Research Article

# Study of Formulation Variables on Bi-Layered Floating Tablets of Diltiazem Hydrochloride

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**ABSTRACT**

In the present study an attempt was made to study the effect of formulation variables on bi-layered floating tablet of Diltiazem hydrochloride. Immediate release layer was formulated by using various super disintegrants such as sodium starch glycolate, cross carmellose sodium, crospovidone and sustained release layer was formulated with different grades hydrophilic polymers i.e. HPMCK100M, HPC, HEC and MC by wet granulation method. The prepared tablets were characterized and rate of drug release from an immediate release layer was 99.9% were found at the end of 20 mins followed by sustained the drug release for 12hrs from sustained release layer.The dissolution data were fitted into zero order, first order, Higuchi and Peppas euations. Results revealed that the drug release from the formulation $F_{15}$ followed first order kinetics and exhibited Peppas transport mechanism.

## INTRODUCTION

One of the novel approaches in the area of sustained drug delivery was Gastro retentive drug delivery systems (GRDDS).Several techniques have been proposed to increases the Gastric residence time of dosage forms such as floating systems, swelling systems, hydro dynamically balanced systems and low density systems etc.

In the present investigation Diltiazem Hydrochloride was selected as model drug is a calcium channel blocker and it is widely used in the treatment of hypertension. The drug has short biological half life 3-4 hrs, low bioavailability and narrow absorption window in upper part of GIT. Multi layer concepts have been utilized in this present investigation. The compatibility studies were conducted by FT-IR spectroscopy, no compatibility between drug and polymers were found. Bi-layered floating tablets having immediate release layer and sustained release layer, the drug was released within 20 mins from the IR layer leads to a sudden raise in blood concentration, blood level was maintained at steady state as the drug was released from the sustained release layer.

## Experimental

### MATERIALS

Diltiazem Hydrochloride, gift sample from Medreich ltd Banglore, Sodium starch glycolate, Croscarmellose sodium, Crospovidone, HPMCK100M, HPC, HEC and MC were procured from (Medreich ltd Bangalore),PVPk-30 and Lactose (SD Fine Chem., Mumbai, India),Talc and Magnesiumstearate was obtained from (Qualigens Fine Chem., Mumbai, India).

### Preparation of Diltiazem Hydrochloride Bilayer Floating tablets

The preparation of Bilayer floating tablets involved two steps prepared by wet granulation method, the following excipients used in the formulation superdisintegrants SSG, Croscarmellose sodium, Crospovidone, PVP in isopropyl alcohol as binding solution, HPMCK4M, HPMCE5,HPMCK100M,HPC,HECandMC as polymers, lactose as diluent, talc and magnesium stearate as glidant and lubricant. The dose calculation for the loading dose and maintaince as given below

**Pharmacokinetic Parameters of Diltiazem Hydrochloride**

| | | |
|---|---|---|
| Fraction of drug absorbed (F) | = | 0.44 |
| Elimination half life ($t_{1/2}$) | = | 3.7 hrs |
| Elimination rate constant ($K_e$) | = | 0.187$hr^{-1}$ |
| Clearance | = | 12 ml/min/kg |
| Volume of distribution | = | 3.1 lit/kg |

**Calculation of Loading dose($D_L$)**

| | | |
|---|---|---|
| Loading dose | = | $(C_{ss\ avg} \times V_d) \div F$ |
| But, $C_{ss\ avg}$ | = | $(F \times Dose/\tau) \div Clearance$ |
| $C_{ss\ avg}$ | = | $(0.44 \times 90mg/12hrs) \div 12ml/min/kg$ |
| $C_{ss\ avg}$ | = | $6.54 \times 10^{-8} mg/ml$ |
| So, $D_L$ | = | $(6.54 \times 10^{-8} mg/ml \times 3.1lit) \div 0.44$ |
| Loading dose ($D_L$) | = | 34.57 |

**Calculation of Maintainance dose ($D_M$)**

| | | |
|---|---|---|
| Maintainance dose | = | $K_o\ (T\text{-}t_{1/2})$ |
| But, $K_o$ | = | $K_e \times$ loading dose |
| Maintainance dose | = | $K_e \times$ loading dose$\times(T\text{-}t_{1/2})$ |
| Maintainance dose | = | $0.187 \times 34.57 \times (12\text{-}3.7)$ |
| So, $D_M$ | = | 54.87 mg |

Based on the above calculation, the immediate release dose was considered as 35mg and the maintainance dose was considered as 55mg.

**Preparation of the immediate release layer**

The immediate release layer was prepared as per the formula shown in table 1. The damp mass was passed through sieve no 12. The granules thus obtained were dried in an oven at 50 $^{O}$C. The dried granules were sieved through sieve no16 and lubricated with talc and magnesium stearate.

**Preparation of the floating sustained release layer**

The SR layer was prepared as per the formula shown in table2. The damp mass was passed through sieve no 12 to obtain granules. The granules thus obtained were dried in an oven at 50 $^{O}$C . The dried granules were sieved through sieve no 16 and lubricated with talc and magnesium stearate.

**Compression of bilayer floating tablets**

The required quantity of granules for the SR layer were compressed slightly by using a rotary punch tablet machine with 9mm punches. Then the required quantity of granules for the IR layer were placed over the above compact ,both the layers were compressed by 9 mm round shaped punches with Cadmach CMS 25 tablet machine to get tablets.

**Evaluation of Diltiazem Hydrochloride bi-layered floating tablets**

All the prepared bi-layered floating tablets were evaluated for following parameters.

**Weight Variation**

Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

$$\% \text{ Weight Variation} = \frac{\text{Average Weight - Individual Weight}}{\text{Average Weight}} X100$$

**Hardness**

The hardness of tablets was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm$^2$.

**Friability**

The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus and operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\% \text{ Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X100$$

**Drug content**

**Twenty** tablets were weighed, powdered and quantity of powder equivalent to 100 mg of Diltiazem hydrochloride was dissolved in 0.1 N HC1 diluted to 100ml with 0.1N HC1 then the solution was filtered and suitably diluted. The drug content was estimated spectrometrically at 237 nm.

**Swelling index**

Tablet was weighed ($W_0$) and placed in 0.1N hydrogen chloride maintained at 37°c. At predetermined time intervals the tablets were reweighed and blotted to remove excess water and weighed (Wt). The percentage of swelling index calculated by the following formula

$$\text{Swelling index} = \frac{(Wt - Wo)}{Wt} \times 100$$

Wt= final weight of the tablet

Wo = initial weight of the table.

**Floating characteristics**

Floating characteristics were determined using USP dissolution apparatus at 100rpm using 900 ml of 0.1 N HCl, temperature was maintained at 37°c.

**Floating lag time**

The tablet was placed in dissolution apparatus and the time taken to float on the dissolution medium was noted.

**Floating time**

The total duration of the time that the tablet float on dissolution medium was noted.

**In-vitro dissolution studies**

Dissolution rate was studied by using USP type II paddle dissolution apparatus in 900ml of 0.1N Hydrochloric acid at 37±0.5°at 50 rpm. 5ml of aliquot of dissolution medium was withdrawn at regular time intervals, the same volume of pre-warmed (37±0.5°) fresh dissolution medium was replaced. The samples were filtered and drug content of diltiazem hydrochloride in each sample was analyzed after suitable dilution by Shimadzu UV-spectrophotometer at 237 nm.

**RESULTS AND DISCUSSION**

The formulations of immediate release layer was shown in table1.The *in-vitro* release data were fitted into various kinetic models i.e. First order and zero order, drug release followed first order kinetics,based on the release rate, the order of drug release from the all formulations was F12>F8>F11>F4>F7>F10>F3>F6>F2>F9 >F1>F5 i.e. increasing the concentrations of SSG,Croscarmellose sodium and Crospovidone in formulations the drug release rate was found to be increased. Finally F12 was optimized for development of the bi layer diltiazem hydrochloride tablets.

Micromeritic properties for formulations were evaluated, the results revealed IR layer and SR layer granules exhibited good flow properties; it was also further supported by Carr's Index values and Hausner's ratios values. The formulated tablets were subjected to various quality control tests and the results were shown

in table 3.. The obtained results were found to be within limits specified in pharmacopoeia. The % drug content in all bilayer formulaitons were in the range of 98.6±0.03% to 99.±0.02%.The floating lag time and total floating time of SR layer for F13-F21 were found to be satisfactory.

The *In-vitro* release data were fitted into kinetic models i.e. First order, zero order, Higuchi and Peppas, percent drug release profiels for all bilayer formulations were shown in fig 1, fig2 and fig3. The drug release followed zeroorder kinetics and exhibited the Peppas transport mechanism. The exponential coefficient from the Peppas plots was found to be <0.5 indicating Fickian diffusion based on the release rate, the order of release retardant was as follows HPMCK100M>HPCE>HEC>MC. Release rate was retarted by increasing the concentration of the polymer.

## CONCLUSION

The drug and excipients were found to be compatable. The characteristics of the granules such as angle of repose, bulk density, tapped density, carr's index, hausner's ratio were studied, found to be good flow properties. Evaluation parameters of the tablets such as weight variation, hardness, friability, drug content, swelling index, floating characteristics, was found to be satisfactory. The buoyancy lag time was found to be satisfactory. The swelling index was found to be increased with increase in the amount of the polymer employed. The formulations F20 was found to be, sustained the drug release for 12hrs.The optimized tablet formulations showed a satisfactory dissolution profile and floating characteristics.The drug release from all formulations followed zero order kinetics and Fickian diffusion.In the present investigation, successfully developed bilayer floating tablets of Diltiazem Hydrochloride by wet granulation method using super disintegrants Crospovidone for IR layer and HPMCK100M for SR layer .

## ABBREVIATIONS

IRLayer=Immediatereleaselayer,SRLayer =Sustainedreleaselayer,HPMC=Hydroxypropylmethylcellulose,HPC=Hydroxypropylcellulose,HEC=Hydroxyethylcellulose,MC=Methylcellulose,PVP=Polyvinylpyrrolidine, Hcl=Hydrochloricacid,hrs=Hours,rpm=Rotation per Minute.USP=United States Pharmacopoeia and UV=Ultra-Violet.

## ACKNOWLEDGEMENTS

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**Table 1: Composition of Immediate release layer for bi-layered floating tablets of Diltiazem Hydrochloride formulated with SSG, Croscarmellose sodium, Crospovidone**

| S.No | Ingredients | Quantity per single tablet(mg) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ | $F_9$ | $F_{10}$ | $F_{11}$ | $F_{12}$ |
| 1. | Diltiazem hydrochloride | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| 2. | Sodium starch glycolate | 1.5 | 2.25 | 3 | 3.75 | - | - | - | - | - | - | - | - |
| 3. | Croscarmellose sodium | - | - | - | - | 1.5 | 2.25 | 3 | 3.75 | - | - | - | - |
| 4. | Crospovidone | - | - | - | - | - | - | - | - | 1.5 | 2.25 | 3 | 3.75 |
| 5. | PVPk-30 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| 6. | Lactose | 35.5 | 34.75 | 34.75 | 33.25 | 35.5 | 34.75 | 34 | 33.25 | 35.5 | 34.75 | 34 | 33.25 |
| 7. | Talc | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 |
| 8. | Magnesium stearate | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 |
| Total weight(mg) | | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |

**Table 2: Composition of bi-layered floating tablets of Diltiazem Hydrochloride formulated with HPMCK100M, HPC, HEC and MC**

| S NO | Ingredients | Quantity per tablet (mg) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | F13 | F14 | F15 | F16 | F17 | F18 | F19 | F20 | F21 | F22 | F23 | F24 |
| **Immediate release layer** | | | | | | | | | | | | | |
| 1 | Diltiazem hydrochloride | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| 2 | Crospovidone | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 | 3.75 |
| 3 | PVPk-30 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| 4 | Lactose | 33.25 | 33.25 | 33.25 | 33.25 | 33.25 | 33.25 | 33.25 | 33.25 | 33.25 | 33.25 | 33.25 | 33.25 |
| 5 | Talc | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 |
| 6 | Magnesium stearate | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 | 0.75 |
| **Sustained release layer** | | | | | | | | | | | | | |
| 7 | Diltiazem hydrochloride | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 |
| 8 | HPMCK100M | 60 | 80 | 100 | - | - | - | - | - | - | - | - | - |
| 9 | HPC | - | - | - | 60 | 80 | 100 | - | - | - | - | - | - |
| 10 | HEC | - | - | - | | | | 60 | 80 | 100 | - | - | - |
| 11 | MC | - | - | - | - | - | - | - | - | - | 60 | 80 | 100 |
| 12 | Sodium bi carbonate | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| 13 | Lactose | 49 | 31 | 11 | 49 | 31 | 11 | 49 | 31 | 11 | 49 | 31 | 11 |
| 14 | Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 15 | Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 16 | Total weight (mg) | 275 | 275 | 275 | 275 | 275 | 275 | 275 | 275 | 275 | 275 | 275 | 275 |

**Table 3: physico-chemical evaluation of the for bi-layered floating tablets of Diltiazem Hydrochloride**

| S. No. | Formulation | Average weight (mg) | Hardness (kg/sq cm) | Friability (%) | Drug content (%) | Swelling index(%) | Floating lag time (sec) | Total floating time (hrs) |
|---|---|---|---|---|---|---|---|---|
| 1 | F13 | 275±0.21 | 3.9±0.31 | 0.68 | 97.3±0.01 | 37.4±0.03 | 77 | 10 |
| 2 | F14 | 275±0.23 | 4.5±0.22 | 0.66 | 97.8±0.04 | 52.5±0.03 | 60 | 12 |
| 3 | F15 | 275±0.34 | 5.3±0.17 | 0.75 | 98.6±0.05 | 56.2±0.04 | 55 | >12 |
| 4 | F16 | 275±0.3 | 4.2±0.24 | 0.70 | 96.5±0.02 | 39.4±0.03 | 68 | 3 |
| 5 | F17 | 275±0.12 | 5.4±0.18 | 0.67 | 97.4±0.03 | 46.1±0.02 | 60 | 6.5 |
| 6 | F18 | 275±0.24 | 5.2±0.2 | 0.64 | 98.1±0.04 | 54.5±0.02 | 58 | 8.5 |
| 7 | F19 | 275±0.3 | 4.6±0.15 | 0.73 | 99.1±0.05 | 45.9±0.03 | 71 | 5 |
| 8 | F20 | 275±0.18 | 4.9±0.36 | 0.71 | 98.2±0.04 | 46.1±0.05 | 59 | 6.5 |
| 9 | F21 | 275±0.19 | 3.6±0.24 | 0.68 | 97.6±0.02 | 48.2±0.04 | 55 | 8.5 |
| 10 | F22 | 275±0.25 | 3.3±0.45 | 0.7 | 96.6±0.03 | 37.5±0.03 | 69 | 2.5 |
| 11 | F23 | 275±0.12 | 3.5±0.36 | 0.72 | 96.2±0.05 | 45.1±0.03 | 60 | 4.5 |
| 12 | F24 | 275±0.26 | 5.6±0.01 | 0.61 | 99.3±0.02 | 49.6±0.02 | 59 | 6 |

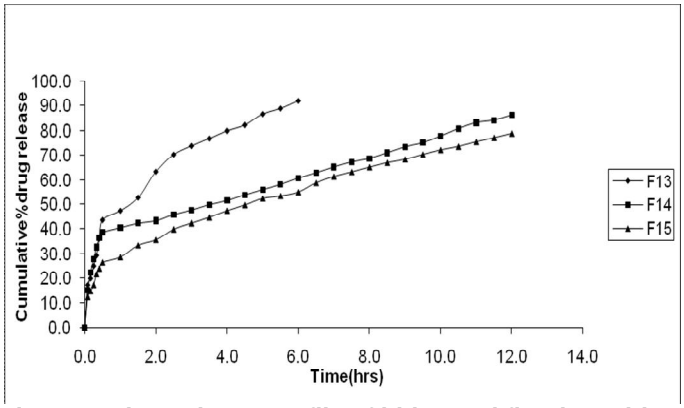


**Fig. 1: In-vitro release profile of bi-layered floating tablets of Diltiazem Hydrochloride formulated with HPMCK100M**

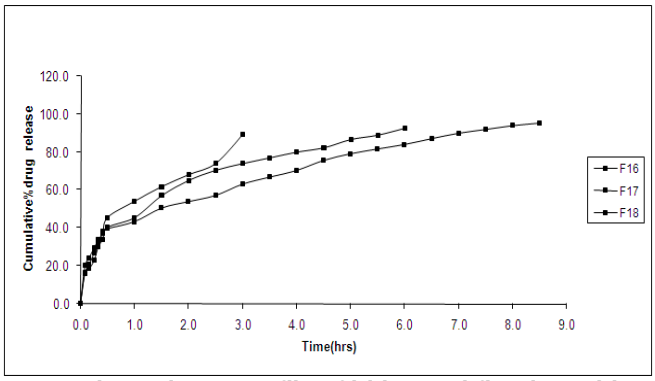


**Fig. 2: In-vitro release profile of bi-layered floating tablets of Diltiazem Hydrochloride formulated with HPC**

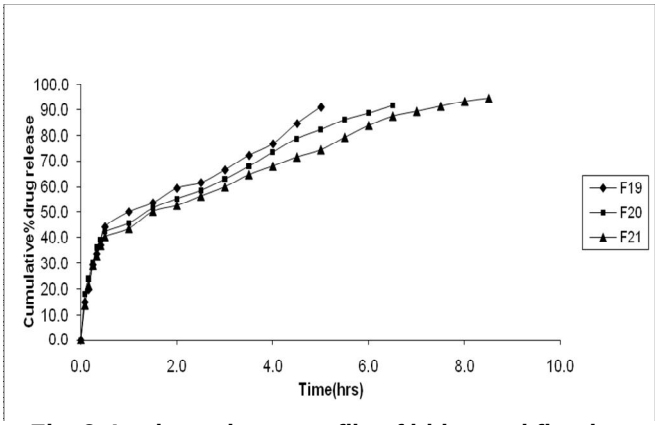


**Fig. 3: In-vitro release profile of bi-layered floating tablets of Diltiazem Hydrochloride formulated with HEC**

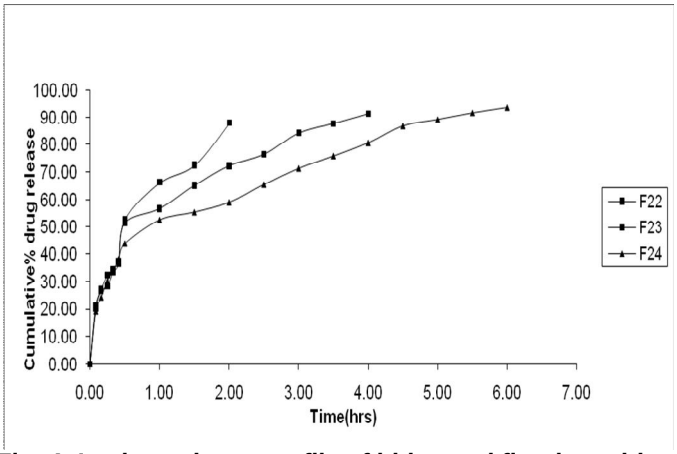


**Fig. 4: In-vitro release profile of bi-layered floating tablets of Diltiazem Hydrochloride formulated with MC**

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