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Der Pharmacia Lettre, 2016, 8 (16):31-39
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Preparation of Highly Porous Gastroretentive Diltiazem Hydrochloride Tablets Using a Sublimation Method

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ABSTRACT

The present investigation is aimed to formulate floating gastroretentive (GR) tablets containing diltiazem hydrochloride using a sublimation material.Three different grades of hydrophilic polymer Methocel® (hydroxypropyl methyl cellulose (HPMC)) K4M, K15M and K100M were used in different combinations at different ratios for the preparation of tablets. In this study, the release of the drug from tablet was highly dependent on the polymer concentrations. Camphor was used as the sublimation material to prepare GR tablets that are low-density and easily floatable.Camphor was changed to pores in the tablet during the sublimation process. SEM revealed that the GR tablets have a highly porous morphology. Floating properties of tablets and tablet density were affectedby the sublimation of camphor. Prepared floating gastroretentive tablets floated for over 24 h and had nofloating lag time. However, as the amount of camphor in the tablet matrix increased, the crushing strength of the tablet decreased after sublimation. Release profiles of the drug from the GR tablets were not affected by tablet density or porosity.

Key words: Gastroretentive, Diltiazem Hydrochloride, Floating tablet, Sublimation, Highly porous.

INTRODUCTION

Oral administration is the most common route for drug delivery. The bioavailability of a drug via oral administration can be affected by many factors such as the dosage form, the drug release profile, gastric emptying, the gastrointestinal transit time, and the site of drug absorption. Several drugs are unstable in the acidic environment of the stomach and have a narrow absorption window in the upper small intestine. Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability [1]. Diltiazem hydrochloride (DTZ) is a calcium channel blocker belonging to the benzothiazepine family. It is widely prescribed for the treatment of hypertension and angina [2]. DTZ undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A [3], which results in less than 4%of its oral dose being excreted unchanged in urine [4]. Bioavailability of DTZ is ~30% to 40% owing to an important first pass metabolism [2,4,5]. It has an elimination half-life of 3.5 hours and has an absorption zone from the upper intestinal tract [4,5]. Efficacy of the administered dose may get diminished due to incomplete drug release from the device above the absorption zone [6]. DTZ requires multiple daily drug dosage in order to maintain adequate plasma concentrations. Therefore, it is a suitable model candidate for gastroretentive formulation. The gastroretentive drug delivery systems can be retained

in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastro-intestinaltract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability [7]. High solubility of DTZ was a major challenge in designing its controlled drug delivery system. In this study HPMC K4M, K15M and K100M were used as a gel forming as well as a release-retarding polymer.Camphorwas used as the sublimation material to prepare gastroretentive tablets that are low-density and easily floatable.

MATERIALS AND METHODS

Diltiazem Hydrochloride and different grades of HPMC was donated by Dr. Reddys laboratory (Hyderabad, India). D,L-Camphor was purchased from Merk chemical Co. Ltd.(Mumbai, India. Magnesium stearate was purchased from S.D lab chemicals (Mumbai, India). Allother ingredients, reagents, and solvents were of analytical grade.

1.1 Drug- excipients interaction study and identification

2.1.1. Fourier transform infrared spectroscopy (FTIR)

An infrared spectrum of pure drug and physical mixture of optimized formulation was recorded using BRUKER, FTIR Spectrophotometer. The scanning range was 400 to 4000 cm^{-1} and the IR spectra of samples were obtained using KBr disc method. Any change inspectrum pattern of drug due to presence of polymers was investigated to identify any chemical interaction.

2.1.2. UV spectroscopy (determination of λmax)

The stock solution (1000µg/ml) of DTZ was prepared in 0.1 N HCl (hydrochloric acid, pH 1.2). This solution was appropriately diluted with 0.1 N HCl to obtain a concentration of 2µg/ml. The UV spectrum was recorded in the range of 200 to 350 nm on Lab India double beam UV-visible spectrophotometer.

2.2. Preparation of standard curve

The stock solution (1000µg/ml) of DTZ was prepared in 0.1 N HCl. From this 20 µg/ml second stock solution was made. This was withdrawn as 1, 2, 3, 4, and 5 ml and diluted each with 0.1 N HCl (pH 1.2) to obtain concentrations of 2,4, 6, 8 and 10µg/ml. The absorbance of these solutions were measured at 236 nm against blank i.e. 0.1 N HCl. The coefficient of correlation and equation for the line are determined.

2.3. Preparation of gastroretentive tablets of DTZ

The composition of different formulations of DTZ gastroretentive tablets are shown in table 1. Diltiazem Hydrochloride, HPMC K4M, HPMC K15M, HPMC K100M, Camphor were passed through sieve no. 80 separately. MCC add directly to the above ingredients. The powder blends were lubricated with Magnesium stearate (1%w/w) and Talc (2 %w/w) and mixed for two to three minutes. These lubricated blends were compressed into tablets using 12mm flat faced round tooling on a multiple punch tablet machine (Karanavati Mini Press). The compression force was adjusted to obtain tablets with hardness in the range of 4 to 5kg/cm^2. Each tablet contained 90mg of DTZ. Then the tablets were kept in hot air oven for 12hrs for complete sublimation of camphor. Twelve formulations were prepared and those were coded from F1 to F12.

Table 1. Composition of different floating tablet formulations (F1 to F12) of DTZ

(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Diltiazem Hydrochloride	90	90	90	90	90	90	90	90	90	90	90	90
Camphor	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K4M	90	135	180	225								
HPMC K15M					90	135	180	225				
HPMC K100M									90	135	180	225
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Talc	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
Magnesium stearate	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%

2.4. Pre-compression evaluation

The granules were evaluated for flow property i.e. angle ofrepose, bulk density, tapped density, compressibility index (Carr's index) and Hausner's ratio using standard procedures [8,9].

2.5. Post-compression evaluation

The prepared tablets were evaluated for their physical parameters like hardness, thickness, weight variation, friability and drug content [8,9].

To study weight variation, twenty tablets of each formulation were weighed using an electronic balance and the test was performed. Thickness and diameter of tablets was determined using Vernier caliper. Ten tablets from each batch were used, and their average values calculated. Hardness of ten tablets of each formulation was determined using Monsanto hardness tester.

Friability of twenty tablets was determined using the Roche friabilator. This test subjects a number of tablets to the combined effect of shock and abrasion by utilizing a plastic chamber which revolves at speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche friabilator, which was then operated for 100 revolutions for 4 min. The tablets were then dusted and reweighed.

Ten tablets containing DTZ were crushed to a fine powder. A quantity equivalent to 100 mg of DTZ was added into 100 ml volumetric flask and dissolved in 0.1 N HCl (pH 1.2). After suitable dilutions the absorbance was determined by UV-Visible spectrophotometer (Lab India) at 236 nm against blank. The drug content wascalculated by using calibration curve [10].

The in vitro buoyancy test was determined by floating lagtime, as per the method described [11,12]. The tablets were placed in a 100ml beaker containing 0.1 N HCl (pH 1.2). The time required for the tablet to rise to the surface and float was determined as floating lagtime (FLT) and the time for which the tablet constantly floats on the surface of the medium (duration of floating), was measured.

The release rate of DTZ floating tablets was determined using USP Type II Apparatus (Paddle Type). The dissolution test was performed, using 900 ml of 0.1 N HCl, at 37 ± 0.5 ^{0}C at 50 rpm for 12 h. A 5 ml sample was withdrawn from the dissolution apparatus at specified time and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 mm membrane filter and sufficiently diluted. Absorbance of these solutions was measured at 236 nm using UV-visible spectrophotometer [10].

2.6. Kinetic analysis of release data

The obtained dissolution data was fitted to zero order, first order, Higuchi and Korsmeyer-Peppas equations to understand the rate and mechanism of drug release from the prepared formulations. The correlation coefficients values were calculated and used to find the fitness of the data.

Zero order equation [13],

$Q_t = Q_0 + K_0 t$ ----------(1)

describes the systems where the drug release rate is independent of concentration of the dissolved substance, where,Q_0= initial amount of drug, Q_t= cumulative amount of drugrelease at time t, K_0= zero order release constant, t = time in h.

First order release equation[13]

$\text{Log } Q_t = \text{Log } Q_0 + K_t/2.303$ ---------- (2)

the drug release rate depends on its concentration, where, Q_0=initial amount of drug, Q_t= cumulative amount of drug release at time t, K = first order release constant, t = time in h.

Higuchi release equation [14],

$Q = KHt^{1/2}$ or $M_t/Mo = Kt^{1/2}$ ---------- (3)

the Higuchi equation suggests that the drug releases by diffusion mechanism. Q =cumulative amount of drug releaseat time t, KH = Higuchi constant, t = time in h.

Korsmeyer-Peppas equation [15]

$F = (M_t/M_\infty) = Kmt^n$ ---------- (4)

which describes the drug release from a polymeric system,where F = fraction of drug released at time t, M_t= amount of drug released at time t, M_∞= total amount of drug in dosage form, Km = kinetic constant, n = diffusion or release exponent,t = time in h.

2.7. Stability study

The optimized formulation (F5) packed in silver foil and subjected to stability studies at $40^0C \pm 2^0C$/75 ± 5% RH. Sample was withdrawn at pre-determined time intervals of 0 (initial),30, 60 and 90 days. Tablet was evaluated for the different physicochemical parameters viz. appearance, weight variation,thickness, hardness, friability, drug content and in vitro release.

RESULTS AND DISCUSSION

3.1. Drug- excipients interaction and identification

The wavelength of maximum absorbance was obtained at 236 nm. The calibration curve was found to be linear in the range of 2-10 µg/ml and straight line equation was obtained having the regression coefficient value of 0.999.

FTIR spectrum of DTZ showed a characteristic stretching band of aliphatic C-H at 2966 cm^{-1}, C-O (acetone) stretching at 1743.12 cm^{-1}, C-O (lactone) stretching at 1678.13 cm^{-1}, o-substituted aromatic C-H out of plane bending at 839.11cm^{-1}, p-substituted aromatic C-H out of plane bending at 780.13cm^{-}1 wavenumber .These characteristic stretching bands were slightly varied after pre-formulation study, revealing no chemical interaction (Fig.1).

3.2. Physical characteristics

The powder blend of twelve formulations (F1-F12) were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio showed the pre-compressed blend has good flow property table 2. Formulated tablets evaluated for physical parameters such as hardness, thickness, weight variation, friability, and drug content, the results are shown in table 3. It was found that all the blends have good flow property as they showed angle of repose value was between 25 and 30^0, represents good flow property. Carr's index value was found to be less than 10 showing excellent property except formulation F9 and F12 which showed 13.01 and 13.19 respectively. Hausner's ratio was found to be less than 1.12 showing excellent flow property except formulation F9 and F12 which showed 1.14 and 1.13 respectively.

The total weight of each formulation was maintained constant; the weight variations of the tablets were within the permissible limits. According to IP specification, for tablets weighing more than 250 mg, ±5% deviation from the mean weight is acceptable. The weight of the tablet was fixed at 500 mg and was maintained for all the batches in order to minimize the effect of weight on the drug release. Hardness of tablets was found to be in the range of 3-4 kg/cm^2. The thickness of floating tablets ranged from 5.16 to 5.58 mm. Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion less than 1%. Drug content in all formulations was calculated and the presence of active ingredient ranged from 97 to 102%. The in-Vitro buoyancy studies in 0.1N HCl reveled the floating lag time was zero sec and floats more than 24hr. In-vitro buoyancy results showed in table 4.

3.4. In Vitro drug release

In vitro dissolution studies were performed in 0.1 N HCl (1.2 pH) and results depicted in Figs.3-5. Percentage drug release was calculated at one hour time intervals for 12h. Among all formulations, Formulation F5 gave desired release in first hour for loading dose and also retarded the drug release for 12h (90.5%).

3.5. Stability studies

According to ICH guidelines, three months stability studies conducted at controlled temperature $40^0C \pm 2^0C$ and humidity75 ± 5% RH showed negligible changes in results table 5.

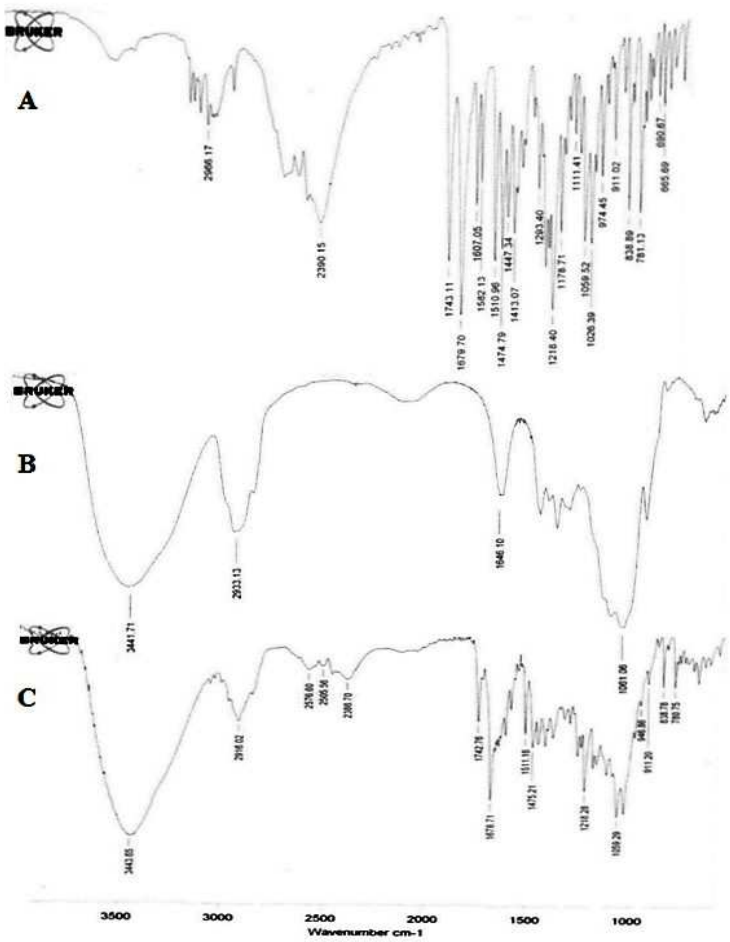


Fig 1. – FTIR of A) pure Diltiazem HCl, B) HPMC K15M and C) optimized formulation (F5)

Table 2. Pre-compression evaluation

Formulation code	Angle of repose[a]	Bulk density	Tapped density	Compressibility index	Hausner's ratio
F1	27.20±0.10	0.410 ± 0.12	0.430 ± 0.13	6.95 ± 0.04	1.06 ± 0.13
F2	27.06±0.2	0.402 ± 0.17	0.437 ± 0.08	7.77 ± 0.17	1.06 ± 0.08
F3	31.11±0.08	0.417 ± 0.05	0.450 ± 0.13	7.35 ± 0.09	1.08 ± 0.02
F4	30.2 ± 0.11	0.418 ± 0.01	0.444 ± 0.03	8.13 ± 0.08	1.09 ± 0.15
F5	26.78±0.14	0.420 ± 0.12	0.463 ± 0.09	9.25 ± 0.11	1.07 ± 0.06
F6	29.3 ± 0.06	0.403 ± 0.04	0.443 ± 0.16	10.03± 0.06	1.13 ± 0.12
F7	27.6± 0.05	0.416 ± 0.06	0.446± 0.11	6.56 ± 0.15	1.06 ± 0.04
F8	26.16± 0.18	0.436 ± 0.12	0.468 ± 0.09	8.69 ± 0.02	1.16 ± 0.11
F9	30.78 ±0.06	0.421 ± 0.08	0.484 ± 0.07	13.01 ± 0.14	1.14 ± 0.03
F10	27.45± 0.12	0.407 ± 0.05	0.437 ± 0.05	7.07 ± 0.07	1.07 ± 0.08
F11	30.6 ± 0.05	0.410 ± 0.14	0.450 ± 0.08	8.30 ± 0.18	1.10 ± 0.05
F12	31.24± 0.11	0.422 ± 0.02	0.462 ± 0.12	13.19 ± 0.07	1.13 ± 0.12

[a] *(ø ±S.D) n = 3.*

Table 3. Post-compression evaluation

Formulation code	Hardness (kg/cm^2± SD)[a]	Thickness (mm ± SD)[a]	Wt. variation (mg ± SD)[b]	Friability (%w/w)[b]	Drug content (% ± SD)[a]
F1	3.10 ± 0.10	5.24 ± 0.005	500 ±0.83	0.58 ± 0.06	99.2 ± 1.14
F2	3.06 ± 0.15	5.33 ± 0.026	501.10± 2.06	0.64 ± 0.11	98.6 ± 2.12
F3	3.11 ± 0.12	5.43 ± 0.015	502.5 ± 2.52	0.48 ± 0.02	100.5± 0.09
F4	3.46 ± 0.05	5.24 ± 0.011	500.0 ± 2.62	0.78 ± 0.05	98.6 ± 2.05
F5	3.23 ± 0.05	5.43 ± 0.020	503.3 ± 2.26	0.54 ± 0.02	99.8 ± 0.12
F6	4.36 ± 0.11	5.16 ± 0.015	499.4 ± 1.89	0.67 ± 0.12	98.5 ± 2.02
F7	4.38 ± 0.02	5.55 ± 0.005	502.20± 1.75	0.54 ± 0.07	97.8 ± 0.05
F8	3.53 ± 0.07	5.36 ± 0.015	498.33± 2.36	0.45 ± 0.11	101.5± 0.09
F9	3.63 ± 0.05	5.24 ± 0.015	499.5 ± 1.25	0.64 ± 0.05	99.4 ± 1.08
F10	3.11 ± 0.07	5.27 ± 0.005	500.1 ± 2.33	0.72 ± 0.07	97.3 ± 0.15
F11	4.13 ± 0.11	5.58 ± 0.010	501.9 ± 1.66	0.59 ± 0.13	102.3± 0.06
F12	4.0 ± 0.10	5.26 ± 0.020	502.4 ± 2.06	0.68 ± 0.02	99.3 ± 2.12

[a]n=10[b]n=20

Table 4. Post-compression evaluation

Formulation code	FLT (Sec)	FD (h)
F1	0	>24
F2	0	>24
F3	0	>24
F4	0	>24
F5	0	>24
F6	0	>24
F7	0	>24
F8	0	>24
F9	0	>24
F10	0	>24
F11	0	>24
F12	0	>24

n = 3, FLT -floating lag time, FD - floating duration.

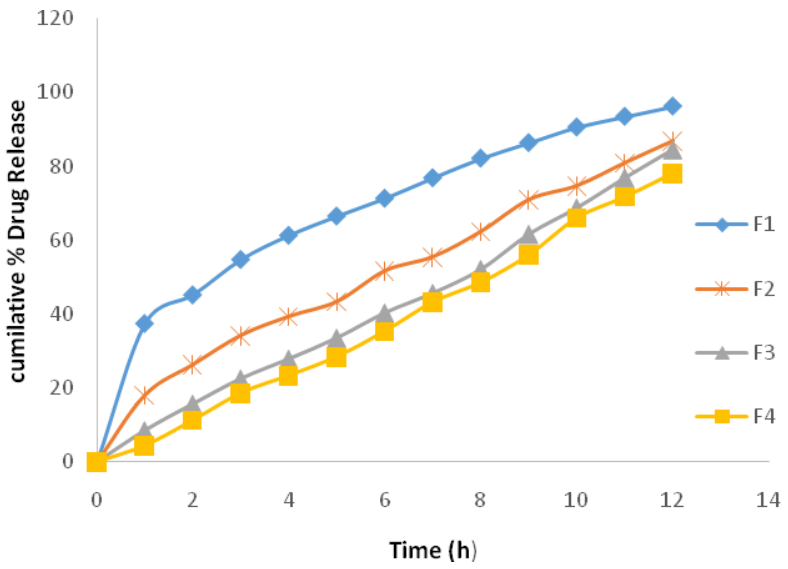


Fig.3- In-vitro drug release profiles of formulations F1-F4

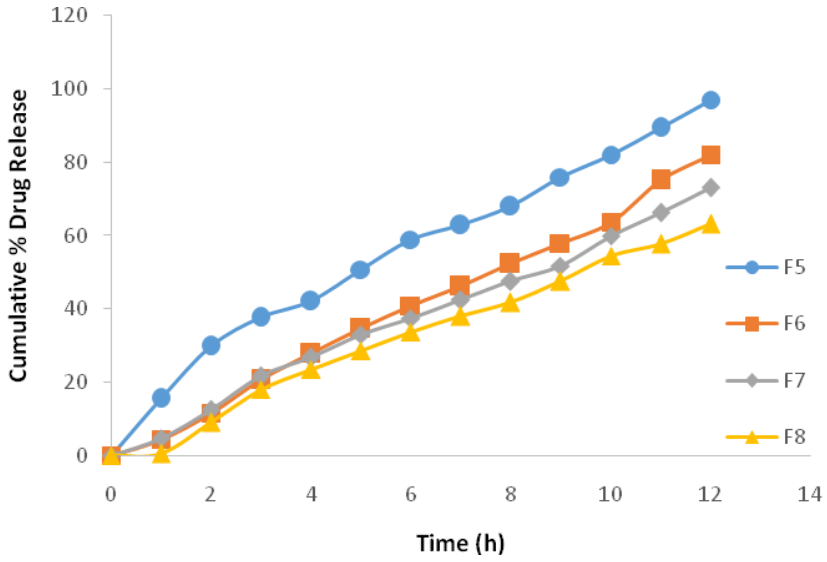


Fig.4- In-vitro drug release profiles of formulations F5-F8

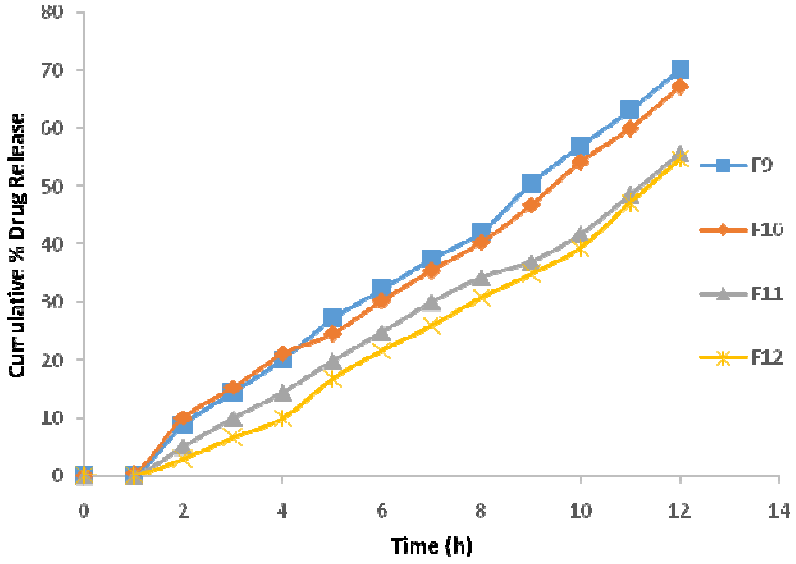


Fig.5- In-vitro drug release profiles of formulations F9-F12

Table 5.Stability studies of optimized formulation (F5)

Parameters	After30 days	After60 days	After90 days
Physical appearance	No change	No Change	No Change
Weight variation (mg ± SD)[b]	500.33 ± 2.36	500.28 ± 2.1	499.86 ± 1.94
Thickness (mm ± SD)[a]	5.36 ± 0.015	5.38 ± 0.021	5.42 ± 0.026
Hardness (kg/cm2 ± SD)[a]	3.53 ± 0.07	3.53 ± 0.11	3.64 ± 0.23
Friability (% ± SD)[b]	0.45 ± 0.11	0.45 ± 0.08	0.45 ± 0.14
Drug content (%)[a]	101.2 ± 0.15	101.12 ± 0.32	100.96 ± 0.21
Buoyancy lag time (sec)[c]	0	0	0
Duration of floating (h)	>24	>24	>24

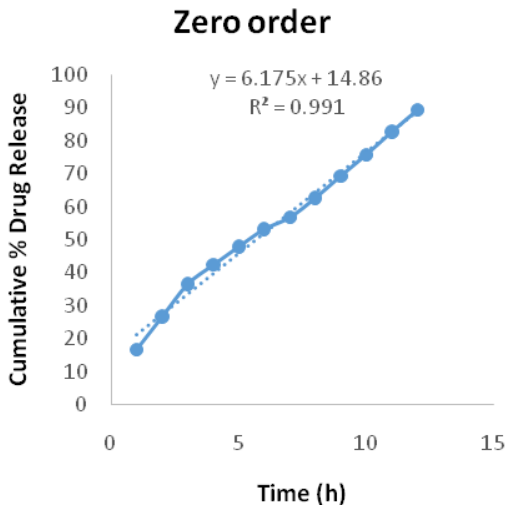
[a]n=10, [b]n=20, [c]n=3

3.5 Kinetic analysis of release data

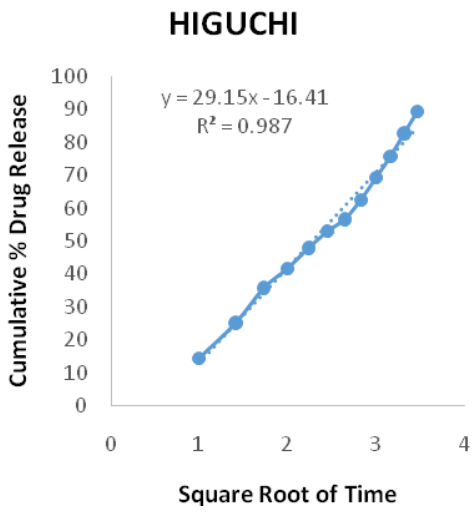
To understand the rate and mechanism of drug release from optimized tablet formulation, dissolution data was fitted into different release kinetic models. The model that best fitted the release data was selected based on the correlation coefficientvalue (r2) obtained from various kinetic models table 6. Correlation coefficients of optimized formulation F5 showed higher correlation with zero order plots and then value of Korsemayer-peppas equation is 0.75 indicating that drug transport mechanism is Non Fickian diffusion.

Table 6. Different Kinetic Models for Diltiazem Hydrochloride Floating Tablets

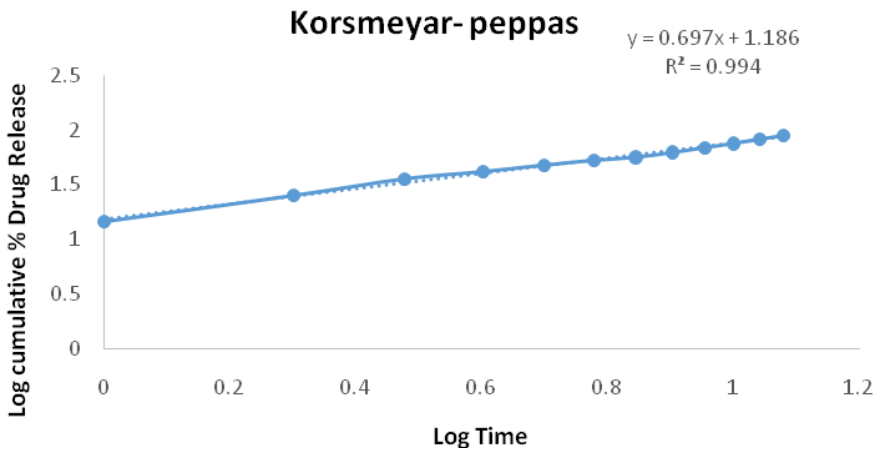
Formulation code	Zero order	First order	Higuchi	Korsemayer- Peppas
	r^2	r^2	r^2	r^2
F1	0.984	0.991	0.997	0.998
F2	0.993	0.989	0.980	0.987
F3	0.996	0.993	0.972	0.995
F4	0.997	0.986	0.974	0.996
F5	0.991	0.974	0.987	0.992
F6	0.993	0.998	0.994	0.989
F7	0.986	0.997	0.997	0.985
F8	0.979	0.993	0.998	0.972
F9	0.996	0.998	0.986	0.997
F10	0.991	0.994	0.988	0.998
F11	0.997	0.996	0.984	0.991
F12	0.993	0.983	0.958	0.990



(a)



(b)



(c)

Fig.10 -Kinetic evaluation of optimized formulation (F5): (a) zero order plot, (b) Higuchi plot, (c) Korsmeyer-Peppas plot

CONCLUSION

The low density -based floating drug delivery system was the promising system. The use of hydrophilic and gel forming polymers had its own advantages of maintaining integrity and buoyancy of tablets. It could be conclude that for proper floating and in vitro release nature and concentration of polymer is important. Formulation F5 followed zero order, Higuchi and Korsmeyer-Peppas release kinetics. The aim of Preparation of highly porous gastro retentive diltiazem hydrochloride tablets using a sublimation method was achieved.

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