Innovations in Pharmaceuticals and Pharmacotherapy

www.innpharmacotherapy.com

eISSN: 2321–323X

Research Article

Development of Gastro Retentive Floating Tablets of Diltiazem Hydrochloride

Bisen Aashish, Shukla Vaibhav *, Kharia Ankit Anand, Chatterjee D. P.

Oriental College of Pharmacy, Thakral Nagar. Bhopal, India 462021

Abstract

Gastroretentive drug delivery systems are the systems which are retained in the stomach for a longer period of time and thereby improve the bioavailability of drugs. Diltiazem hydrochloride is a Calcium channel blocker, an anti-hypertension and antianginal drug, Diltiazem Hydrochloride undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A, which results in less than 4% of its oral dose being excreted unchanged in urine. Suffers from poor bioavailability (~30% to 40%) owing to an important first pass metabolism. It has an elimination half-life of 3.5 hrs and an absorption zone from the upper intestinal tract. Thus the present work is aimed to formulate floating tablets of Diltiazem hydrochloride using an effervescent approach for gastroretentive drug delivery system. Floating tablets were prepared using direct compression technique using Hydrophilic polymer like HPMC K4M, HPMC K15M and hydrophobic polymer like Ethylcellulose as matrix materials in various quantities (%w/w), sodium bicarbonate, citric acid, magnesium stearate, talc and lactose in varying ratio to formulate the floating tablets. Observations of all formulations for physical characterization had shown that, all of them comply with the specification of official pharmacopoeias and/or standard reference. It was observed that tablets of batch F6 followed the results obtained, it was concluded that the formulation F6 is the best formulations as the extent of drug release was found to be around 99.81 % at the desired time 12 hrs.

Keywords: Floating tablets, swelling index, Diltiazem Hydrochloride, in-vitro buoyancy studies

***Corresponding Author: Vaibhav Shukla,** Oriental College of Pharmacy, Thakral Nagar, Raisen road, Bhopal-462021, India E-mail: vaibhav689@rediffmail.com

1. Introduction

Various approaches have been worked out to improvement on the retention time of an oral dosage form like floating tablets in the stomach. Floating drug delivery systems is Hydro dynamically Balanced Systems contain a bulk density lower than gastric fluid contents and after that remain floating materials in the stomach without affecting the gastric emptying rate for a prolonged period of time [1]

Floating drug delivery systems are very successful for drugs those long acting locally in the GI tract, and for poorly soluble drugs in intestinal fluid. Floating tablets float on gastric fluid, floating tablet should be release slowly with desired rate and after complete release residual system is expelled from the stomach. Floating drug delivery system used for better control over fluctuations in plasma drug concentrations and increase gastric residual time of tablets in stomach. [1]

Gastric retention systems are important for those drugs which are degraded in small intestine or for drugs like enzymes and antacids that should act locally in stomach. If the drug is less soluble in intestine its retention in gastric region may increase the solubility before they are emptied, resulting in increased bioavailability. Floating drug delivery systems are more useful in improving gastro intestinal absorption of drug with narrow absorption window as well as for better controlling [1]

Basic Gastrointestinal Tract Physiology:

Anatomically the stomach is divided into 3 regions: 1 Fundus, 2 Body, and 3 Antrum (pylorus). Proximal part made of Fundus and Body acts as a reservoir for undigested material, whereas the Antrum is the main

©Innovations in Pharmaceuticals and Pharmacotherapy, All rights reserved

site for mixing motions and act as a pump for gastric emptying by propelling actions [3]

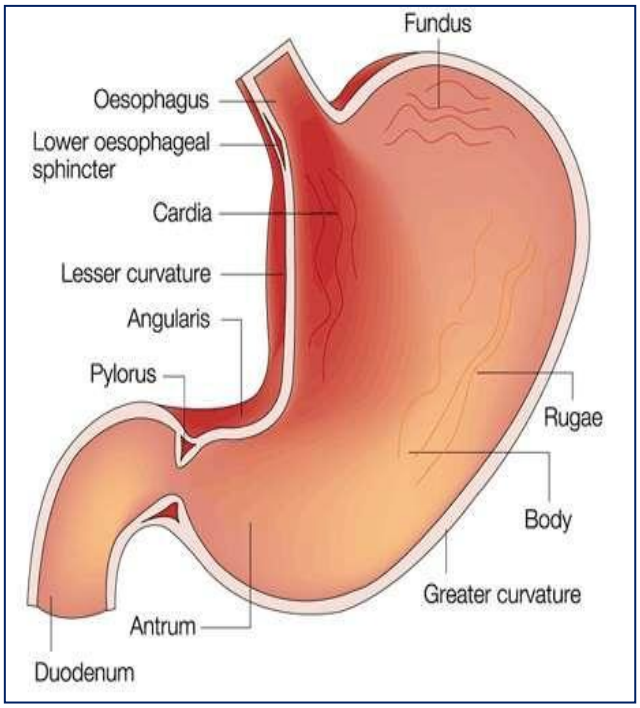

Figure 1: Structure of Stomach.

Stomach Physiology

The stomach is a main part of the digestive system and it's situated between Esophagus and small intestine. And wall of stomach is structurally same like other parts of the digestive system, whole digestive system contain same structure with exception that stomach contain extra, oblique layer of smooth muscle under the circular layer, these layer helps in the work of complex grinding motions of food materials. But in the empty state, stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds known as rugae. [1]

Given below four types of secretary epithelial cells that cover the stomach surface:

- Mucous cells are responsible for alkaline mucus secretion that protects the epithelium against acid.
- Parietal cells are responsible for secretion of HCL.
- Chief cells are responsible secretion of pepsin, and proteolytic enzyme.
- G cells are responsible secrete the gastrin hormone. The contraction of gastric smooth muscle serves two basic work.
- Administered food is crushed, grind, mixed and liquefy to form Chyme in the stomach.
- Chyme of food is moved by the pyloric canal into the small intestine, these is Gastric emptying.

Experimental

2. Methods and Materials

Diltiazem Hydrochloride drug was obtained gift by P.D.P.L. Jalandhar Punjab, India respectively and HPMC K4M, HPMC K15M was gifted by Promate lab Indore, MP, INDIA and Ethyl cellulose, Sodium bicarbonate was also gifted by Promate lab INDORE, MP, India. Citric acid (anhydrous), Magnesium stearate, Talc, Spray dried lactose was also gifted by Promate lab Indore, MP, India.

Preparation of standard curve of diltiazem hydrochloride

For the prepration of standard curve first f all weighed accurately 100 mg of Diltiazem Hydrochloride and transferred in to a 100ml volumetric flask which already containing 100 ml of 0.1 N HCl. After that shaked well and dissolved well to the solution. The solution resulted is ≈1000 µg/ml. After that 10 ml of this solution is transferred to another volumetric flask to achive solution of 100 µg/ml as stock. Then again 10 ml of this solution is transferred to another volumetric flask to achive solution of 10 µg/ml and the absorbance was taken on double beam U.V. spectrophotometer using λ max at 236.80nm. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Preparation of 0.1 N HCl Dilute 8.5 ml of concentrated HCl in 1000 ml of distilled water to get 0.1 N HCl.

Formulation of floating tablets:

- Formulation of Diltiazem Hydrochloride floating tablets Diltiazem Hydrochloride was used in all formulation with various grades of HPMC & Ethyl cellulose in different-different concentration to formulate the Diltiazem Hydrochloride floating tablets.

- In which Lactose was used as a Diluents in the preparation of the Diltiazem Hydrochloridetablets.

- Sodium bicarbonate was used as buoyancy providing agent to the floating tablets Diltiazem Hydrochloride,due to liberation of CO2 when floating tablets come in contact with acidified dissolution medium.

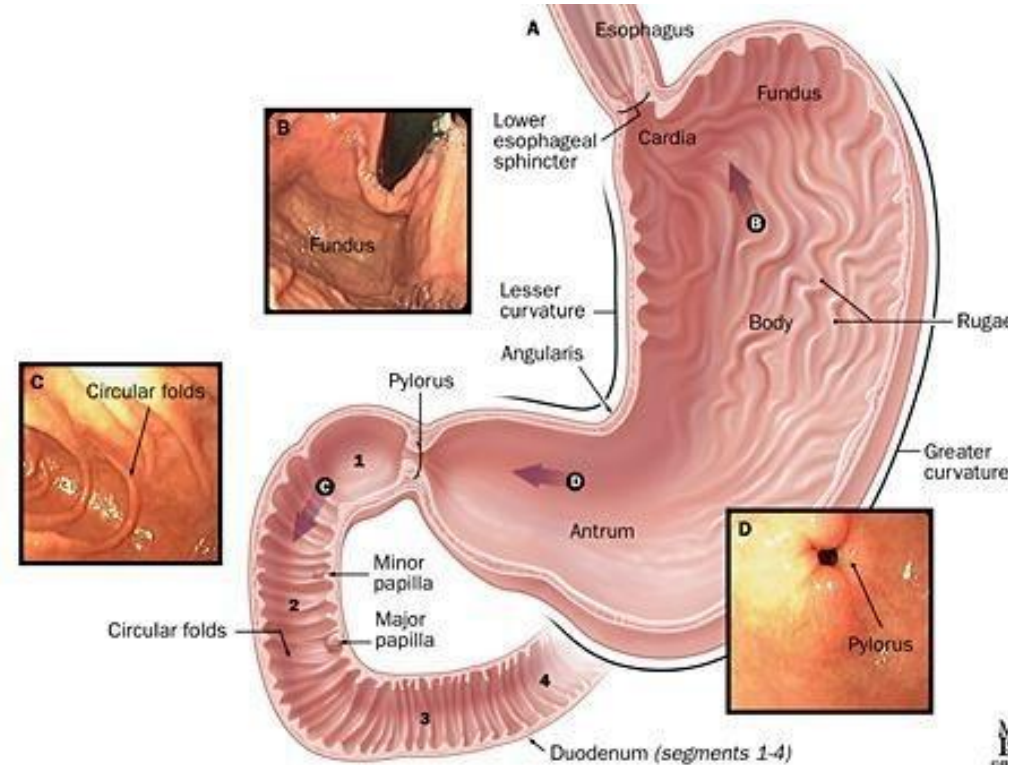

Figure 2: Stomach Physiology.

Table 1: Formula for formulation F1 –F12

Ingredients	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
HPMC K4M	75		37.7	60		30	45		22.5	90		
HPMC K15M		75	37.7		60	30		45	22.5		90	
Ethylcellulose	15	15	15	30	30	30	45	45	45			90
Sodium bicarbonate	30	30	30	30	30	30	30	30	30	30	30	30
Citric acid	15	15	15	15	15	15	15	15	15	15	15	15
Magnesium Stearate	6	6	6	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6	6	6	6
Lactose	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total Weight	300	300	300	300	300	300	300	300	300	300	300	300

Citric acid was incorporated in the floating Diltiazem Hydrochloride tablets formulation used to nullify the effect of the acidic dissolution media on the releasing of drug.

- The level of the drug Diltiazem Hydrochloride in all of the formulation was kept constant at 30% and tablet weight was adjusted so as to contain 90 mg of Diltiazem Hydrochloride in each tablet.
- Different Diltiazem Hydrochloride tablets formulations were prepared by Direct Compression Technique.
- All Diltiazem Hydrochloride tablets formulation powders should be passed through #80 no of mesh sieve.
- Required quantity of drug Diltiazem Hydrochloride and low-density polymer and hydrophobic polymer ethylcellulose were mixed thoroughly. Talc (2% w/w) and magnesium
- Stearate (2% w/w) were finally at last added as glident and lubricant respectively [3,2].
- The blend was directly compressed (9mm diameter punches) using tablet compression machine. The tablet weight was adjusted to 300 mg and 250 tablets for each batch were prepared. The formula for the different batches is given in the table.

Evaluation of Floating Tablets of Diltiazem Hydrochloride

I. Pre-Compression Evaluation Parameters

(a) Angle of Repose

Funnel method is used to determine the angle of repose of powder blend. First of all accurately weighed powder blend and taken in the funnel and adjust the funnel height and tip of the funnel just touched the apex of powder blend. Then powder blend was allowed to flow on the surface through the funnel. After that we measured the diameter of powder cone and calculated the angle of repose by these formulas. [2,3]

$$\mathbf{Tan\ \theta = h/r}$$

$$\mathbf{1\ \theta = tan\ h/r}$$

(Where, θ = angle of repose, h = height, r = radius.)

Table 2: The relationship between Angle of repose and powder flow

Angle of repose	Powder flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

(b) Bulk Density

Bulk density (g/ml) measured by pouring preserved bulk 2gm of powder from each formulations in to a 10 ml of cylinder and measures the volume and weight. Bulk density of powder is depending on the particle packing. A consolidate powder contain grater strength. A powder Consolidation is an indirect method of qualifying powder. Bulk density was calculated by the following formula. [12]

$$\mathbf{Bulk\ density = W/Vo}$$

(Where, W = wt. of powder, Vo = initial volume.)

(c) Tapped Density

Tapped density measurement by the tapping the 2gm of powder which to taken for bulk density blend in to the 10 ml measuring cylinder. Not the initial volume and tapped volume is continued until any further changes in cylinder volume. Then note tha tapped volume of powder blend. Tapped density was calculated by these formulas.

$$\mathbf{Tapped\ density = W/Vf}$$

(Where, W = wt. of powder, Vf = final volume.)

(d) Compressibility Index (Carr's Consolidation Index)

Compressibility index is measurement of the natural tendency to behave in a particular way of powder to b compressed. Compressibility index contain ratio of bulk and tapped density both densities will be closer in a value for poored flowing powder materials there are more chances of interparticle interaction and grater difference between the bulk and tapped densities. Compressibility index was calculated by these formulas.

Compressibility index = Dt-Db /Dt X 100

(Where D = Bulk density, D = Tapped density)

II. Post- Compression Parameters

(a) Tablet Dimensions

Tablet dimension measurement means measurement of diameter and thickness of five randomly selected tablets. By using vernier calipers as instrument. The pharmacopoeia states that the deviation in a batch of tablet should not more than the limit of ± 5% of their determined standard values of tablet dimensions.

(b) Hardness Test

Hardness test is used to measure of crushing strength kg/cm of prepared randomly selected tablets. For the

measurement of hardness we used Monsanto tablet hardness tester. Hardness of tablet indicate the ability of withstand mechanical during handling and transportation. The measured hardness of tablets of each batch ranged between 4.8 to 5.6kg/cm^2 .This ensures good handling characteristics of all batches.

(c) Friability Test

Instrument for friability test we used Roche Friabilator result of friability test expressed in percentage (%). Then we randomly selected 10 tablets and weighed initially and 0 transferred in to Roche Friabilator. Roche Friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolution then tablets weighed again percentage of friability calculated by these formula. [3,4]

$$\%F = (1 - W/W\ ) \times 100\ 0$$

Where, Wo = weight of tablet before test,
W = weight of tablet after test.

(d) Weight Variation Test

In these test we randomly selected 20 tablets from each batch and weighed individually using electronic balance and calculated the weight variation.

(e) Drug Content Estimation

For Drug content Estimation randomly selected 10 tablets and converted in to powder form and weighed 60 mg of Diltiazem hydrochloride and transferred in to 100 ml of volumetric flask and dissolved in 0.1 N HCL and maintain the (pH at 1.2). Then keep the flask in to the flask shaker for 24hr and keep 12 hr for the sedimentation of undissolved material. then filter the solution with using Whatterman filter paper. And after that taken 1 ml of above solution and diluted to 100 ml with 0.1 N HCL and absorbance measured by UV / visible spectrophotometer (Shimadzu UV 1600/1700) λ max 236.8 nm absorbance of Diltiazem Hydrochloride. percentage of Diltiazem Hydrochloride was determined by using calibration curve.

(f) In Vitro Buoyancy Test

For in vitro Buoyancy test taken prepared tablets in to 250 ml beaker containing 200 ml of 0.1 N HCL with pH 1.2 and maintain the temperature (37±0.5 C). Dosage form or formulation buoyancy in the medium and the floating durations of tablets was calculated for the determination of lag time and total buoyancy time by visual observation. On immersion in 0.1N HCL solution pH (1.2) at 37^{0}C, the tablets floated, and remained buoyant without disintegration.

Table no.8 shows the results of Buoyancy study From the results it can be concluded that the batch containing HPMC K4M or HPMC K15M polymer and Ethylcellulose showed good Buoyancy lag time (BLT) and Total floating time (TFT). Formulation F3, F6, F9 containing HPMC K4M, HPMC K15M and Ethylcellulose showed good BLT of 135,120,165 sec. respectively, while the formulation F12 containing Ethylcellulose (alone) did not float. This may be due to the nature of polymer and gas generating agent, which were kept constant in the present study. The gas generated cannot be entrapped inside the gelatinous layer, and it escapes leading to variation in BLT and TFT. [16]

(g) Swelling Study:

Swelling study was performed on all the batches (F1 to F12) for 5 hr. From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form.

In the present study, the higher swelling index was found for tablets of batch F6 containing HPMC K4M, HPMC K15M and Ethylcellulose having nominal viscosity of more than 1, 04,000 cps. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer. [13]

(h) In Vitro Dissolution Studies

We used for the in vitro Dissolution Studies apparatus USP II (paddle method) in 900 ml of 0.1 N HCl and maitained pH at (pH 1.2) for 12h. And maintained temperature of the dissolution medium was kept at 37± 0.5 ºC and set the paddle at 100 rpm. At specified interval of time withdrown 10 ml of sample solution and filtered through whattman filter paper sample should be replaced with fresh dissolution medium. Sample dilution should be 0.1 N HCL and absorbance of withdrown sample was measured at 236nm using a Shimadzu UV / max 1600/1700 series spectro photometer.

3. Result and discussion

Table 3: Evaluation of granules

Pre-compression parameters of Formulation $F_1 – F_{12}$

Powder Blend Batch no	Balk density (g/ml)	Tapped density(g/ml)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (^{0})
F1	0.454	0.501	9.38	1.10	21^o
F2	0.452	0.519	12.90	1.15	22^o
F3	0.449	0.503	10.74	1.12	21^o
F4	0.451	0.526	14.25	1.16	24^o
F5	0.450	0.530	15.10	1.18	24^o
F6	0.448	0.533	15.94	1.18	25^o
F7	0.453	0.523	13.38	1.15	23^o
F8	0.452	0.518	12.74	1.14	24^o
F9	0.452	0.537	15.82	1.18	22^o
F10	0.455	0.522	12.83	1.14	22^o
F11	0.451	0.527	14.42	1.16	21^o
F12	0.452	0.535	15.32	1.18	23^o

Table 4: Evaluation of Tablets

Table no.4→ Post-compression parameters of Formulations F1 – F1 2

Tablets Batch	Weight variation test	Friability (%)	Hardness (kg/cm^2)	Thickness (mm)	Drug Content (%)
F1	Pass	0.42	5.5	3.23	97.8
F2	Pass	0.43	5.6	3.10	98.3
F3	Pass	0.33	5.4	3.06	98.6
F4	Pass	0.23	5.0	3.13	98.0
F5	Pass	0.26	4.8	3.16	97.7
F6	Pass	0.39	5.0	3.10	99.8
F7	Pass	0.30	4.9	3.06	98.2
F8	Pass	0.36	4.93	3.23	98.1
F9	Pass	0.29	4.8	3.13	97.9
F10	Pass	0.32	5.0	3.16	98.0
F11	Pass	0.43	5.0	3.03	99.4
F12	pass	0.29	4.8	3.16	98.5

***In Vitro* buoyancy studies**

Table 5: In vitro Buoyancy study of formulations F1-F12

Batch	Buoyancy Lag Time(sec.)	Total Floatation time(hrs.)
F1	100	12
F2	120	12
F3	150	12
F4	120	12
F5	125	>12
F6	132	>12
F7	140	>12
F8	155	>12
F9	170	>12
F10	150	11
F11	165	10
F12	---	---

Table 6: Swelling Index of Tablets of Batches F1 to F12

Batch	TIME (HRS)					
	0	**1**	**2**	**3**	**4**	**5**
F1	0	42	55	60	70	88
F2	0	48	61	72	83	90
F3	0	35	48	55	70	79
F4	0	45	59	68	82	92
F5	0	32	43	57	63	78
F6	0	46	55	69	85	93
F7	0	36	48	59	67	89
F8	0	45	55	69	74	86
F9	0	33	45	58	71	88
F10	0	28	42	54	68	79
F11	0	38	48	60	76	86
F12	0	49	61	72	82	92

Figure 5: Graph of Swelling Index v/s Time (hrs)

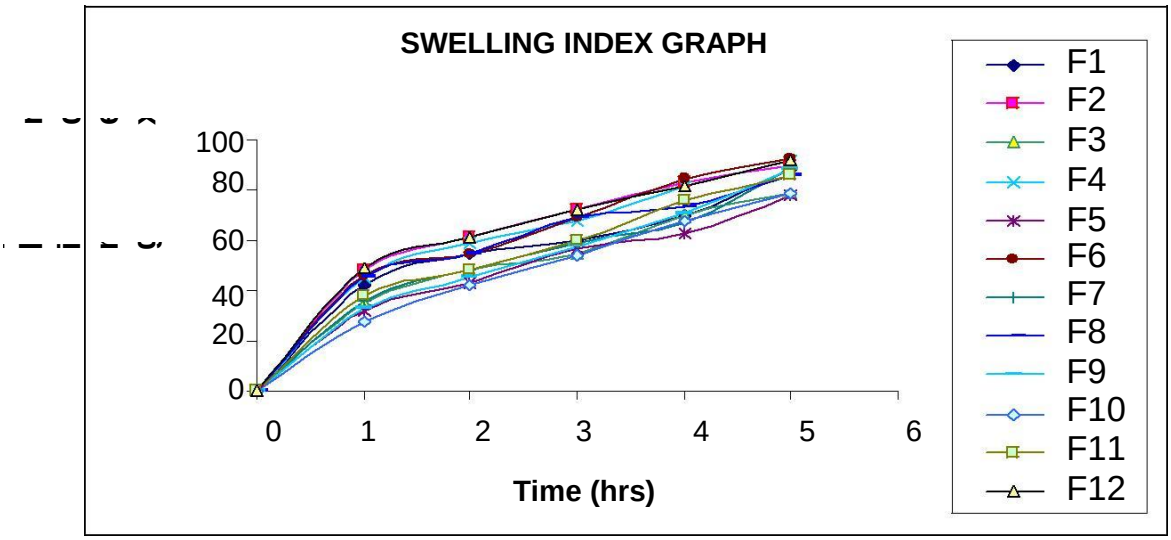

Table 7: Effect of hardness on Buoyancy Lag Time of formulation F6

Hardness in kg/cm^2	Buoyancy Lag Time (sec)
4	85
5	132
6	168
7	230
8	300

Hardness v/s Buoyancy Lag Time F6

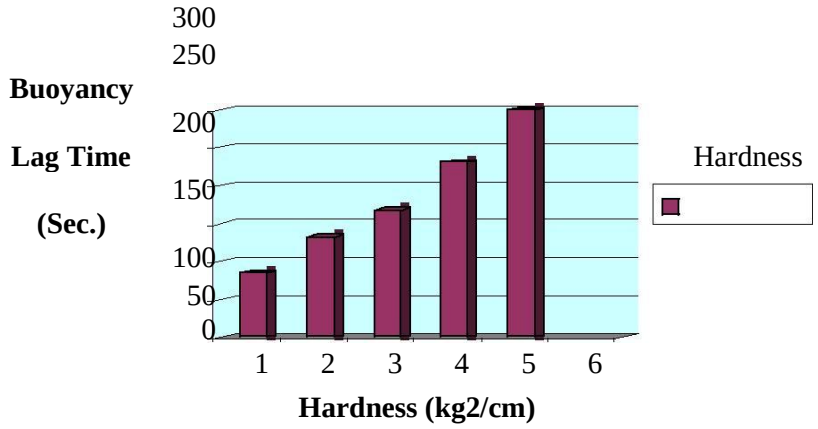

Figure 6:Plot Of Hardness V/S Buoyancy Lag Time Of F6

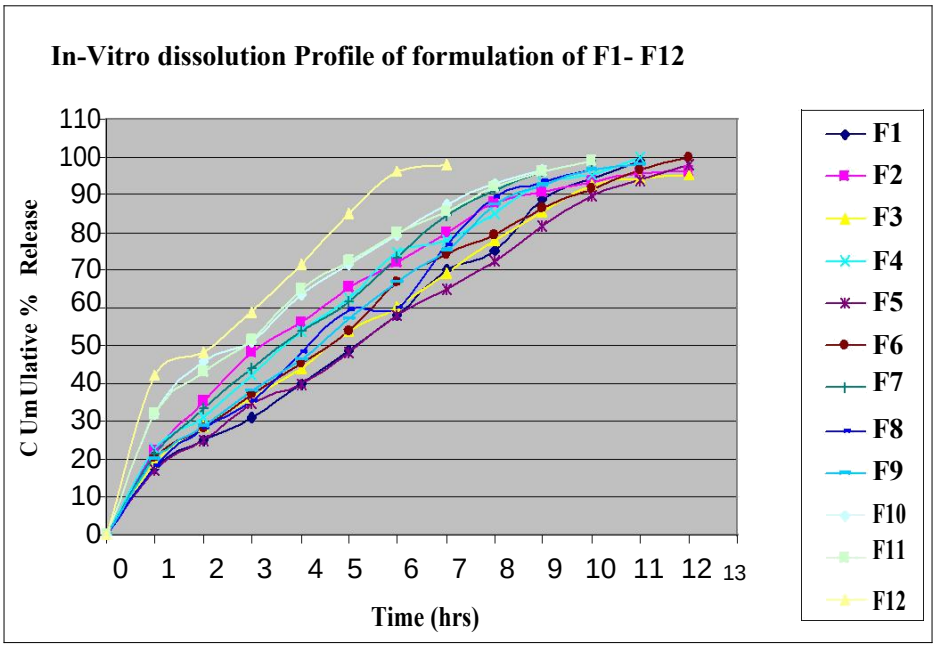

Figure7: In-Vitro Dissolution Profile Of Formulations F1 To F12

The paddle was set at 100 rpm. 10 ml of sample solution was withdrawn at specified interval of time and filtered through Whattman filter paper. The sample was replaced with fresh dissolution medium. The sample diluted to a suitable concentration with 0.1 N HCL. The absorbance of the withdrawn samples was measured at ë 236 nm using a Shimadzu UV- max 1600/1700 series spectrophotometer. [13]

Effect of hardness on Buoyancy Lag Time

The effect of hardness on buoyancy lag time for batch F6 was studied. The results of floating lag time of tablets with hardness of 4 kg/cm^2 ,5kg/cm^2, 6kg/cm^2, 7kg/cm^2 and 8 kg/cm^2 were 90,120,168,230 and 300 sec. respectively. Buoyancy of the tablet were influenced by both the swelling of the hydrocolloid particle on surface when it contacts the

gastric fluid which in turn results in an increase in the bulk volume and porosity buoyancy lag time will increases when the hardness increases, at high compressed, reduces of porosity of tablets occurs, the compacted hydrocolloid particles on the surface of the tablet cannot hydrate rapidly when the tablet reaches the gastric fluid and as a result, the capability of the tablet to float is significantly reduced [3]

(i) Stability Studies

The stability studies of all the formulations were studied at different temperatures using the reported standard procedure. Diltiazem Hydrochloride tablets are wrapped by auminum foil and kept in to petri dishes. Container were stored
At humid condition,
At room temperature (27 °C),
At oven temperature (40 °C),
At refrigeration temperature (8°C).
For a period of weeks. After 8 weeks the sample were analyzed on the basis of physical changes example as texture, color, and in vitro floating time by using same as above method. [6]
The tablets were wrapped in aluminum foil and placed in Petri dishes. These containers were stored at ambient humid conditions, at room temperature (27 ±2 °C), oven temperature (40 ± 2 °C) and in refrigeration temperature (7 ± 2 °C) for a period of 8 weeks. The samples were analyzed for physical changes such ascolor, texture, in vitro floating time.

I. Pre-Compression Evaluation Parameters

- Aangle of repose for powders- It concludes all the formulations blend was found to be in the range 21^o to 25. result indicating excellent flow properties.

- Compressibility index was carried out, it found between 9.38%to 15.94% indicating the powder blend have the required flow property for compression.

All of these values obtained from the study of Pre-Compression evaluation parameters indicates that the powder blend have the required flow property to undergo tablet formulation by Direct compression technique.

II. Post-Compression Parameters

Tablet Dimensions
Result of Thickness and diameter of tablets of the seven formulations did not exceed the limit of ± 5% of the determined standard value; hence all the formulations comply with the Proposed limits of Pharmacopoeia. The values are shown in the tablets.

Hardness Test
The measured hardness of tablets of each batch ranged between 4.8 to 5.6kg/cm^2 .This ensures good handling characteristics of all batches. given on table no -07

Friability Test
The values of friability test were tabulated in Table no.07. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Drug Content Estimation
Drug content estimation result in percentage between range of 97.82% to 99.41% was found as tablets of diltiazem hydrochloride, it complies with official specifications.

In Vitro Buoyancy Test
On immersion in 0.1N HCL solution pH (1.2) at 37^0C, the tablets floated, and remained buoyant without disintegration. Table no.5 shows the results of Buoyancy study From the results it can be concluded that the batch containing HPMC K4M or HPMC K15M polymer and Ethylcellulose showed good Buoyancy lag time (BLT) and Total floating time (TFT). Formulation F3, F6, F9 containing HPMC K4M, HPMC K15M and Ethylcellulose showed good BLT of 135,120,165 sec. respectively, while the formulation F12 containing Ethylcellulose (alone) did not float. This may be due to the nature of polymer and gas generating agent, which were kept constant in the present study. The gas generated cannot be entrapped inside the gelatinous layer, and it escapes leading to variation in BLT and TFT.

Swelling Study
Swelling study was performed on all the batches (F1 to F12) for 5 hr. From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form.

In the present study, the higher swelling index was found for tablets of batch F6 containing HPMC K4M, HPMC K15M and Ethylcellulose having nominal viscosity of more than 1, 04,000 cps. Thus,

the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

CONCLUSION:

Recent scientific and patent literature shows increased interest in academics and industrial research groups regarding novel dosage forms that can be retained in the stomach for prolonged and predictable period of time and the most feasible approach for this is to control the gastric residence time using gastroretentive dosage forms which will provide new and important therapeutic option. But the problem can arise if there is a narrow window for drug absorption in the GIT or drug is unstable in the intestinal fluid. So the development of oral controlled dosage form is not just to prolong the drug release but also to ensure the presence of dosage form in the stomach or upper GIT so that drug is released and absorbed for the desired period of time. Controlling the residence of a drug delivery system in a particular region of the gastrointestinal tract, can utilize several approaches: intragastric floating systems, high density systems, mucoadhesive systems, magnetic systems, unfoldable, extended or expandable systems and superporous, biodegradable hydrogel systems.Diltiazem Hydrochloride is a calcium channel blocker belonging to the benzothiazepine family.

References

1. R. Narayana Charyulu , Amit B. Patil, Lakshmi Deepika C.H, Prabhakar Prabhu, Shastry C.S. "Development of gastro retentive floating matrix tablets of diltiazem hydrochloride". *Nitte University Journal of Health Science.* NUJHS Vol. I, No.1-3, September 2011.

2. Margret Chandira*, Chandramohan, Debjit, Chiranjib, B.Jayakar,K.P.Sampath Kumar. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride". *Scholars Research Library.* 2009, 1 (2) 25-38.

3. Ara N. Patel1, Falguni M. Patel1, Kamal Singh Rathore. "Formulation and characterization of floating tablets of Diltiazem hydrochloride". *JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES.* JPBMS, 2011, 9 (21).

4. Hardik Vaghasiya*, Nirav Solanki, Pratik Upadhyay and Shreeraj Shah. "Formulation Development and Optimization of Bilayered Floating Tablet of Diltiazem Hydrochloride". Vol-2/Issue-6/Nov-Dec 2013.

5. Dumpeti Janardan, Meka Lingam, Chinnala Krishna Mohan, "Formulation and *Invitro* Evaluation gastroretentive drug delivery system for Ranitidine Hydrochloride" Inter J Pharmaceutical Science and Nanotechnology, Oct – Dec 2008, 01 (3), 227 –32.

6. Sanjay S Patel, Thakur RS, "Formulation and evaluation of floating drug delivery system Containing clarithromycin for Helicobacter pylori", Acta Poloniae Pharmaceutical Drug Research, 2006, 63(1), 53 – 61.

7. Sunil K Jhain, NK Jhain, GP, Agarwal, "Gastro retentive floating drug delivery"; an Overview: Drug delivery technology, July August 2005, 5, 21-31.

8. Yeole, P.G., Khan, S., and Patel, V.F., Ind. J. Pharm. Sci., 2005,67(3), 265-272. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

9. http://www.pharmainfo.net/reviews/floating-drug-delivery-system. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

10. S.P.Yyas and Roop.K.Khar, Controlled Drug Delivery Concepts and Advances, First Edition 2002,New Delhi, 196-217. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

11. Brahmankar D. M. and Jaiswal S. B. in "Biopharmaceu tics and Pharmacokinetics", Vallabh Prakashan, 1st edn, 1995, 347- 352. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

12. Chin, Y.W. Novel Drug Delivery Systems, Ed. 2nd, Vol. 50, Revised and Expanded Marcel Dekker, 140-155. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride"

13. Gennaro RA Remington, "The Science and Practice of pharmacy", 20 th Edn, vol.I, 903-913. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride"

14. Banker GS,Rhodes CT.Modern Pharmaceutics.3rd ed.: Marcel Dekker; New York 1996. 678-721. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride"

15. Howard C.Ansel "Pharmaceutical Dosage Form And Drug Delivery Systems", (7 th edition), 229-243. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

16. Rouge, N., Buri. P., Doelker, E., Int. J. Pharm., 1996, 136, 117-139. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

17. Reddy, L., Murthy, R., Crit. Rev. Ther. Drug Carrier Syst., 2002, 19, 553-585. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

18. Arora, S., Ali, J., Ahuja, A., Khar, R. K., Baboota, S. AAPS Pharm Sci. Tech. 2005, 47, 372-390. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

19. Moes AJ. Crit Rev Ther Drug Carrier Syst 1993; 10(2): 193-195. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

20. Deshpande, A.A., Shah, N.H., Rhodes, C.T., Malick, W., Pharm. Res., 1997, 14, 815-819. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

21. Torotora GJ, Grabowski SR. Principles of anatomy and physiology. 10th ed.: John Willey and Sons; New York 2002.78-90. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

22. Wilson KRW, Waugh A. Anatomy and Physiology in Health and Illness. 9th ed. Churchill Livingstone; Londo: 1996. 342-345. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

23. Grubel, P. J. Pharm. Sci., 1987,76,117-122. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

24. Garg, S., Sharma, S., Drug Delivery oral, 2003, 160-166. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

25. Singh, B. N., Kim, K. H., J.control.release, 2000, 63, 235-259. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

26. Chungi, V.S., Dittert, L.W., Smith, R.B., Int. J. Pharm., 1979, 4, 27-38. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

27. Gutierrez-rocca, J., Omidian, H., Shah, K., Pharmatech, 2003, 152-156. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

28. Hou, S.Y., Cowles, V.E., Berner, B., Crit. Rev. Ther. Drug Carrier Syst., 2003, 20(6), 459-97. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

29. Klausner, E.A., Lavy, E., Friedman, M., Hoffman A. J. Control. Rel. 2003, 90, 143-162. "Design and characterisation of sustain release gastro retentive floating tablets of Diltiazem Hydrochloride".

30. Varma M, Singla AK and Dhawan S. Release of diltiazem hydrochloride from hydrophilic matrices of polyethylene oxide and carbopol. Dug Dev and Ind Pharm, Dec 2004; 30(5): 545-553.

31. Shoufeng Li, Senshang Lin, Bruce P Daggy, Haresh L Mirchandani and Yie W Chien. Effect of hydroxypropyl methylcellulose and carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int J Pharm 2003; 253 (1, 2): 13-22