Formulation and Characterization of Floating Tablets of Diltiazem Hydrochloride

Ara N. Patel*, Falguni M. Patel

Department of Pharmaceutics, Bhupal Nobles' Girls' College of Pharmacy,Udaipur, Rajasthan, 313001

*Address for Correspondence

arapatel29@gmail.com

Abstract

The purpose of the present study was to develop an optimized floating drug delivery system of Diltiazem hydrochloride. Diltiazem floating tablets wereformulated with different concentrations of two grades of HPMC polymers (HPMC K4M and HPMC K100M) by using wet granulation technique andevaluated for the different evaluation parameters such as thickness, diameter, drug content uniformity, friability, floating lag time, *in-vitro* buoyancy, *in-vitro* drugrelease studies and stability studies were performed. All the evaluation parameters results were significant. *In-vitro* drug release studies were performed and drugrelease kinetics evaluated using the linear regression method was found to follow both Higuchi and Korsemeyer and Peppa's equation. The drug release mechanismwas found fickian type in most of the formulations. The prepared formulation shows better and significant results for all the evaluated parameters. The formulation A4 containing (HPMC K 4 M) shows maximum percentage of drug release (99.87 %) and prolonged release for time period of about 12 h, therebyimproves the bioavailability and patient compliance.

Keywords:*Floating drug delivery system, DiltiazemHCl, Buoyancy period,Higuchi plots, Accelerated stability studies.*

Introduction

Various approaches have been worked out to improve the retentionof an oral dosage form in the stomach e.g. floating system, swelling and expandingsystem, bioadhesive system, modified shape system, high-densitysystem and other delayed gastric emptying devices[1]. Floating drug deliverysystems (FDDS) or hydrodynamically balanced systems have a bulk densitylower than gastric fluids and therefore remain floating in the stomach withoutaffecting the gastric emptying rate for a prolonged period. These systems areuseful for drugs acting locally in the gastrointestinal tract, drugs which arepoorly soluble and unstable in intestinal fluid. While the system is floating ongastric contents, the drug is slowly released at a desired rate from the floatingsystem and after the complete release; the residual system is expelled from thestomach. This leads to an increase in the gastric residence time and bettercontrol over fluctuations in plasma drug concentrations[2].

Gastric retention drug delivery systems can be retained in the stomachfor a long time. Such retention systems are important for drugs that aredegraded in intestine or for drugs like antacids or certain antibiotics and enzymesthat should act locally in the stomach. If the drugs are poorly soluble inintestine its retention in gastric region may increase the solubility before theyare emptied, resulting in increased bioavailability. Such systems are moreadvantageous in improving GI absorption of drugs with narrow absorptionwindows as well as for controlling release of the drugs having site-specificabsorption limitation. Retention of drug delivery systems in the stomach prolongsoverall GI transit time, there by resulting in improved bioavailability forsome drugs[3].

The rate of gastric emptying depends mainly on viscosity, volumeand caloric content of meals. Nutritive density of meal helps to determine the rate of gastric emptying, increase in acidity and caloric values slows down thegastric emptying rate. Biological factors such as

age, body mass index, gender,posture and diseased states influence gastric emptying. Generally females haveslower gastric emptying rates than males. Stress increases gastric emptying rates while depression slows it down. Gastric emptying of dosage form isdifferent in fasted and fed condition. Volume of liquids affects the gastric emptyingi.e. larger the volumes faster the emptying. Fluids taken at body temperatureleave the stomach more quickly than either colder or warmer fluids. Thegastric residence time may increase by the ingestion of a meal prior to administrationof liquids. Park et al have reported the residence time for both liquid andsolid foods in each segment of the GIT.

Diltiazem hydrochloride is one of the new generation calcium channelblocker with peripheral and coronary vasodilator properties, which is usedin the management of classical, Vasospastic angina pectoris and also in thetreatment of essential hypertension. The plasma half life of the DiltiazemHClis 3 - 4 hrs. The success of a therapy depends on selection of the appropriatedelivery system as much as it depends on the drug itself. Sustained releasedosage forms are designed to complement the pharmaceutical activity of themedicament in order to achieve better selectivity and longer duration of action.Diltiazem is rapidly and almost completely absorbed from the gastrointestinaltract following oral administration, but undergoes extensive first pass hepaticmetabolism. The bioavailability has been reported to be about 40%, althoughthere is considerable inter-individual variation in plasma concentrations[4]. Diltiazem is around 50% bound to plasma protein. It is extensivelymetabolized in the liver, one of the metabolites desacetyldiltiazem has beenreported to have 25 to 50% of the activity of the parent compound. The plasmahalf-life is 3-4 hours. Approximately 60% of the dose is excreted in the bile and35-40% in the urine, 2-4% as unchanged diltiazem.

Materials and Methods:

DiltiazemHCl was obtained as a gift sample from the Cipla Ltd.Goa, India. Hydroxy Propyl Methyl cellulose (HPMC K4M and HPMCK100M) was obtained from the Zydus-Cadila

HealthCare Ltd. Ahmedabad, India. Sodiumcarboxy methyl cellulose was obtained as a gift sample from the BPRL, Bangalore,India. Another excepients and chemicals were purchased from the DrugsIndia, Hyderabad. All the ingredients used were analytical grade only.

Preformulation Studies

Identification of the pure drug and polymer were performed usinginfrared spectroscopy. IR spectroscopy (using Perkin Elmer) by KBr pelletmethod was carried out on drug and polymer. They are compressed under 10tones pressure in a hydraulic press to form a transparent pellet. The pellet wasscanned from 4000 to 400 cm-1 in a spectrophotometer and peaks obtainedwere identified.

Drug Excipient Compatibility Studies

About 90 mg of diltiazem hydrochloride with various excipients in1:1 ratio in glass vials were taken and kept at various accelerated condition(300^0C/65%RH,400^0C/75%RH and 600^0C/80%RH) in stability chamber (OsworldStability Chamber, India) for one month in open and closed condition. Thesample were withdrawn on 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 14th, 21st and 30^{th}day and physical characteristics like colour change, if any was recorded. Finallythe mixtures with no colour change were selected for formulation.

Formulation of Floating Tablets

The composition of different formulations DiltiazemHCl tabletsis shown in Table-01. The floating tablets of DiltiazemHCl were preparedusing low density polymers like HPMC K4M and HPMC K100M (individualand combination) by using the wet granulation technique. Accuratelyweighed quantities of hydroxyl propyl methyl cellulose, lactose, sodium bicarbonateand the active ingredient were mixed homogeneously. Alcoholic solutionof HPMC (1%W/V) was used as a granulating agent. The granules were dried ina conventional hot air oven. The dried granules were sieved through the sieveNo: 40/60. The prepared granules were evaluated for the different flow propertiesparameters. The prepared floating

granules were mixed with the Magnesiumstearate as a lubricant and the granules were compressed into tabletsusing Pilot Press TM 9 station Model No IPM Rotary tablet punching machine.[5]

Flow Proprties of Floating Granules[6, 7]

Angle of repose

The frictional forces in loose granules can be measured by the angle ofrepose (q). The angle of repose of the prepared granules was evaluated by usingthe fixed funnel method. Specified quantity of the granules were taken andpoured into the funnel, so automatically form the heap. So this formed heapdiameter and height were measured. Then calculate the angle of repose by usingbelow mentioned formula:

$$q = Tan - 1 (h/r)$$

Determination of Bulk density and tap density

Apparent bulk density (rb) was determined by pouring the granulesinto a graduated cylinder. The bulk volume (Vb) and weight of the powder (M)was determined. The bulk density was calculated using the formula:

$$rb = M/Vb$$

The measuring cylinder containing a known mass of granules wastapped for a fixed time. The minimum volume (Vt) occupied in the cylinder andthe weight (M) of the granules was measured. The tapped density (rt) wascalculated using the following formula

$$rt = M/Vt$$

Compressibility Index

The simplest way for measurement of free flow of powder is compressibility,a indication of the ease with which a material can be induced to flowis given by compressibility index (I), which is calculated as

$$I = (rt - ro/rt) \acute{} 100$$

The value below 15% indicates a powder which usually give rise togood flow characteristics whereas above 25% indicate poor flow ability.

Hausner ratio is an indirect index of ease of powder flow. It is calculated by theFollowing formula

$$\boldsymbol{Hausner\ ratio\ =\ rt\ /\ rd}$$

Where, rt= tapped density and rd= bulk density

In Vitro Buoyancy Study[8, 9]

The time, tablets took to emerge on the water surface (floating lagtime) and the time, tablets constantly float on the water surface (duration ofFloating) were evaluated. The buoyancy of the tablets was studied in USP 24type II dissolution apparatus at 37±0.5^{0}C with paddle rotation at 100 rpm in900 ml of simulated gastric fluid at pH 1.2. The measurements were carried outfor each formulation of tablets. The time of duration of floatation was observedvisually.

Evaluation of Floating Tablets

Thickness and Diameter[10]

The thickness and diameter of the tablets wascarried out using vernier caliper. Five tablets were selected from each batchand results were expressed in millimeter.

Weight variation test[11]

Twenty tablets were selected at random, individually weighed in asingle pan electronic balance and the average weight was calculated. The uniformityof weight was determined according to I.P. Specifications. As per 1P notmore than two of individual weights should deviate from average weight bymore than 5% and none deviate more than twice that percentage.

Hardness test[10]

Tablet requires a certain amount of strength or hardness and resistanceto friability to withstand mechanical shocks of handling in manufacture,packing and shipping. Monsanto hardness tester was used for the measurementof hardness of the prepared floating tablets. Five tablets were selected fromeach batch and results were expressed in Kg/cm^2.

Friability test[10]

It was done in Roche friabilator apparatus where the tablets weresubjected to the combined effect of abrasion and shock by utilizing a plasticchamber that revolves at 25 rpm dropping the tablets at a distance of six incheswith each revolution. Preweighed samples of 20 tablets were placed in thefriabilator, which was operated for 100 revolutions. The tablets were reweighed.Conventional compressed tablets, loss less than 0.5 to 1.0% of their weight aregenerally considered acceptable.

$$\text{Friability} = \frac{\text{Weight loss}}{\text{Weight of tablets before operations}} \times 100$$

Drug content uniformity[9]

Ten tablets were weighed, taken in a mortar and crushed to powderform. The powder weighed equivalent to 100mg of diltiazem HCL was takenin a 100ml volumetric flask and dissolve with 0.1 N HCl It was then heated at600C for 30 minutes. The solution was filtered using membrane filter (0.45nm)and then its absorbance was measured at 238nm. The amount of drug wascalculated using standard graph.

Study of release profile[9]

The release of Diltiazem hydrochloride from floating tablets wasdetermined by using Dissolution Tester USP XXII. The dissolution test wasperformed using 900 ml 0.1N HCl

solution at 37 ± 0.5ºC and the paddles wererotated at 50 rpm. At every 1 hour interval, samples were withdrawn from thedissolution medium and it was replaced with fresh medium to maintain thevolume constant. The samples were filtered and diluted to suitable concentrationswith 0.1 N HCl solutions. The absorbances of the solutions were measured at 238 nm for diltiazem hydrochloride with a Shimadzu UV-Visibledouble beam spectrophotometer (Shimadzu, Japan). Cumulative percentagedrug release was calculated using an equation obtained from standard curve.

Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to zero order,first order, Higuchi, Korsmeyer and Peppas, equations to ascertain the kineticmodeling of drug release.

Stability Studies

Stability studies were carried out for optimized formulations. Thetablets were packed in aluminum foil placed in airtight container and kept at 40^0Cin refrigerator, 400^0C /75% RH in stability chamber (Oswald, Mumbai) and600^0C in incubator for 1month. At the interval of 15 days, the tablets werewithdrawn and evaluated for physical properties, *In-vitro* drug release.[12]

Table-1: Composition of the ingredients in the different batches of theDiltiazemHCl floating tablets

S No	Ingredients	Quantity of ingredient for particular Batch A 1	A 2	A 3	A4	A 5	A 6	A 7	A 8
1	Diltiazem Hydrochloride	90	90	90	90	90	90	90	90
2	HPMC K 100M	75	120	150	-	-	-	60	60
3	HPMC K 4M	-	-	-	75	125	150	70	100
4	Sodium Bicarbonate	20	20	20	20	20	20	20	20
5	SCMC	25	25	25	25	25	25	25	25
6	Lactose	87	42	12	87	42	12	32	12
7	Magnesium Stearate	3	3	3	3	3	3	3	3

Table-2: Physical Characteristics of Granules

S No	Batch Code	Angle of repose (0)	Bulk density (g/ml)	Tap density (g/ml)	Carr's index	Hausner ratio
1	A1	21.3±0.03	0.56± 0.01	0.65 ± 0.01	13.8 ±0.03	1.16± 0.20
2	A2	24.4±0.02	0.57± 0.03	0.67± 0.04	14.9±0.020	1.17±0.21
3	A3	25.3±0.04	0.64±0.02	0.74±0.031	13.5±0.01	1.15±0.002
4	A4	21.3±0.03	0.60± 0.02	0.67±0.120	10.50± 0.210	1.17±0.004
5	A5	23.1±0.90	0.62± 0.030	0.69± 0.022	10.1± 0.003	1.11±0.03
6	A6	22.5±0.910	0.64±0.281	0.74± 0.208	13.5± 0.02	1.15±0.22
7	A7	26.2±0.04	0.53± 0.027	0.62±0.003	14.5±0.23	11.16 ±0.210
8	A8	20.7±0.05	0.49± 0.040	0.56±0.02	12.5±0.004	1.14±0.302

Table-3: Physicochemical evaluation of Prepared tablet formulations

S No.	Batch Code	Thickness mm ±S.D	Diameter mmVariation (%) ±S.D	Weight (mg)	Friability (%)	Hardness (Kg/cm2)	Content Uniformity
1	A 1	4.98 ±0.01	7.98 ±0.02	300.1 ±0.02	0.9 ±0.024	4.10 ±0.01	99.48 ± 0.02
2	A 2	4.97 ± 0.05	7.97 ± 0.01	299.7±0.03	0.8 ±0.01	4.22 ± 0.02	98.88 ± 0.04
3	A 3	4.98 ± 0.03	7.98 ±0.02	299.8±0.13	0.9 ±0.03	4.42 ± 0.04	99.08 ±0.13
4	A 4	4.14 ± 0.01	8.01 ±0.07	299.9 ±0.01	0.8 ±0.03	4.41 ±0.03	99.89 ± 0.03
5	A 5	4.99±0.02	7.97 ±0.03	300.3 ± 0.02	0.7 ± 0.14	4.20 ±0.03	98.07 ±0.02
6	A 6	5.01 ±0.04	7.99 ± 0.01	299.7 ± 0.18	0.7 ±0.03	5.02 ±0.02	99.69 ± 0.14
7	A 7	4.99 ±0.03	8.02 ±0.02	299.8 ±0.14	0.9 ± 0.01	4.36 ±0.03	97.95 ±0.17
8	A 8	4.97 ±0.03	7.97 ±0.03	299.8±0.02	0.8 ± 0.03	4.41 ± 0.01	98.88 ±0.03

Table-4: Floating properties of tablets formulations

S.No	Batch code	Buoyancy lag time (sec)	Duration of Buoyancy (hrs)
1	A 1	60>	12
2	A 2	40 >	12
3	A 3	70>	12
4	A 4	40>	12
5	A 5	60 >	12
6	A 6	60 >	12
7	A 7	120 >	12
8	A 8	90 >	12

Table-05: Drug release kinetics of prepared formulations of DiltiazemHCl

Batch Code	Regression for zero order plot	Regression for first order plot	Regression for Higuchi's plot	Slope for Peppa's plot
A1	0.983	0.963	0.994	0.981
A2	0.992	0.948	0.988	0.994
A 3	0.995	0.939	0.977	0.985
A 4	0.996	0.663	0.981	0.997
A 5	0.997	0.637	0.973	0.995
A 6	0.990	0.677	0.971	0.992
A 7	0.990	0.970	0.991	0.998
A 8	0.986	0.986	0.990	0.996

FIG-1 COMPARITIVE IN VITRO RELEASE PROFILE OF FORMULATIONS A1 TO A 4

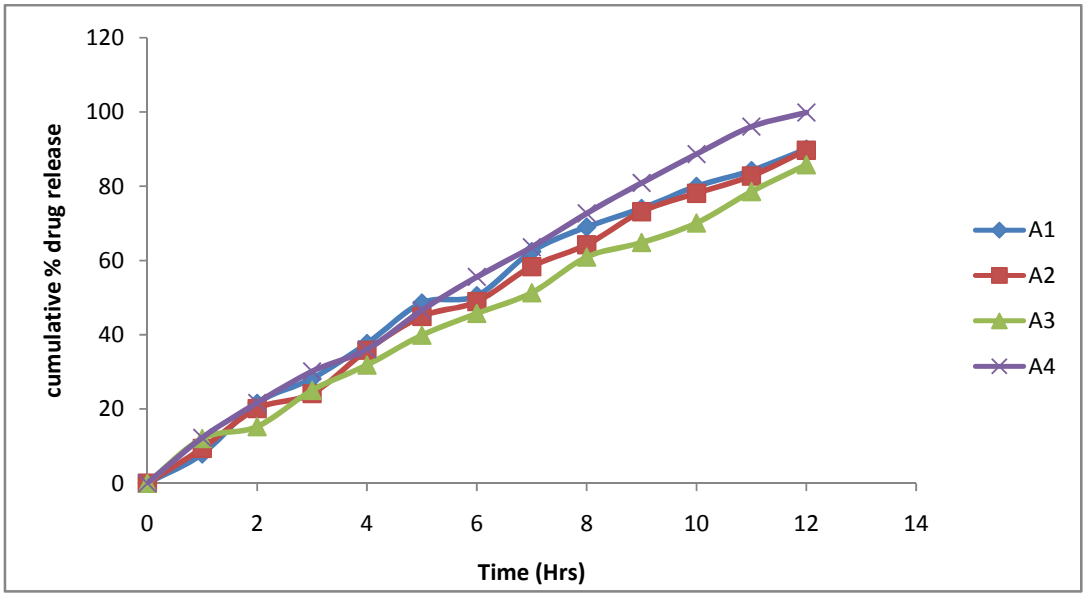


FIG-2 COMPARITIVE IN VITRO RELEASE PROFILE OF FORMULATIONS A5 TO A8

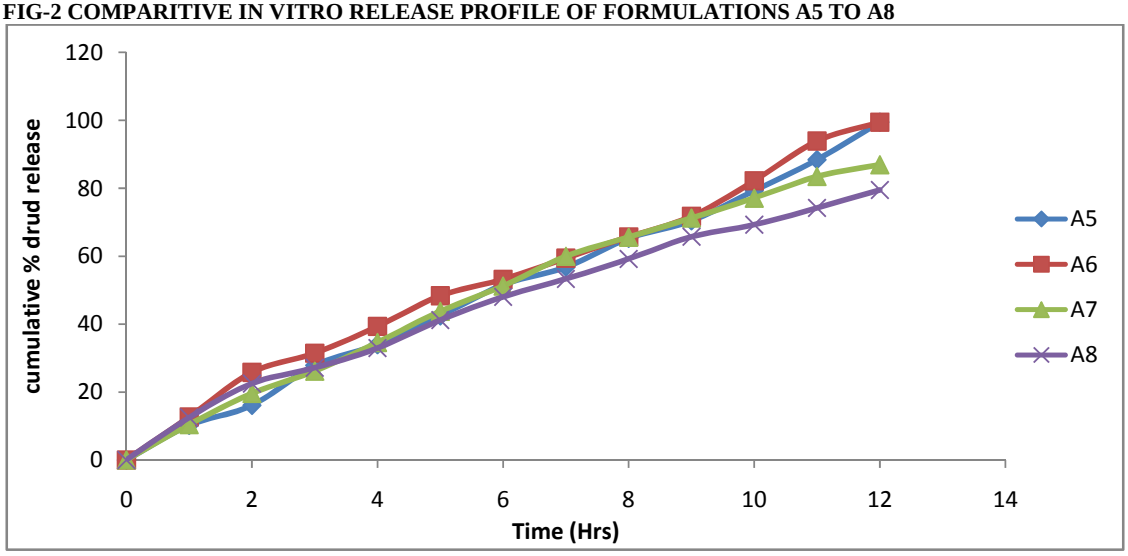
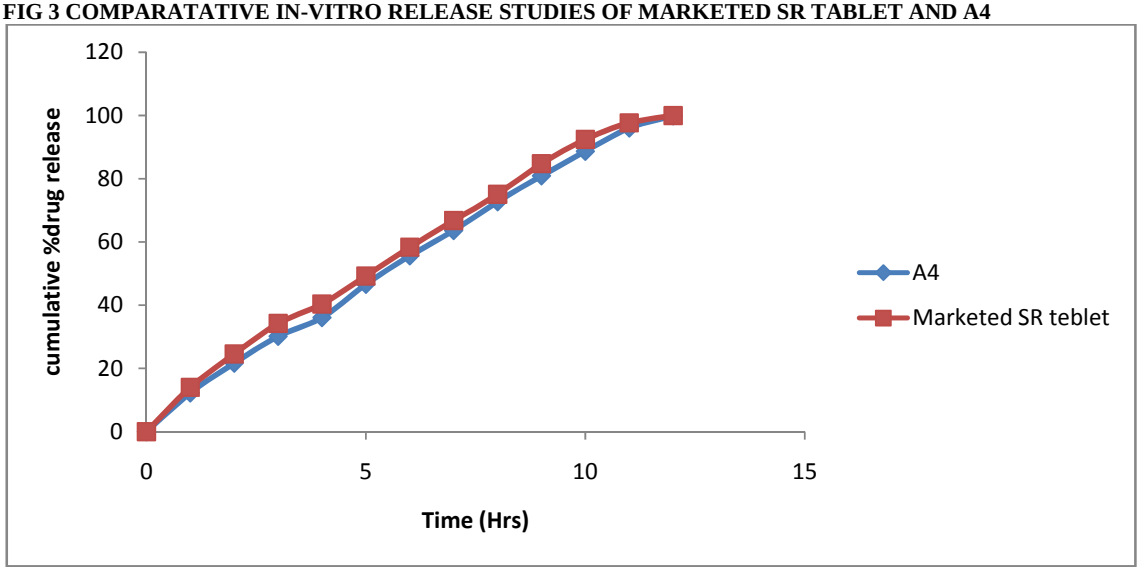


FIG 3 COMPARATATIVE IN-VITRO RELEASE STUDIES OF MARKETED SR TABLET AND A4



Results and Discussion

The present study was planned to prepare and characterize floating tablets of DiltiazemHCl using different polymers by wet granulation technique.Different grades of HPMC (K4M and K100M) and SCMC were used asswellable polymers. HPMC was chosen because it is widely used as a lowdensityhydrocolloid system upon contact with water a hydrogel layer wouldbe formed to act as a gel boundary for the delivery system, but it would fail toretard the release of drug through the matrix because of its solubility in stomachpH. SCMC was used in combination with HPMC to retard the drug release;because of its low solubility at pH 1.2 to 3. No drug polymer incompatibilitywas noted in their FTIR spectral studies.

The granules prepared for compression of floating tablet were evaluatedfor their flow properties (Table-02). Angle of repose was in the range of 20.7 ± 0.05 to 26.20 ± 0.04. Bulk density ranged between 0.49± 0.04 to 0.64 ± 0.28gm/cm3. Tapped density ranged between 0.56±0.02 to 0.74 ± 0.208. Carr's Index was found to be 10.10 ± 0.003 to 14.9 ± 0.02 and Hausnerratio ranged from 1.1 ± 0.03 to 1.17 ± 0.21. These values indicate that theprepared granules exhibited good flow properties.

On immersion in 0.1 N HCl, pH 1.2 solution at 37 ± 0.5^0C allfloating effervescent tablets floats immediately and remain buoyant up to 24 hwithout disintegration. Sodium bicarbonate was added as a gas-generating agent.Sodium bicarbonate induced carbon dioxide generation in presence of dissolutionmedium (0.1 N hydrochloric acid). It was observed that the gas generatedis trapped and protected within the gel, formed by hydration of polymer(HPMC K 100 M), thus decreasing the density of the tablet below 1 and tabletbecomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancystudies.

The thickness and diameter of the tablets were found in the range of 4.14± 0.01 to 5.01 ± 0.04 and from 7.97 ± 0.01 to 8.02 ± 0.02 respectively.The weight of the tablet varies between 299.7 ± 0.18 mg to 300.3 ± 0.02 withlow standard deviation which indicating the uniformity of weight. The variationin weight was within the range of ± 5% complying with

pharmacopoeial specifications.The hardness for different formulation was found to be between 4.10 ± 0.01 to 5.02 ± 0.02 kg/cm2 indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of goodmechanical resistance of the tablet. The drug content uniformity varied between 97.95 ± 0.17 to 99.89 ± 0.03. The results show that all the parameters arewithin limits and are shown in Table-03.

All the batches of tablets were found to exhibit short floating lagtimes and float for longer duration of time due to the presence of sodiumbicarbonate and HPMC which is shown in Table-04 and in Fig-04.

The data obtained from *in vitro* dissolution studies were fitted indifferent models viz. zero order, Higuchi and KorsemeyerPeppa's equation(shown in Table-05). The zero order plots were found to be fairly linear asindicated by their high regression values (r2 = 0.983 to 0.997). To confirm theexact mechanism of drug release from these tablets, the data were fitted toHiguchi and KorsemeyerPeppa's equation. The formulation A 4 with HPMCK 4 M (25%) shows maximum release of 99.87% at a time period of 12 hoursin a controlled manner. The *in-vitro* release plot has shown drug release followedby zero order kinetics, which was envinced from the regression value.From the regression and slope value of Higuchi's (0.981) and Peppa's (n = 0.997) plot respectively, the drug release was confirmed to followed by diffusionmediated non-Fickian transport mechanism. The *in-vitro* drug release resultsfor all the prepared formulations were shown in Fig-01 and 02.

In order to justify the suitability of the *in-vitro* kinetic pattern, tomaintain constant plasma concentration of the drug molecules, the formulationmust be clinically evaluated. Since the clinical studies are difficult to perform, in our study the formulation A 4 (25% HPMCK4M) was compared with amarketed available formulation. The comparative *In-vitro* release studies for prepared formulation A 4 and marketed SR tablet is shown in Fig-03.

The optimized A 4 formulation was subjected to stability studies for1 month. At the interval of 15 days the tablets were withdrawn and evaluatedfor hardness, thickness, weight variation, friability. All the parameters have notshown much variation when compared to the initial data**.** The *in-vitro* dissolutionwas carried out for specified time intervals. Based on the results, weobserved that, drug release profiles were not affected by exposing to temperature and the specified humidity conditions.

Conclusion

The approach of the present study was to develop floating tablets ofDiltiazemHCl and henceforth evaluate the release profiles of these formulations.The results generated in this study, Formulation A4 containing 25%HPMCK4M was found to release a maximum of 99.87% at the 12th hour. The drug release from A4 was found to follow zero order kinetics. It was also foundlinear in Higuchi's plot, which confirms that diffusion is one of the mechanisms of drug release. Comparison of A4 and commercial S.R. formulation of DiltiazemHCL revealed the fact that developed formulation (A4) showed comparablerelease characteristics, thus it may have fair clinical efficacy. Hence, the formulation A 4 has met the objectives of the present study.

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