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R E S E A R C H A R T I C L E

Formulation and Evaluation of Gastro Retentive Effervescent Floating Tablets of Diltiazem

Katta Sridhar*, Kongi Kavya Sudha, Ballavolu Sandeep, Chirumanu Ramadevi

Swathi College of Pharmacy, Venkatachalem, Nellore, Andhra Pradesh, India

A B S T R A C T

In the present research work controlled release floating matrix formulations of Diltiazem by using various concentrations of polymers sodium bi carbonate were developed. After the preformulation studies the formulation blends were subjected to evaluation tests of various precompression and post compression parameters and all the formulations were found to possess good flow properties. Among all the formulations F8 formulation showed minimum floating lag time of 2.25min and 12hrs duration of floating time which retarded the drug release up to desired time period i.e., 12 hours. The dissolution data of optimized formulation followed zero order release kinetics and the mechanism of drug release showed higuchi's release with diffusion exponent indicating case II transport.

Keywords: Diltiazem, Ethyl cellulose, Eudragit S-100, Eudragit L-100, effervescent floating tablets.

A R T I C L E I N F O

Corresponding Author
Katta Sridhar
Principal and Director
Swathi College of Pharmacy,
Venkatachalem, Nellore, A.P, India
MS-ID: JPBMAL3271

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C O N T E N T S

1. Introduction

Oral delivery of drugs is the most preferable route of drug delivery. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient compliance and flexibility in formulation and cost effective manufacturing process. Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue. An important factor, which may adversely affect the performance of an

oral controlled drug delivery system, is the G.I transit time. The time for absorption in the G.I transit in humans, estimated to be 8-10 hr from mouth to colon, is relatively brief with considerable fluctuation. This variability may lead to predictable bioavailability and times to achieve peak plasma levels. One of the important determinants of G.I transit is the residence time in the stomach. An effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the stomach for a long period of time. For this drug, increased or more predictable availability would result if controlled release systems could be retained in the stomach for extended periods of time. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of controlled release dosage form for these drugs. Incorporation of the drug in a controlled release gastroretentive dosage form (CRGRDF) can yield significant therapeutic advantages due to a variety of pharmacokinetic and pharmacodynamic factors.

Advantages of GFDDS

- Sustained Drug Delivery and Site Specific Drug Delivery.
- Absorption/Bioavailability Enhancement divery. Improved plasma levels.
- Less Irritation and Fewer side effects.

Limitations

1. Floating system is not feasible for those drugs that have solubility or stability problems in gastric fluids. Drugs that are not stable at gastric pH are not suitable candidates to be as GFDDS.
2. Drugs that irritate the mucosa are not suitable candidates and should be avoided to be formulated as GFDDS.
3. The drugs, which have multiple absorption sites in the gastrointestinal tract and are absorbed throughout gastrointestinal tract, which under significant first pass metabolism, are not desirable candidates.

2. Materials and Methods

Materials: Diltiazem procured from Yarrow drug pvt ltd, Mumbai, India, Provided by Sura Labs, Dilsukhnagar, Eudragitl- 100, Eudragit S -100, Sodium Bicarbonate, Microcrystalline cellulose, Magnesium Stearate, Talc.

Methodology

Analytical method development:

Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCL UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FT-IR Germany (AlphaT). The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000cm^{-1}- 550 cm^{-1}

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compressions of different formulations are given in Table 6.1 & 6.2.The tablets were prepared as per the procedure given below and aim is to prolong the release of Diltiazem. Total weight of the tablet was considered as 300mg.

Evaluation parameters

Pre Compression parameters

Bulk density (D_B)

Bulk density is the ratio between a given mass of the powder and its bulk volume.

Bulk density = Mass of Powder / Bulk volume of the powder

$$\textbf{Bulk density } (D_B) = W / V_0$$

Tapped Density (D_T)

Tapped density is the ratio between a given mass of powder (or) granules and the constant (or) fixed volume of powder or granules after tapping.

Tapped density = mass of the powder/ tapped volume

Hausner's ratio Hausner's ratio is an indirect index of ease of powder flow and was calculated by the formula,

$$\textbf{Hausner's ratio} = D_T / D_B$$

Where, D_T is the tapped density

D_B is the bulk density

Compressibility index

Compressibility index (CI) was determined by measuring the initial volume (V_o) and final volume (V_f) after hundred tapping's of a sample in a measuring cylinder. It indicates the powder flow properties and expressed in terms of percentage and given in table no. 14 and calculated by using the formula

$$\textbf{\% Compressibility index} = V_o - V / V_o \times 100$$

Table6.3: Carr's index value (as per USP)

Angle of repose: Angle of reponse was measured by fixed funnel method. It determines flow property of the powder. It is defined as maximum angle formed between the surface of the pile of powder and the horizontal plane. The powder was allowed to flow through the funnel fixed to a stand at definite height (h). By measuring the height and radius of the heap of powder formed (r), angle of repose was calculated by using formula given below and the calculated values obtained was shown in table no. 14.

$$\theta = \tan^{-1} (h / r)$$

Where, θ is the angle of repose

h is the height in cm

r is the radius in cm

Evaluation of post compression parameters for prepared Tablets: The designed formulation floating tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

Twenty tablets were randomly selected and weighed, to estimate the average weight and that were compared with individual tablet weight. The percentage weight variation

was calculated as per Indian Pharmacopoeial Specification. Tablets with an average weight 250 mg so the % deviation was ±5 %.

Friability test

Twenty tablets were weighed and subjected to drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The friabilator was operated for 4 minutes and reweighed the tablets. % loss (F) was calculated by the following formula.

F =100 (W0-W)/W0

Where W0 = Initial weight, W = Final weight

Hardness test

The hardness of tablets was measured by using Monsanto hardness tester. The results were complies with IP specification.

Thickness test

The rule of physical dimension of the tablets such as sizes and thickness is necessary for consumer acceptance and maintain tablet uniformity. The dimensional specifications were measured by using screw gauge. The thickness of the tablet is mostly related to the tablet hardness can be used as initial control parameter.

Drug content

The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch were weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml of volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.

In vitro Buoyancy studies:

The *in vitro* buoyancy was determined by floating lag time, and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

In-vitro drug release studies

Dissolution parameters:

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCL
RPM	--	50
Sampling intervals (hrs)	--	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Temperature	--	37°c ± 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$Log (100-F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = K\ t^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.

3. Results and Discussion

The present study was aimed to developing sustained release floating tablets of Diltiazem using synthetic polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Preformulation parameters of powder blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.44 ± 0.08 to 0.58 ± 0.05 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.52± 0.03 to 0.66 ± 0.06 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 8.82 ± 0.06 to 15.38 ± 0.05 which show that the powder has good flow properties. All the formulations have shown the hausner's ratio ranging from 0 to 1.25 indicating the powder has good flow properties.

Post compression Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the tablets. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Weight variation and thickness:

All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 7.3. The average tablet weight of all the formulations was found to be between 298.4 ± 1.34 to 301.8 ± 0.75**.** The maximum allowed percentage weight variation for tablets weighing >250 mg is 5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 3.61 ± 0.01 to 3.91 ± 0.03.

Hardness and friability:

All the formulations were evaluated for their hardness, using monsan to hardness tester and the results are shown in table 7.3. The average hardness for all the formulations was found to be from 4.5 ± 0.14 to 4.8 ± 0.09 Kg/cm^2 which were found to be acceptable. Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using roche friabilator and the results were shown in table 7.3. The average percentage friability for all the formulations was between 0.56 ± 0.08 and 0.66 ± 0.07, which was found to be within the limit.

Drug content:

All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 7.3. The drug content Values for all the formulations were found to be in the range of **(**98.26 ± 0.53 to 99.52 ± 0.67**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the formulations comply with the standards given in IP.

***In vitro* buoyancy studies:**

All formulations were examined for buoyancy studies, in that to determine the floating lag time and duration of floating time. The floating lag time of most of the formulations were showed within 3mins. But duration of floating time was difference, it dependence on the concentration of polymer and type of polymer. Among all the formulation F3, F6, F8, F9 were showed 12 hours or more than 12 hours.

Drug – Excipient compatability studies

Fourier Transform-Infrared Spectroscopy:

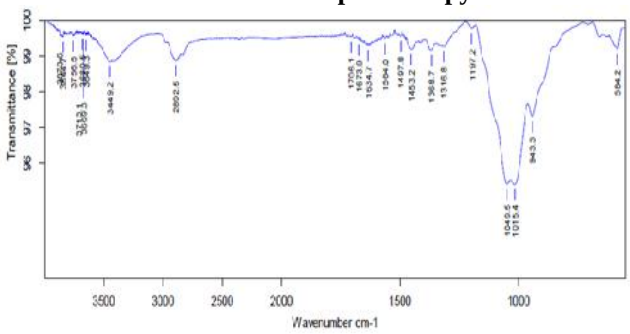

Figure 1: FT-TR Spectrum of Diltiazem pure drug

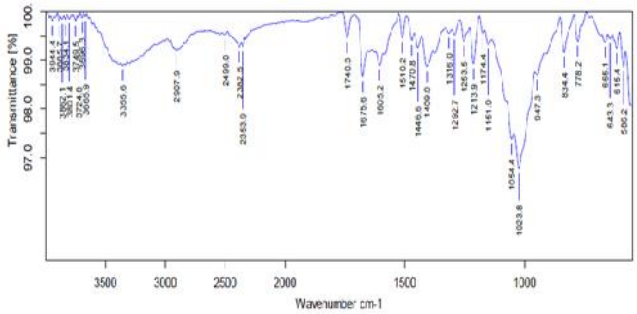

Figure 2: FT-IR Spectrum of Optimized Formulation

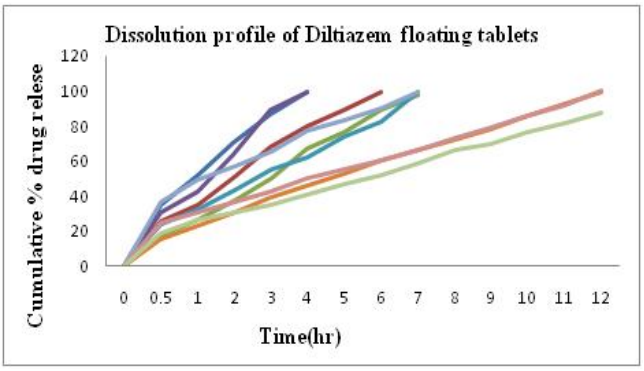

Figure 3: Dissolution profile of Diltiazem floating tablets (F1, F2, F3,F4,F5,F6,F7,F8,F9 formulations).

Table 1: Evaluation parameters

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Diltiazem (mg)	60	60	60	60	60	60	60	60	60
Ethyl cellulose (mg)	30	60	90	-	-	-	-	-	-
Eudragit S-100 (mg)	-	-	-	30	60	90	-	-	-
Eudragit L-100 (mg)	-	-	-	-	-	-	30	60	90
$NaHCO_3$ (mg)	45	45	45	45	45	45	45	45	45
Mag. Stearate (mg)	3	3	3	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3	3	3	3
MCC pH102 (mg)	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight (mg)	300	300	300	300	300	300	300	300	300

Table 2: Dissolution Data of Diltiazem Tablets Prepared with Ethyl cellulose in Different Concentrations

TIME	**CUMULATIVE PERCENT DRUG RELEASED**								
(hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**

0	0	0	0	0	0	0	0	0	0
0.5	34.57	25.09	16.98	30.21	24.09	15.61	36.23	24.61	18.77
1	52.12	34.45	26.67	42.34	32.12	23.22	49.42	30.53	25.91
2	70.45	51.28	37.35	63.22	43.21	30.81	56.90	36.84	30.23
3	86.56	68.31	50.63	89.22	55.18	39.11	65.56	42.53	35.13
4	99.48	79.67	67.45	99.15	62.33	46.15	77.54	49.76	40.51
5		88.78	76.43		73.54	53.16	83.56	55.21	46.67
6		99.32	89.63		82.63	60.21	90.45	60.25	51.57
7			98.15		99.24	66.25	99.67	66.13	58.69
8						72.36		73.24	65.67
9						78.28		79.09	69.22
10						85.52		85.34	76.32
11						92.45		91.41	81.39
12						99.55		99.98	87.21

4. Conclusion

The present study concludes that sustained release floating tablets of Diltiazem prepared by effervescent method and using different concentration of ethyl cellulose, Eudragit S-100 and Eudragit L100 as retarding polymers. Among all the formulations, F8 formulation has shown optimized results. Present study concludes that gastro retentive floating system may be a suitable method for Diltiazem.

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