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Research Article

FORMULATION AND EVALUATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF DILTIAZEM HYDROCHLORIDE

N. Krishnakanth*, CVS. Raghu Kiran and Vijaya Kuchana

Department of Pharmaceutics, Teegala Krishna Reddy college of pharmacy
Meerpet, Saroornagar, Hyderabad – 500 097, Telangana, India.

ABSTRACT

Diltiazem Hydrochloride is calcium channel blocker used in the treatment of Hypertension.The problems of frequent administration and variable low bioavailability (40-60%) after oral administration of conventional dosage forms of Diltiazem Hydrochloride can be attenuated by designing it in the form of microspheres which would prolong the residence time at the absorption site to facilitate intimate contact with the absorption surface and thereby improve and enhance the bioavailability. Floating microspheres of Diltiazem Hydrochloride were formulated using Sodium alginate, HPMC and Chitosan in varying levels by Ionotrophic gelation technique with an aim to prolong its release. Twelve formulations are prepared and were evaluated for different parameters. The drug content was found to be in the range of 82.10 to97.24 and entrapment efficiency in the range of 75.10 to 92.78. The scanning electron microscopic study indicated that the microspheres were spherical in shape and the drug remained dispersed in the polymer matrix at amorphous state, *In vitro dissolution* studies were carried out at pH 1.2 acidic buffer for a period of 10 hours. All the formulations shown a floating time of 8 to 12hrs Drug polymer interaction was absent as evidenced by FT-IR and DSC Studies.

Keywords: Diltiazem Hydrochloride, Floating microspheres, Ionotrophic Gelation Technique.

1.INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon factors such as gastric emptying process, gastro intestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastro intestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage forms in stomach. This leads to incomplete drug absorption having absorption window especially in the upper part of small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver the drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine).

Gastro Retentive Drug Delivery System (GRDDS) is chosen since these system can retains the drug in the stomach for a sufficient period of time and releasing active moiety in a controlled manner, and finally metabolized in the body. Diltiazem Hydrochloride is a calcium channel blocker and BCS class I drug has low bioavailability of (40-60%) and half life of 2-4 hours requires frequent administration of drug for maintaining optimum levels of drug in the plasma.Since Diltiazem Hydrochloride is well absorbed in upper part of GI, it is formulated in multi particulate dosage form to improve its bioavailability and make it patient

complianceand used widely in treatment of hypertension and Angina.

2. MATERIALS AND METHODS

Diltiazem Hydrochloride is obtained as a gift sample from Divis Laboratories,Hyderabad and all other reagents used are of analytical grade.

2.1 Preparation of Diltiazem Hydrochloride Floating Microspheres

A solution was prepared by dissolving 500mg of Diltiazem Hydrochloride in small quantity of distilled water and diluted to 5ml.The solution was dispersed in 30ml sodium alginate solution(3%v/v) Containing Hydroxy propyl Methyl Cellulose and Chitosan. Then gas forming agents such as Sodium bicarbonatewas added to the solution gas forming agent which was kept under continuous stirring. This mixture was degassed under bath sonicator.The resulting solution was dropped through a 21G needle in to 1%(W/V) $Cacl_2$ solution containing10% (v/v) Acetic acid.The solution containing microspheres was stirred for 10 min to improve the mechanical strength and allowed to complete the reaction to produce gas. The fully formed microspheres were collected and washed with ethanol and air dried.

3. EVALUATION TESTS

3.1 Solubility studies

Diltiazem hydrochloride is found to be soluble freely soluble in water. Formic acid, methanol, Chloroform and sparingly soluble in absolute alcohol and insoluble in ether.

3.2 Melting point Determination

Melting point of Diltiazem Hydrochloride is determined by Capillary tube method. A few crystals of the drug is in a thin walled Capillary tube of 10-14 cm long with a diameter of 1mm and is sealed at one end. The capillary which contains the sample is tied to the Thermometer(360^0c)at the bulb and suspended in liquid paraffin taken in boiling tube and is heated by using Bunsen burner The temperature at which the sample inside the capillary tube melts is taken as melting point and it was found to be 210^0 C.

3.3 Fourier Transform infrared spectroscopic studies

A Fourier Transform-Infrared spectrophotometer was used to study the non thermal analysis of Drug-Excipient (binary mixture of drug: excipient of 1:1 ratio) compatibility. The spectrum of each sample was recorded over the 450-4500 cm^{-1}.Pure drug of Diltiazem hydrochloride with physical mixture (excipients) compatibility studies were performed. Infra red spectrum of Diltiazem Hydrochloride was carried out using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various excipients by IR Spectrophotometer. Scanning was performed between the range 4000-500 cm^{-1}.

3.4 Particle size and morphology

Particle size of microspheres was determined by using an optical microscope under regular polarized light in which a stage micrometer was employed. A minute quantity of microsphere was spread on a clean glass slides and a average size of 100 microspheres was determined in each batch.

3.5 Swelling index

The swelling index of the microspheres is an indication of the capacity of the microspheres to imbibe water and swell. For estimating swelling index, the microspheres (100) were weighed initially then suspended in pH 1.2 acidic and After every 1h microspheres were removed, surface water trapped with tissue paper and weighed. The increase in weight of microspheres used for calculation of swelling index.

$$\text{Swelling Index} = \frac{\text{wt.of wet microspheres}}{\text{wt.of dry microspheres}} \times 100$$

3.6 Surface Morphology

Surface morphology of microspheres was investigated by Scanning Electron Microscopy (SEM) using JSM 6380A (JOEL, Japan). The microspheres, coated with Platinum by ion sputtering using Auto fine coater JFC-1600 (JOEL, Japan), for 20 s at 1.1V under argon atmosphere were mounted onto metal stubs using double-sided carbon adhesive tapze and the scanning electron micrographs were taken.

3.7 Invitro Floating Studies

The in vitro floating Studies was conducted for all the formulations in simulated gastric fluid of pH1.2 to estimate the floating lag time and floating hours.

3.8 Determination of Encapsulation Efficiency

The amount of Diltiazem hydrochloride present in the microspheres was determined by extracting the drug into phosphate buffer of (pH 7.4). Accurately weighed 0.1g powdered microspheres were extracted in to 50 ml of phosphate buffer (pH 1.2) by magnetic stirring for a period of 2h. The solution was filtered through Whatman filter paper no.5, suitably

diluted and estimated for drug content spectrophotometrically at 236 nm using UV–Visible Spectrophotometer (UV – 1601).

3.9 In Vitro Drug Release Studies

The in vitro drug release studies were performed using Dissolution Apparatus USP Type -II (Paddle, DISSO2000, Lab India) using simulated gastric fluid pH 1.2 for ten hours. An accurately weighed amount of drug loaded microspheres, equivalent to 120 mg of Diltiazem hydrochloride, was added to 900 ml of dissolution medium and the release of Diltiazem hydrochloride from microspheres was investigated at about 100 rpm at temp 37 °C ± 0.5 °C. During dissolution 5 ml aliquot was withdrawn at different time intervals of 1 to 10 h and same was replaced with equal volume of fresh medium. The withdrawn samples were filtered through Whatmann filter paper no.42 and absorbance was measured at 236 nm using UV-Visible Spectrophotometer (UV - 1601). Cumulative percent drug released was found out at each time interval and graph was plotted between cumulative % drug released and time in minutes.

3.10 Differential Scanning Calorimetry Studies

Differential scanning calorimetry (DSC) thermograms of the Diltiazem Hydrochloride, and drug loaded microspheres were recorded on a differential scanning calorimeter DSC . The samples weighing 1 – 4 mg were weighed in an aluminium cuvette and sealed with an aluminium lid. The cuvettes were placed into the DSC under a nitrogen flux (10 ml/min) and heated from 35 to 300 °C at a scanning rate of 10 °C/min.

Table 1: Composition of Floating microspheres of Diltiazem Hydrochloride

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Diltiazem HCL (mg)	500	500	500	500	500	500	500	500	500	500	500	500
Sodium Alginate (mg)	500	600	700	500	600	350	400	300	200	300	200	100
HPMC(mg)	300	200	100	200	100	350	300	400	500	300	200	100
Chitosan	-	-	-	-	-	-	-	-	-	100	200	300
Sodium bicarbonate (mg)	-	-	-	100	100	100	100	100	100	100	200	300
Glacial Acetic Acid(ml)	5	5	5	5	5	5	5	5	5	5	5	5
Calcium Chloride (mg)	500	500	500	500	500	500	500	500	500	500	500	500
Purified water(ml)	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 Wt(gm)	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8

Table 2: Particle size data

Formulation code	Mean diameter (mm)	Particle Morphology
F1	103.33	Spherical
F2	114.46	Spherical
F3	123.22	Spherical
F4	108.86	Spherical
F5	146.64	Slightly irregular
F6	178.78	Spherical
F7	165.34	Spherical
F8	196.34	Slightly irregular
F9	165.45	Spherical
F10	178.87	Slightly irregular
F11	198.96	Spherical
F12	224.62	Slightly irregular

Table 3: Swelling Index

Formulation code	%Swelling index (pH 1.2)
F1	1.116
F2	1.121
F3	1.134
F4	1.154
F5	1.657
F6	1.847
F7	1.214
F8	1.115
F9	1.457
F10	1.546
F11	1.601
F12	1.987

Table 4: Floating Studies

Formulation Code	Floating sec	Floating hours
F1	-	-
F2	-	-
F3	-	-
F4	25	7
F5	28	8
F6	34	8
F7	30	9
F8	26	8
F9	38	8
F10	20	10
F11	19	12
F12	23	12

Table 5: Drug content and Entrapment data

Formulation Code	Drug Content	%Entrapment
F1	85.45	78.88
F2	84.67	79.26
F3	82.10	84.56
F4	88.55	78.95
F5	87.86	77.42
F6	89.91	86.29
F7	92.14	75.48
F8	88.25	76.98
F9	89.28	88.20
F10	91.14	86.67
F11	96.64	92.78
F12	97.24	77.86

Table 6: Dissolution data of all formulations

CUMULATIVE % DRUG RELEASE												
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
15	21.42	7.71	9.17	19.70	18.84	25.70	16.27	24.84	17.56	6.85	18.84	9.57
30	27.84	11.13	11.77	23.13	22.27	29.55	19.7	27.41	22.27	9.75	23.99	12.37
45	36.41	14.56	13.56	26.58	26.56	32.55	23.13	33.41	32.5	14.9	31.70	15.76
60	42.84	17.56	14.96	29.98	29.55	37.6	30.14	38.12	35.98	20.56	38.55	18.35
120	51.40	23.99	19.75	37.27	35.55	41.12	36.84	43.69	40.69	25.27	45.41	22.14
240	59.97	29.55	21.94	51.40	41.12	45.41	44.55	52.69	47.98	33.41	54.83	26.73
360	68.54	38.77	26.73	54.83	47.98	53.12	53.97	63.4	56.54	41.98	65.97	31.52
480	79.25	46.23	30.33	63.4	57.40	63.83	67.68	69.40	67.68	49.20	76.25	39.5
540	85.68	53.64	35.51	74.54	73.25	69.40	79.68	77.90	77.96	58.64	85.25	42.90
600	89.96	67.26	39.11	87.82	83.96	78.82	88.25	86.10	82.10	68.10	94.24	45.09

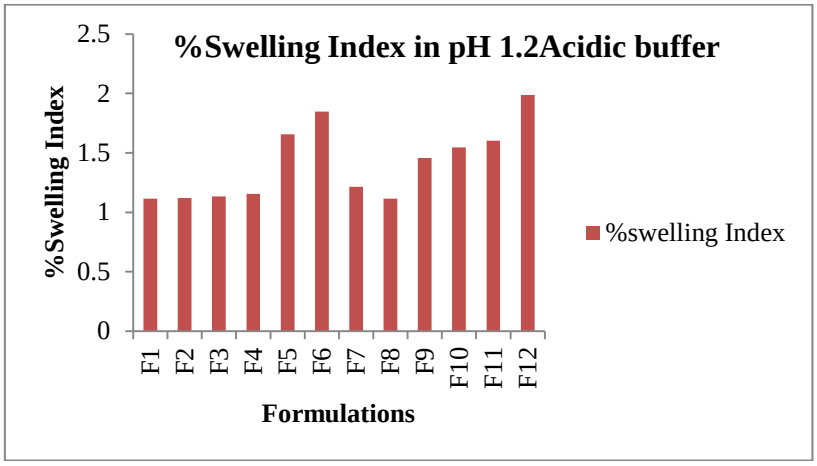

Fig. 1: Data Representation of Swelling Index

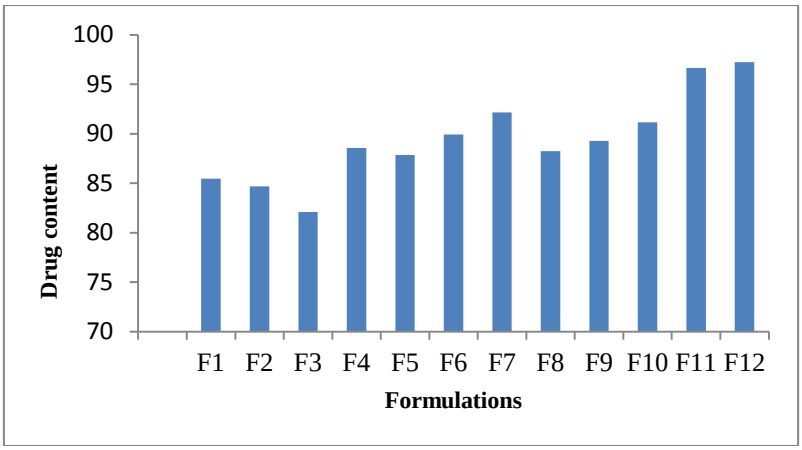

Fig. 2: Data Representation of Drug Content

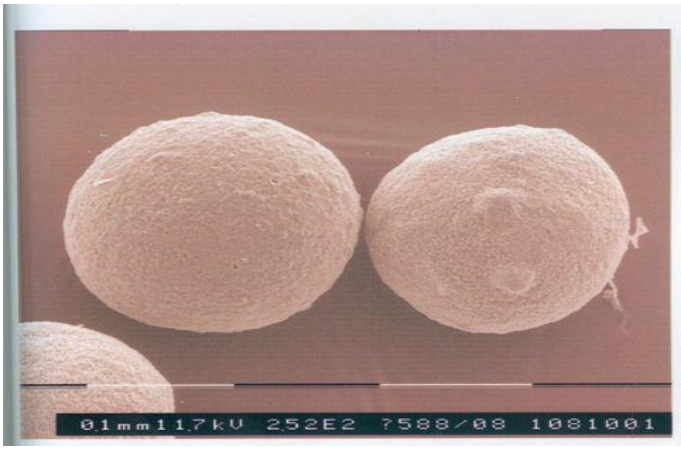

Fig. 3: Surface morphology of floating microspheres

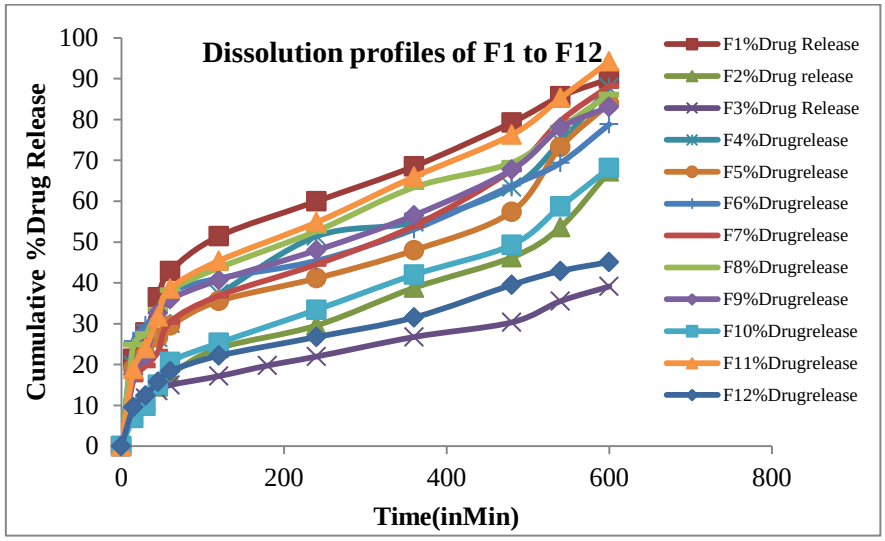

Fig. 4: Dissolution profiles of all formulations

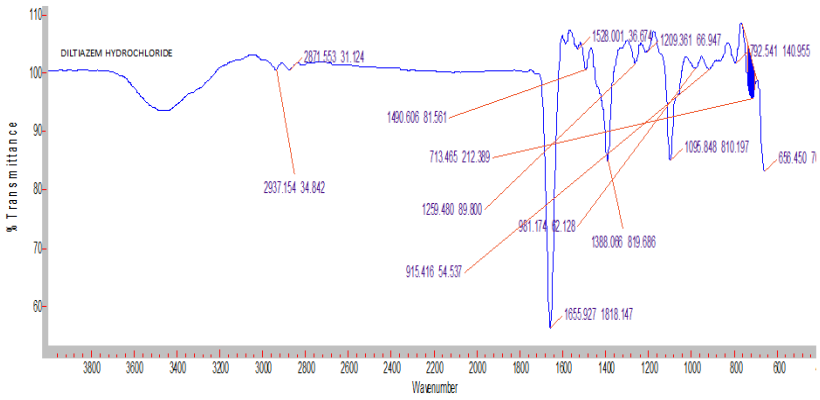

Fig. 5: FT-IR Spectra of pure Drug

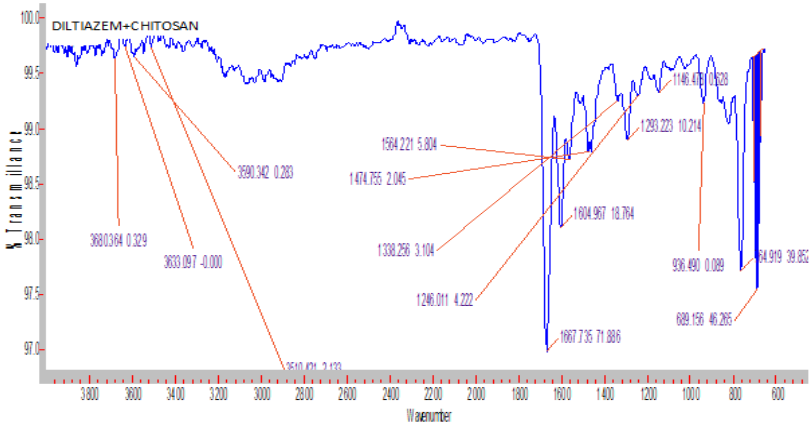

Fig. 6: FT-IR Spectra of Drug and Chitosan

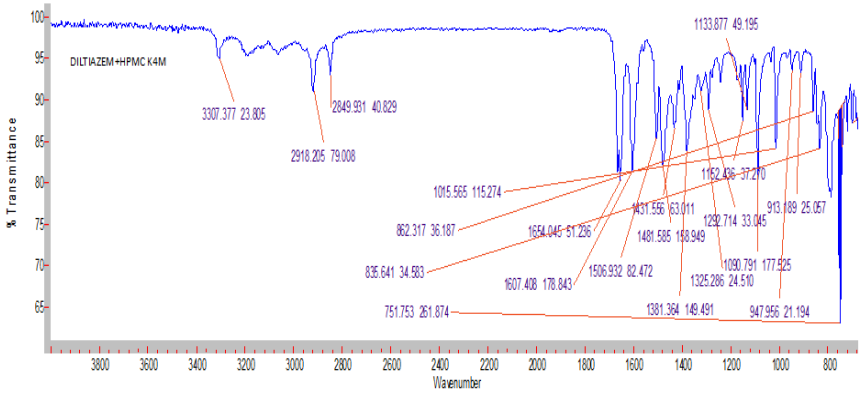

Fig. 7: FT-IR Spectra of Drug and Hpmc K4M

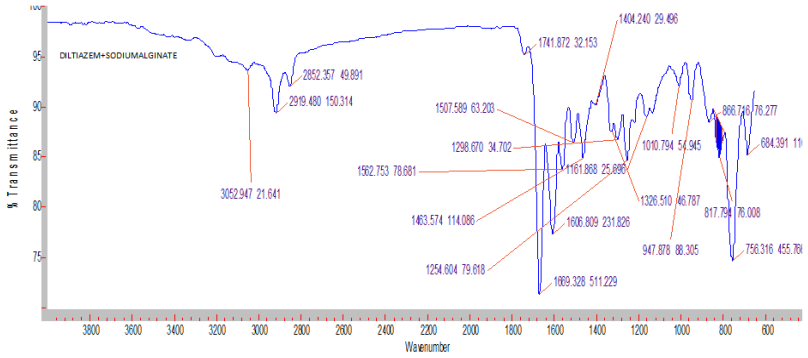

Fig. 8: FT-IR Spectra of Drug and Sodium Alginate

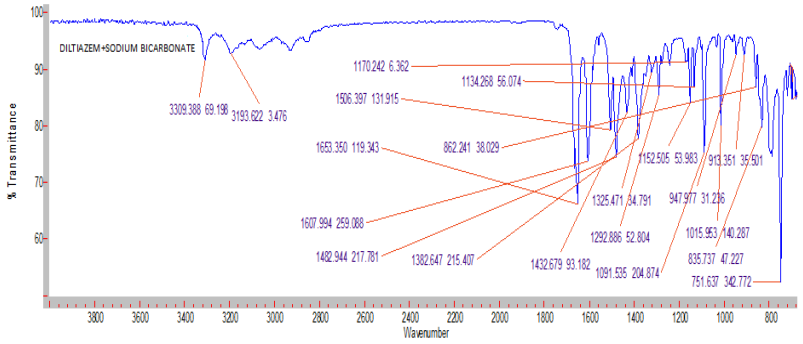

Fig. 9: FT-IR Spectra of Drug and Sodium Bicarbonate.

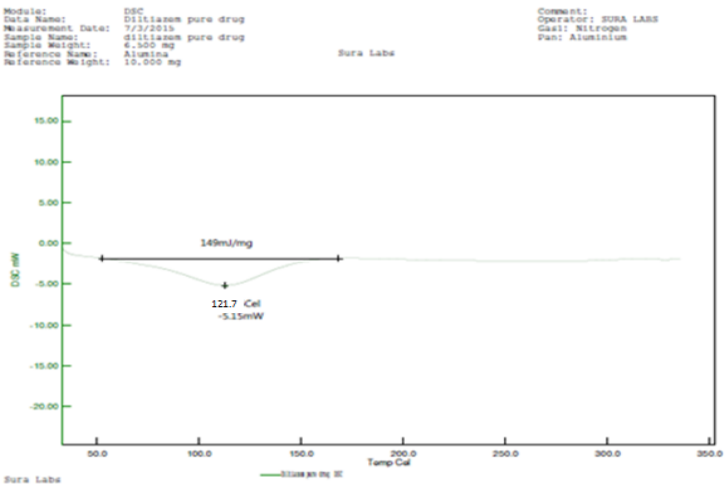

Fig. 10: DSC of pure Drug

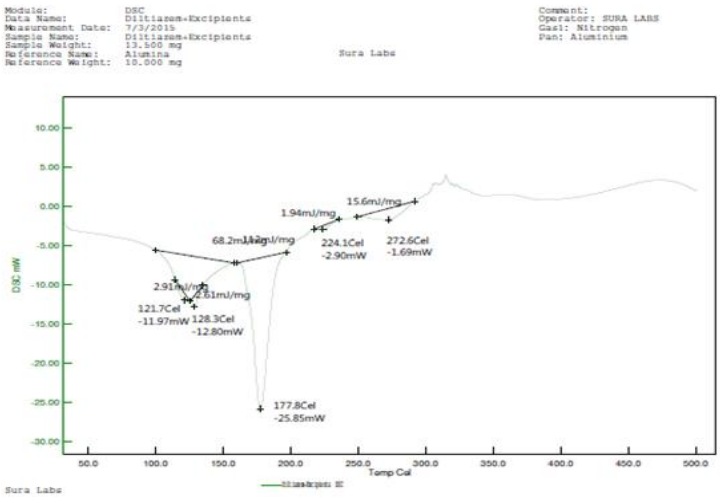

Fig. 11: DSC of optimised formula

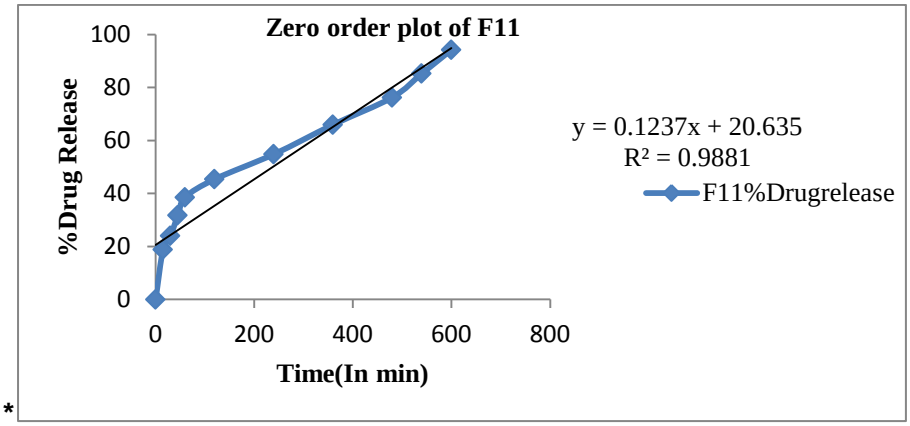

Fig. 12: Zero order plot of optimised formulation

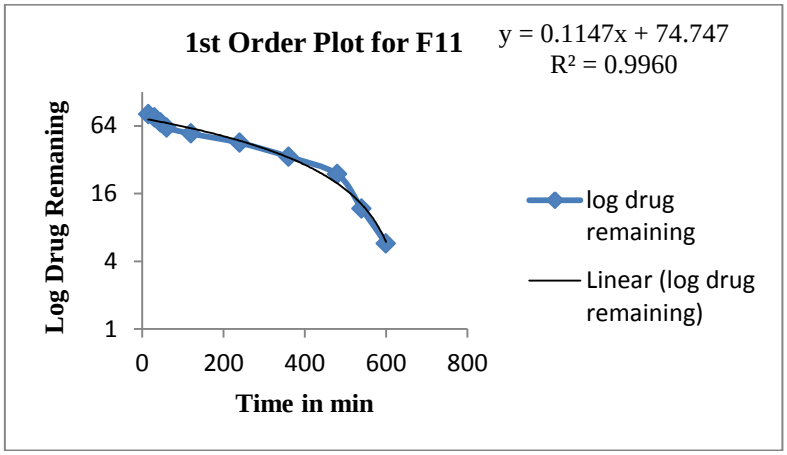

Fig. 13: 1st order plot of optimised formulation

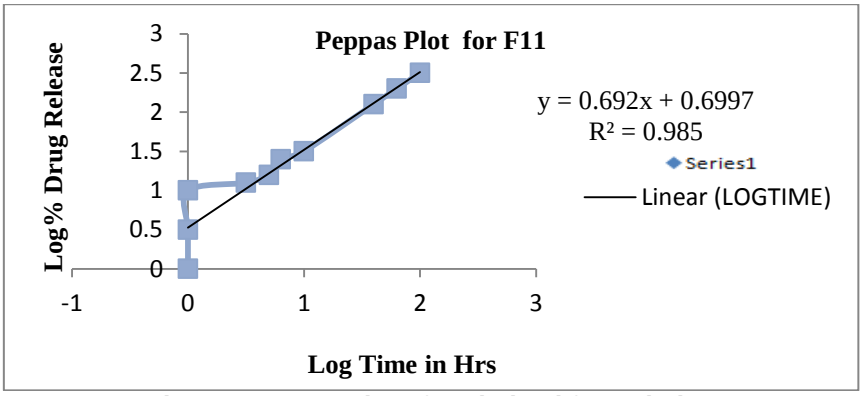

Fig. 14: peppas plot of optimised formulation

4. RESULTS AND DISCUSSION

The morphology of the formulations were found to be spherical except F_5,$F_8$$F_{10}$,$F_{12}$ were found to be irregular. The swelling ratio is calculated by using the respective formula for the study carried about for 6hours in simulated gastric fluids of pH 1.2 was noted down. The swelling index for the formulations ranges from 1.116 to1.987. Formulation **F_{11}**have shown a floating lag time of 19seconds. Remaining formulations have a lag time of above 20sec and the all the formulations have shown a floating time of 8 to12 hrs. The SEM photographs revealed that the microspheres were discrete and spherical in shape with a rough outer surface morphology which could be because of the surface association of the drug with the polymer.The drug contents were in the range of 82.10 to 97.24. Encapsulation efficiency of the drug was found to be in range of 77.42 to 92.78% consistently higher in the formulation **F_{11}**. Cumulative % drug release of **F_{11}**was found to be 94.28 in 10hrs of dissolution. Remaining formulations shows slightly lesser drug release rate. DSC curve of Diltiazem Hydrochloride showed a sharp endothermic peak at 121.7°C, corresponding to its melting point. The drug-loaded microspheres have shown an endothermic peak at 121.7^{0}C indicating melting temperature of the polymer. The FT-IR Studies has been carried out with the pure drug and excipients and all the peaks are found to be in with range of respective wave number.The *in vitro* release profiles were applied on various kinetic models in order to find out the mechanism of drug release. The best fit with the highest correlation coefficient was shown in zero-order, and followed by first order equations. The rate constants were calculated from the slope of the respective plots.

The data obtained were also put in Korsmeyer-Peppas model in order to find out n value, which describes the drug release mechanism. The n value of microspheres of different drug to polymer ratio was ranged between 0.969to 0.995, indicating that the mechanism of drug release was Non-Fickian.

5. CONCLUSION

Gastro retention based on the Floating drug delivery system for controlled release of Diltiazem Hydrochloride can be achieved by

varying levels of rate retarding polymers and effervescent agent . Sodium alginate and Hpmc with 1:1 ratio along with Chitosan (200mg)was found promising and shown better results. Thus helps in overcoming the problem of shorter GI residence time and control the release of highly soluble drug like Diltiazem Hydrochloride

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