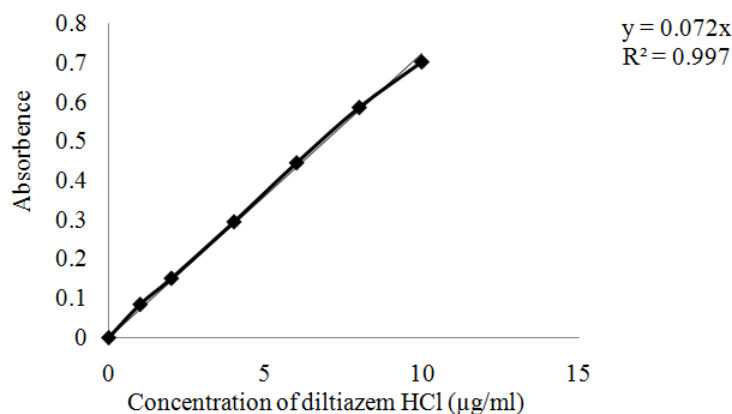


Fig. 2: Calibration curve of Diltiazem HCl in USP phosphate buffer solution, PH 6.8

In-vitro Dissolution Study

The drug release from the capsule beads was studied using dissolution rate test apparatus (TDL-08L, Electro lab, Mumbai, India)¹⁴. Accurately weight, 20mg of capsule beads were placed in 500 ml of pH 6.8 phosphate buffer solution and maintained at 37± 0.5°C. The paddle was rotated at 50 rpm. Five milliliters aliquot was removed from the dissolution medium at specified time interval and was replenished immediately with same volume of fresh medium. Aliquots, following suitable dilution, were analyzed spectrophotometrically at 236nm. Each sample was tested and analyzed in triplicate.

Drug entrapment efficiency

Accurately weighed, 10 mg of capsule beads were crushed with a mortar-pestle and were transferred into 250 ml of pH 6.8 phosphate buffer solution. After 12 hour, the suspension was filtered and the samples were analyzed with a spectrophotometer (UV-1800, Shimadzu, Japan) at λ_{max} 236 nm. All the samples were analyzed in triplicate. The drug entrapment efficiency (%) was calculated using the equation:

$$\text{Entrapment efficiency (\%)} = (\text{actual drug content} / \text{theoretical drug content}) * 100$$

Drug release kinetics

The in-vitro drug release was fitted into Korsmeyer-peppar Eq.(1).¹⁵

$$\frac{M_t}{M_\infty} = Kt^n \quad (1)$$

Where $\frac{M_t}{M_\infty}$ is the fractional solute release at time t, k is a constant which incorporates the structural and geometric characteristics of

the device, and n is diffusion exponent. The mechanism of drug release from spherical polymeric devices may be Fickian diffusion when the value of n= 0.43 or less, anomalous (non-Fickian) transport when the value of n lies between 0.43 and 0.85, and case II transport when n= 0.85. An exponent value of n greater than 0.85, signifies super case II transport mechanism.¹⁶

Statistical analysis

By one-way analysis of variance the differences in physicochemical properties were evaluated using GraphPadInstat software. When P is <0.05 differences were considered significant.

RESULTS AND DISCUSSION

Three brands of Diltiazem hydrochloride capsules having 90mg potency were purchased from local retail pharmacy. All the brands of Diltiazem hydrochloride capsules used were within their shelf life during the study period. Weight variation, drug content and dissolution are compendial standards. Capsules were subject to Weight variation study (Table. 2) for uniformity of weight. All brands showed different mean weight which indicates the use of different excipients in the different brands. It is evident that the deviation from the average weight is within limits in all brands since all brands having uniform weight.

The weight variation test is clearly not sufficient to assure uniform potency of capsules. Then potency of capsules is expressed in term of gram, milligram or micrograms of drug per capsule and is given as the label strength of product. The BP specification is that the content of drug should not be less than 95% and not more than 105%. The potency of the capsules was found to be 98.17 - 99.52% (Table 2). The results ascertain the presence and compendial quantity of Diltiazem hydrochloride in all the brands and so could not be judged as counterfeits without active pharmaceutical ingredients. However, statistically no significant difference (p = 0.5427) of drug content was observed in different capsule brands.

Table 2: Weight variation and drug content of diltiazem hydrochloride capsules

Code	Weight (mg) (Mean±SD, n=20)	Drug content (%) (Mean±SD, n=3)
A	0.2748 ± 0.0075	98.36 ± 0.5515
B	0.2029 ± 0.0061	99.52 ± 0.5515
C	0.3178 ± 0.0088	98.175 ± 1.9021

Table 3: Characterization of diltiazem hydrochloride capsules

Code	A	B	C
t _{50%} (hrs)	9.528864 (0.0016)	8.482702 (0.0074)	4.448398 (0.0029)
DE ₁₀ (hrs)	18.11046 (0.0353)	29.85806 (0.0852)	54.23184 (0.3516)

Figures in parentheses indicate ± SD, n=3 for t_{50%} and DE_{10 hrs}

The drug release study is a measure of the amount of the drug released into dissolution medium with time. This studies given an idea of the amount of the drug available for absorption after oral administration. Drugs with poor dissolution profile will not be available in the body system to elicit therapeutic effect. The

result of dissolution test in terms of dissolution efficiency and time to dissolve 50% drug (t_{50%}) are collected in Table 3.

Whereas the dissolution curves of Diltiazem hydrochloride capsule from different manufactures are shown in Figure 3.

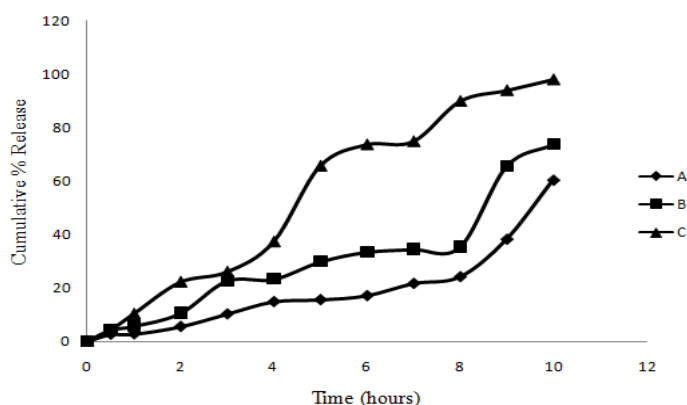


Fig. 3: Dissolution profiles of three brands of Diltiazem hydrochloride capsules

The dissolution efficiency (DE) is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

$$DE = \left[\frac{\int_0^t y \cdot dt}{y_{100} \cdot t} \right] \times 100\%$$

Where, y is the drug percent dissolved in time t.

DE can have a range of values depending time on the time interval chosen. However while comparing a set of data a constant time interval should be selected. In the present study DE_{10hrs} (dissolution efficiency up to 10 hours) were calculated from the dissolution profile of three brands of Diltiazem hydrochloride capsule and used for comparison.

The time required for 50% of the drug to be released from three brands of capsules A, B and C was 9.52, 8.48 and 4.44 hours respectively (Table 3). Moreover the DE also follows the same trend with brands A, B and C respectively. Dissolution efficiency curves of capsules are presented in Figure 4.

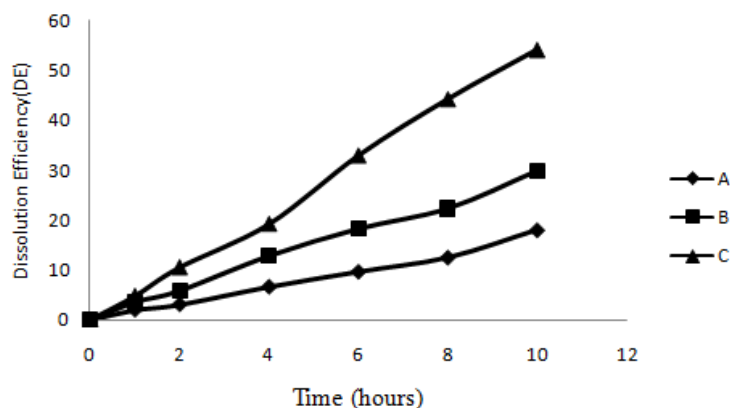


Fig. 4: Dissolution efficiency of three brands of Diltiazem HCl capsules

From the dissolution efficiency profiles, it was observed that the dissolution efficiency increased in following order. The swelling studies were performed with capsules beads to understand the drug release

kinetics. The swelling ratio of the capsule beads of A, B and C were 3.4, 3.53 and 3.6 respectively at 4 hours (Table 4). This was reflected by differences in cumulative percentage drug release of the capsule beads.

Table 4: Swelling ratio and drug release kinetics of diltiazem HCl capsules

Code	Swelling ratio in 4 hours, Mean \pm SD, n=3	Korsmeyer-Peppas model	
		n	ar ²
A	3.4 \pm 0.173	1.006	0.929
B	3.53 \pm 0.058	0.925	0.955
C	3.6 \pm 0.1	1.056	0.99

ar² is correlation coefficient

To explain the drug release mechanism, the release data obtained for the capsule beads in pH 6.8 phosphate buffer solution was fitted to the well known Korsmeyer-Peppas model. The value of diffusion exponent of all the capsule, n lies between 0.925 and 1.056 (Table). It was observed that the drug release from all the capsule beads followed super case II transport since the value of diffusion exponent, n was greater than 0.85 (Table 4). For the system exhibiting super case II transport, the dominant mechanism for drug transport was polymer relaxation as the gel swells.

CONCLUSION

The three brands of the Diltiazem HCl sustained release capsules evaluated in this study could be regarded as being pharmaceutically and chemically equivalent and can therefore be freely interchanged. Drug content, dissolution profiles of all sustained release products used in the study were within specified limits. The study also emphasized the need of constant surveillance on marketed drug product by the government, manufacturer and independent research groups to ensure supply and availability of quality medicines for the patients.

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