Formulation and *in vitro* evaluation of Diltiazem controlled release tablets

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Article Info

ISSN (Online): 2582-8940
Volume: 05
Issue: 01
January-March 2024
Received: 02-01-2024;
Accepted: 05-02-2024
Page No: 38-41

Abstract
The aim of the present work is to Formulate and Evaluate controlled release of Diltiazem matrix tablets used for treat high blood pressure and control angina. Development of CR Diltiazem is proposed considering the adverse event profile and high fluctuation index of Diltiazem observed with IR dosage forms. In the present work, attempts were made to formulate and evaluate controlled release of matrix tablets of Diltiazem. Diltiazem was subjected to preformulation studies, based on the results obtained Diltiazem controlled release tablets were successfully formulated. Formulations prepared by wet granulation using HPMC and carbopol 934 as control release polymers and 5% W/W of povidone in isopropyl alcohol as binder solution have showed desired in vitro release. Set of trials were formulated for which Diltiazem evaluated parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) were found to lie within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in pH 6.8 phosphate phosphate buffer.

Keywords: Diltiazem, polymers, wet granulation technique, in vitro drug release studies, FTIR studies

Introduction
Controlled release DDS release drug at rates, which are significantly different from conventional dosage forms. The controlled release dosage forms are designed to control the rate of drug delivery, target the delivery of the drug to a tissue and/or maintain the duration of therapeutic efficacy [1]. Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process [2]. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption [3]. Diltiazem hydrochloride is a Calcium channel and broadly utilized in the treatment of specific kinds of cardiovascular issues [4]. The therapeutic impacts of Diltiazem hydrochloride are identified with its capacity to hinder the flood of calcium particles in cardiovascular and vascular smooth muscle during membrane depolarization [5]. A basic dosing plan with more than once every day administration of the antihypertensive agent is known to expand patient compliance [6].

Materials
Diltiazem was obtained from Hetero labs, HYD. HPMC, Carbopol 934 were procured from Synpharma Research Labs, Hyderabad, and other chemicals the reagents used were of analytical grade.

Methodology
FT-IR study [7]
Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any

changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR study.

Preparation method

Table 1: Formulation of Controlled release tablets of Diltiazem

Ingredients(mg)	F1	F2	F3	F4
Diltiazem	100	100	100	100
HPMC K_5M	50	100	--	--
Carbopol 934	--	--	50	100
Povidone	10	10	10	10
Microcrystalline cellulose	135	85	135	85
Talc	2	2	2	2
Magnesium Stearate	3	3	3	3
Total wt	300	300	300	300

Preparation method: [8]

Different tablet formulations were prepared by wet granulation method. The formulations are composed of polymers HPMC K_5M, and carbopol 934. All powders were passed through 100-mesh sieve. The microcrystalline and the polymer were mixed uniformly. Drug was added to the polymers and blended for 20 min. Solution of PVP K30 added to the above mixture for making dump mass. Dump mass was passed through sieve no.40 and dried the granules for 2 hrs at 50° c. The resulting granules were mixed with magnesium Stearate and talc in polyethylene bag for 10 min. The lubricated granules were compressed using 10mm punch (single punch tablet machine) in to tablets. Compression pressure was adjusted during tableting of each formula to get the tablet hardness in the range of 5 to 7 $Kg/cm^{3.}$ The total weight of tablet was kept at 300 mg.

Evaluation of tablet [9, 10, 11]

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage.

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity

The drug content was determined by triturating tablets in a mortar and pestle. The 100 mg of sample powder was dissolved in 6.8 phosphate buffer. The solution was filtered through Whattmann filter paper. The filtrate was analyzed by U.V. spectrophotometer (LAB INDIA).

***In- Vitro* Release study**

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time. Temperature maintained at 37±1. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 5 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask. The diluted samples were assayed.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared controlled release Matrix tablets of Diltiazem were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 90 days.

Results and Discussion

Compatibility Study

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied.

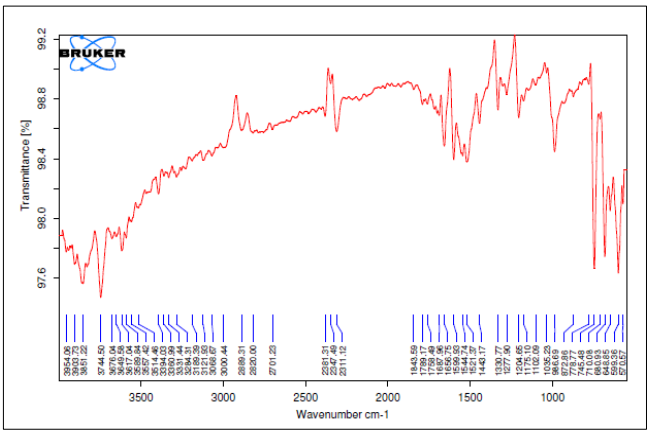

Fig 1: FTIR Spectra of Diltiazem

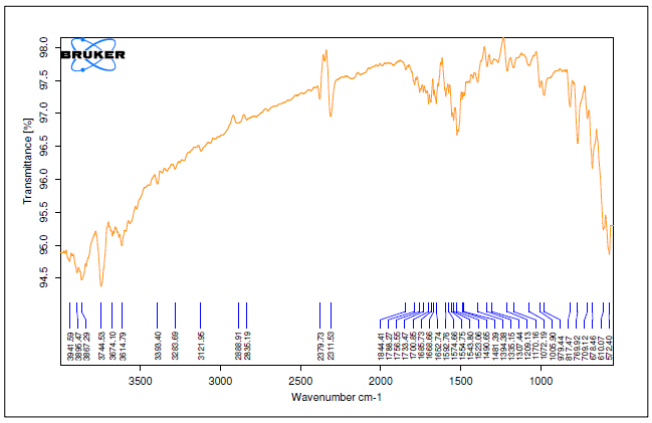

Fig 2: FTIR Spectra of physical mixture of drug and excipients

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Evaluation Studies

Weight variation

All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness

Tablets mean thickness were uniform in F1 to F4 formulations and were found to be in the range of 3.12mm to 3.21 mm.

Hardness

The measured hardness of tablets of each batch ranged between 5.18 to 5.25 kg/cm^2. This ensures good handling characteristics of all batches.

Friability

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity

The percentage of drug content for F1 to F4 was found to be between 94.56% and 98.86% of Diltiazem it complies with official specifications.

Table 2: Results of Evaluation parameters of tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	300	3.18	5.18	0.28	96.91
F2	299	3.21	5.22	0.30	95.88
F3	301	3.17	5.25	0.31	94.56
F4	300	3.12	5.19	0.29	98.86

***In-vitro* Dissolution Study**

Table 3: *In vitro* release data of tablet F_1 to F_4

Time (hrs.)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	26.72	26.50	25.22	28.30
2	35.63	31.15	32.81	32.42
3	40.92	38.65	39.90	41.18
4	52.65	48.23	53.41	50.90
5	61.25	59.95	65.50	63.82
6	73.12	72.82	74.84	73.86
7	80.19	81.84	83.90	84.82
8	91.16	92.32	93.25	98.12

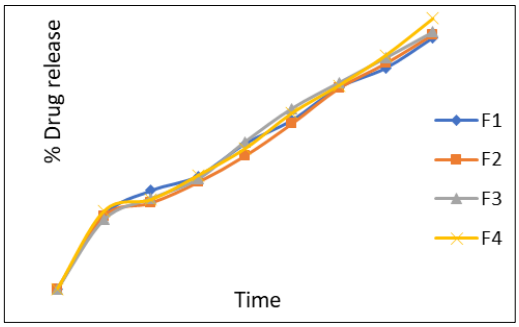

Fig 3: *In vitro* drug release studies of (F1-F4) Formulations

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-4 after 3 months. Parameters quantified at various time intervals were shown;

Table 4: Results of stability studies of optimized formulation F4

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-4	25^{0}C/60%RH % Release	98.12	98.07	97.48	96.85	Not less than 85 %
F-4	30^{0}C/75% RH % Release	98.12	97.98	97.21	96.48	Not less than 85 %
F-4	40^{0}C/75% RH % Release	98.12	97.52	96.99	96.41	Not less than 85 %

Conclusion

In subsequent studies, the prepared tablets were evaluated. Among all the formulations F4 showed a better drug release over 8 hours of time and it released over 98.12 % of the drug out of 8 formulations with a controlled effect. Data of *in-vitro* drug release were fit into different equations and kinetic models to explain the release kinetics of Diltiazem from the controlled release tablet. It also found to be that there was no interaction between the drug and polymer in all the formulations. Among all the formulations, the optimized formulation F4 fulfilled all the objectives.

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