Research Article **ISSN: 2349 – 7114**

Asian Journal of Research in Pharmaceutical Sciences and Biotechnology

Journal home page: www.ajrpsb.com

PREPARATION, CHARECTERIZATION AND PREFORMULATION STUDIES OF DILTIAZEM SUSTAIN RELEASE TABLET

S. Shahid Mohammed[*1]

[*1]Department of Pharmaceutical Sciences, Seven Hills College of Pharmacy, Tirupathi, Andhra Pradesh, India.

ABSTRACT

To overcome the drawbacks of conventional drug delivery systems, many strategies are available for the design and development of modified- release drug delivery formulations. The primary purpose of these drug delivery devices is to improve the state of disease management by modifying the pharmacokinetic profiles of therapeutic agents normally administered as conventional tablets or capsules. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because they make it easier to achieve a desirable drug - release profile, they are cost - effective, and they have broad US Food and Drug Administration (US FDA) acceptance. The aim of this present work is to formulate a sustained release matrix tablet of diltiazem by wet granulation method using various polymers such as HPMC, SCMC, Sodium alginate, PVP, Eudragit and Ethyl cellulose**.**

KEY WORDS

Diltiazem, Sustain Release system and Hydrophilic polymer.

Author of correspondence:
S. Shahid Mohammed,
Department of Pharmaceutical Sciences,
Seven Hills College of Pharmacy,
Tirupathi, Andhra Pradesh, India.

Email: rsreshasulthana@gmail.com.

INTRODUCTION

Diltiazem is a nondihydropyridine (non-DHP) member of the class of drugs known as calcium channel blockers, used in the treatment of hypertension, angina pectoris, and some types of arrhythmia. It is a benzothiazepine, which differentiates it from the other classes of non-DHP calcium channel blockers such as the phenylalkylamines. It is also an effective preventive medication for migraine. It is a class 3 antianginal drug, and a class IV antiarrhythmic. It is a common adulterant of cocaine seized in the

UK, and has been found to reduce cocaine cravings in rats, indicating it may prolong the "high". It incites minimal reflex sympathetic changes. It is based upon a 1, 4-thiazepinering[1].

The oral route of drug delivery is the most popular, desirable and preferred method of administering therapeutic agents for systemic effects because it is nature, convenient for the patient, and cost effective to manufacturing process. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians. Pharmaceutical products designed for oral delivery are mainly conventional drug delivery system, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as; the hydrophilic polymers selected for the present study were hydroxylpropyl Methylcellulose (HPMC), carboxymethylcellulose (CMC), sodium Alginate (NaAlg). This polymer provides p^H-independent drug release to oral dosage forms that can be used formulating the sustained-release dosage forms. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to include hydrophobic polymers in the matrix system. Hence in the present work, an attempt has been made to formulate the extended - release matrix tablets of DTZ using hydrophilic matrix material in combination with hydrophobic polymers such as polyvinylpyrrolidone (PVP), Eudragit, and ethyl cellulose[2-4].

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug deliver, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue. The concept of controlled release systems is to deliver a constant supply of the active ingredient by continuous release for a certain period of time, an amount of the drug equivalent to that eliminate by the body[5]. For drugs with short half-lives and with a clear relationship between concentration and response, it will be necessary to dose at regular, frequent intervals in order to maintain the concentration within the therapeutic range. Higher doses at less frequent intervals will result in higher peak concentrations with the possibility of toxicity. For some drugs with wide margins of safety, this approach may be satisfactory, e.g. amoxicillin has a half-life of approximately one hour, but a dosage frequency of 8 hours[6].

The selection of both the drug and retardant polymers along with the filler excipients will impact on the mechanism and rates of drug release from the dosage formulation. Various physicochemical, biological properties of a drug and its biopharmaceutical characteristics influencing in product design and performance[7-10].

MATERIALS AND METHODS

MATERIALS

Diltiazem potassium was provided Mylon Andhra Pradesh. HPMC 15cps and Ethyl cellulose were supplied by S.D. Fine chemicals Ltd, India. Eudragit were received from Evonik Degussa India Pvt. Ltd., Mumbai.

Preformulation studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form[11].

Fourier Transform Infrared Spectroscopic studies

The present work a study was carried out by using FT-IR spectrophotometer to find out if there is any possible chemical interaction of diltiazem with hydroxypropyl methylcellulose (HPMC); Carboxymethycellulose (CMC); sodium alginate (NaAlg); Polyvinypyrolidone (PVP); Eudragit RL100 (RL100); Ethylcellulose (EC); Micro crystalline cellulose (MCC); and Magnesium stearate[12].

Procedure

To study the compatibility of various formulation excipients with DTZ, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ration of 1:1 and stored in air tight containers at 30 $\pm 2^0$c/65±5%RH. The solid

admixtures were characterized using fourier transform infrared spectroscopy (FT-IR).

Construction of Standard Curve for Diltiazem

Diltiazem can be estimated spectrometrically at 237 nm as it obeys Beer's - Lambert's law limit is the range of 5 - 25 μ/ml.

Preparation of Reagents

Potassium Dihyrogen Phosphate (0.2M)

27.22 gm of potassium dihyrogen phosphate is dissolved in distilled water and makeup to 1000 ml with the same.

Sodium Hydroxide Solution (0.2M)

8 gm of sodium hydroxide was dissolved in 1000 ml of distilled water.

Phosphate buffer pH 6.8

50 ml 0.2M of potassium dihydrogen phosphate solution and 24.4 0.2M sodium hydroxide solution were mixed and made up to 200 ml with distilled water.

Preparation of Standard drug solution

Stock Solution

100mg of diltiazem was dissolved in 100ml of Phosphate buffer saline pH 6.8 so as to get a stock solution of 1000 μ/g/ml concentration.

Standard Solution

5ml of stock solution was made to 100ml with phosphate buffer saline pH 6.8 thus giving a concentration of 50 μg/ml. Aliquot of standard drug solution ranging from 1ml to 5ml were transferred in to 10ml volumetric flask and were diluted up to the mark with pH 6.8 phosphate buffer. Thus the final concentration ranges from 5-25 μ/g/ml. Absorbance of each solution was measured at 237 nm against phosphate buffer saline pH 6.8 as a blank. A plot of concentrations of drug vs. absorbance was plotted[13].

Preparation of Diltiazem Matrix Tablets

Fifteen different tablet formulations were prepared by wet granulation technique (Formulation 1-15). The composition of 300 mg diltiazem of the drug, polymer (HPMC, CMC, NaAlg) and filler (MC) was dry mixed thoroughly and sufficient volume of granulating agent (ethanol 95%). Ethanolic solution of PVP, ERL-100, EC) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22 meshes. The granules were dried at 55^0c for 1 hour. This granule mixture was blended with magnesium stearate (2%w/w) as lubricant; the appropriate and then compressed using a 16 station tablet compression machine round, flat-faced punches of 10-mm diameter and die set. All compressed tablets were stored in an airtight container at room temperature for the study[14].

Characterization of Granules

Prior to compression, granules were evaluated for their characteristic parameters such as:

Angle of Repose

The angle of repose of granules was determined by the fixed funnel and freestanding cone method, where by accurately weighed granules (3gm were carefully poured through the funnel with its tip at 2 cm height (h) until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter (r1, of the base for the powder cone was measured and angle of repose (0) was calculated using the following equation.

$\theta = \tan^{-1}$ (h/r) (Where, θ = angle of repose, h = height, r = radius).

Bulk Density

Both loose bulk Density and tapped bulk density were determined. Whereby a quantity (3g) of granules from each formula, previously lightly shaken to break any agglomerates cylinder. After the initial volume was observed, the cylinder was allowed to full under its own weight onto a have surface from the height of 2.5cm at 2-Second intervals. The tapping was continued until no further change in the volume was noted LBD and TBD were calculated using the following formulas

LBD = Weight of the powder/ volume of the packing

TBD = weight of the powder / tapped volume of the packing.

Hauser's Ratio

It indicates the flow properties of the powder and it measured by the ratio of TBD to the LBD

$$\text{Hauser's Ratio} = \frac{\text{TBD}}{\text{LBD}}$$

Compressibility index (Carr's index)

To analyze flowability, the carr's index was calculated on the basis of the LBD and TBD. The

compressibility index of the granules was determined by carr's compressibility index

Carr's index (%) = [BD – LBD) x 100)] / TBD

Drug content uniformity

Standard preparation

An accurately weighed amount of pure diltiazem (100mg) and transferred into 100ml volumetric flask. It was dissolved and made up to volume with pH-8 phosphate buffer and absorbance was measured at 237 nm.

Sample preparation

An accurately weighed amount of powdered diltiazem granules (100mg) was extracted with water and the solution was filtered through 0.45m membrane and absorbance was measured at 237nm after suitable dilution.

Characterization of Tablets

The properties of the compressed matrix tablet, such as Hardness, Friability, weight variation and drug content Uniformity.

Hardness Test

For each formulation, the hardness of 5 tablets was determined using a Monsanto hardness tester, mean and SD were calculated.

Friability Test

For each formulation, 6 tablets were weighed. The tablets were placed in a friabilator (Roche friablator) and subjected to 25 rpm in 4 minutes. The tablets were then declusted and reweighed. The friability was calculated as the percentages weight loss.

F = 100 (1-wo/wt) (Where, Wo = weight of tablets before friability test, Wt = weight of tablets after friability test).

Weight variation Test

To study weight variation, to tablets of each formulation were weighed using an electronic balance and the test was performed according to the USP official limits of percentage deviation of tablet is presented.

Drug content uniformity

Standard preparation

An accurately weighed amount of pure diltiazem (100mg) and transferred into 100ml volumetric flask. It was dissolved and made up to volume with pH.8 phosphate buffer and absorbance was measured at 237 nm.

Sample preparation

Five tablets were weighed individually then placed in a mortar and powdered with a pestle. An amount of powdered diltiazem (100mg) was extracted in water. The solution was filtered through o.45µm membrane and absorbance was measured at 237 nm after suitable dilution.

Calculation

The amount of diltiazem present in tablet can be calculated using the formula: $A_t/As \times S_w/100 \times 100/S_t \times A_v$ (Where, A_t = Absorbance of sample preparation, A_s = Absorbance of Standard preparation, S_w = weight at diltiazem working standard (mg), S_t = weight of diltiazem tablet (mg), Av = Average weight of tablet (mg).

RESULTS AND DISCUSSION

In the present study nine formulations (F1-F9) with variable concentrations (10%-30%) of polymers namely Hydroxy propylmethylcellulose, Sodium carboxy methyl cellulose and sodium alginate were prepared and evaluated for various physico-chemicals, In this best formulation (F3) formulated into six formulation (F10-F15) by using different concentration of hydrophobic polymers such as Polyvinyl pyrrolidone, Eudragit RL 100 and ethyl cellulose.

Preformulation studies (Compatibility studies)

Compatibility studies were performed by using FT-IR spectrophotometer. The IR Spectrum (Figure No.1) of pure diltiazem drug was compared with the IR spectrum of physical mixture of Diltiazem (Diltiazem, Hydroxy propylmethylcellulose, Sodium carboxy methyl cellulose, sodium alginate, Polyvinyl pyrrolidone, Eudragit RL 100 and ethyl cellulose)[15-18].

There is no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug, polymer and excipients used in the tablets.

Standard calibration curve of diltiazem

Standard Curve of diltiazem was determined by plotting absorbance (nm) verses concentration

(mcg/ml) at 237 nm and it is follows the Beer's law (Figure No.2). The results are given in Table No.1.

Characterization of Granules

The blended granules of different formulation were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index, Hauser's ratio and drug content uniformity[19]. The results of these evaluations are as follows:-

Angle of repose

Angle of repose ranged from 21^{o} 64"± 1.1868 to 29^{o}69"±1.837. The results were found to be below 30^{0} and hence the blend was found to have good flow ability.

Bulk density and tapped density

Bulk and tapped densities are used for the measurement of Compressibility index. The LBD and TBD ranged from 0.2119± 0.006 to 0.3109±0.016 and 0.2407± 0.005 to 0.3483±0.020 respectively.

Compressibility index (Carr's index)

The compressibility index (%) ranged from 9.61± 1.19 to 16.59± 0.97. The blend was found to have free flowing property as the result were found to be below 16%.

Hauser's Ratio

The Hauser ratio ranged from 1.020± 0.011to 1.199± 0.014. The result indicates the free flowing properties of the granules.

Drug content uniformity

The drug content in a weighed amount of granules blend of all SR formulations ranged from 99.073±0.185 to 99.678±0.252.

Physical Evaluation of oral sustained-release tablets of diltiazem

Diltiazem oral sustained-release tablets were evaluated for various physical parameters namely - Thickness, Hardness, Weight variation, Friability, Drug Content uniformity test etc.

Hardness test

The hardness of all batches ranged from 7.18±0.26 - 7.46±0.48 Kg/cm^2.

Weight variation test

All the formulations passed weight variation test as per the Pharmacopoeias limits of 5%

Friability test

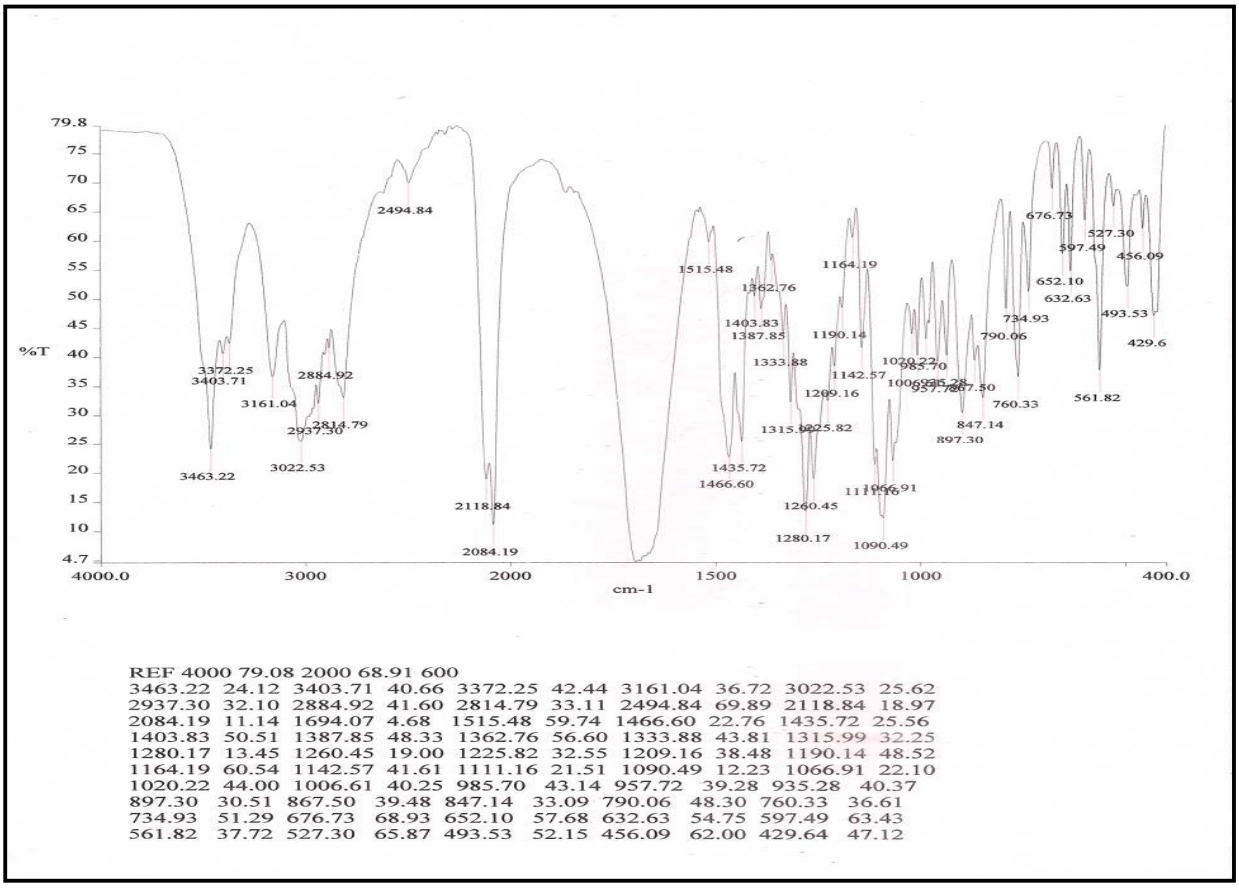
The percentage friability of all batches ranged from 0.039 % to 0.199.

Drug content uniformity

Drug content was found to be uniform among the all formulations and ranged from 98.87±0.14 to 99.36±0.304.

Table No.1: Data's for Calibration Curve of diltiazem in phosphate buffer 6.8

S.No	Concentration (mcg/ml)	Absorbance (237 nm)
1	0	0
2	5	0.174
3	10	0.362
4	15	0.593
5	20	0.781
6	25	0.961
Slope		**0.0413**
Regression		**0.9991**



REF 4000 79.08 2000 68.91 600

3463.22	24.12	3403.71	40.66	3372.25	42.44	3161.04	36.72	3022.53	25.62
2937.30	32.10	2884.92	41.60	2814.79	33.11	2494.84	69.89	2118.84	18.97
2084.19	11.14	1694.07	4.68	1515.48	59.74	1466.60	22.76	1435.72	25.56
1403.83	50.51	1387.85	48.33	1362.76	56.60	1333.88	43.81	1315.99	32.25
1280.17	13.45	1260.45	19.00	1225.82	32.55	1209.16	38.48	1190.14	48.52
1164.19	60.54	1142.57	41.61	1111.16	21.51	1090.49	12.23	1066.91	22.10
1020.22	44.00	1006.61	40.25	985.70	43.14	957.72	39.28	935.28	40.37
897.30	30.51	867.50	39.48	847.14	33.09	790.06	48.30	760.33	36.61
734.93	51.29	676.73	68.93	652.10	57.68	632.63	54.75	597.49	63.43
561.82	37.72	527.30	65.87	493.53	52.15	456.09	62.00	429.64	47.12

Figure No.1: IR Spectra of diltiazem with HPMC

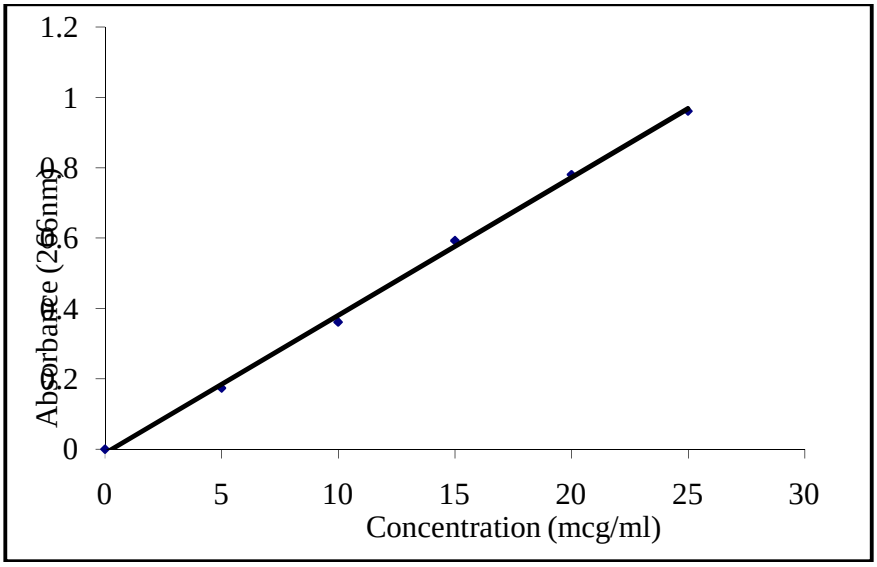


Figure No.2: Standard calibration curve of diltiazem in phosphate buffer 6.8

CONCLUSION

All these results indicate that the granules possessed satisfactory flow-properties, compressibility and drug-content. Finally, both polymer level and polymer type did not affect the physical properties of the prepared granules. All the tablet formulations showed acceptable pharmacopoeial limit specifications for weight variation, drug content, hardness and friability.

ACKNOWLEDGEMENT

Author is thankful to Department of Pharmaceutical Sciences, Seven Hills College of Pharmacy, Tirupathi, Andhra Pradesh, India for providing necessary facilities.

BIBLIOGRAPHY

1. Tripathi K D. Essentials of medical pharmacology, *Jaype publishers New delhi*, 6th edition, 2008, 528-545.
2. Chien Y W. Novel Drug Delivery systems, *Marcel Dekker*, 1992, 139-143.
3. Brahmankar D M and Jaiswal S B Biopharmaceutics and pharmacokinetics a treatise, *Vallabh prakashan, New Delhi,* 1st edition, 1995, 64-70.
4. Vyas S P and Khar R K. Controlled Drug Delivery. Concepts and Advances, 1st edition, 2002, 155-195.
5. Sallsa T, Veiga F, and Pina M E. Oral controlled - release dosage forms L Cellulose ether polymers in hydrophilic - matrices, *Drug Dev Ind Pharm*, 23, 1997, 929 - 938.
6. Alderman D A. A review of cellulose ethers in hydrophilic matrices for oral controlled - release dosage forms, *Int S Pharm Tech*, 5, 1984, 1-9.
7. Gohel M C, Patel T P and Barigya S H. Studies in preparation and evaluation of pH independent sustained - release matrix tablets of Verapamil Hcl using directly compressible Eudragits, *Pharam Dev Technol*, 8, 2003, 323 - 333.
8. Liv J, Zhang F and Ginity J W. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot - met extrusion, *Eur J pharm Biopharm*, 42, 201l, 181 - 190.
9. Robinson J R and Lee V H L. Controlled drug delivery Fundamentals and application, *Marcel-Dekker, New York*, 2nd edition, 1987, 24-36.
10. Herbert A. Liberman L and Joseph B. Pharmaceutical Dosage Forms and Tablets, 2nd edition, 1988, 201-206.
11. Gilbert S, Banker and Christopher T. Modern Pharmaceutical, 3rd edition, 2001, 576-578.
12. Lisa B. Polymers in controlled Drug Delivery, *Medical plastics and Biomaterials Magazine archive*, 1997.
13. Ronga R K V, Padmalatha D K and Buri B. Cellulose matrices for Zero order release of soluble drugs, *Drug Ind pharm*, 14, 1988, 2299 - 2320.
14. Parojcic J, Duric Z, Jovanovic M and Ibrics. An investigation into the factors influencing drug release from hydrophilic matrix tablets - based on novel carbomer polymers, *Drug Deliv*, 11, 2004, 59 - 65.
15. Lourdes O, Manuele L, Rosa M, Hernandez and Alicia R. Preparation of sustained release hydrophilic matrices by melt granulation in a high shear mixer, *J Pharm Pharmaceut Sic*, 8, 2005, 132 - 140.
16. Shan L, Mei J, and Kung-Hsu L. Hydrophilic Excipients Modulate the Time Lag of Time controlled Disintegrating Press coated Tablets, *AAPP Pharmsci Tech*, 5, 2004, 1-5.
17. Pruthvipathy R. Ethyl cellulose matrix controlled release tablets of a water - soluble drug, *Elsevier Science B.V*, 1995.
18. Saleh M and Yellela S R. *In Vitro* and *In vivo* evaluation of Guar Gum Matrix Tablets for oral controlled Release of Water - Soluble Diltiazem Hcl", *AAPS Pharm Sci Tech*, 8, 2005, 12-18.
19. Umit G, Melike U, Gulgun Y and Turan A. Introduction of sustained Release Opipramol Dihydrochloride Matrix tablets as a New Approach in the Treatment of Depressive Disorders, *Int J Biomed Sci*, 2, 2006, 24-26.