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Research Article

DESIGN AND EVALUATION OF BUOYANT MATRIX SYSTEM OF NATEGLINIDE

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ABSTRACT

The objective of the present study was to develop and optimize a buoyant tablet of Nateglinide to prolong the gastric residence time leading to reduce dose frequency which is an effective drug in the treatment of type II diabetes. The tablets were prepared by wet granulation technique using chitosan as a natural polymer in different ratios with sodium bicarbonate as gas generating agent. The compatibility of Nateglinide and all excipients were confirmed by FTIR spectroscopy. Pre-compression properties of granules are found within the prescribed limits and indicated good flow property. The tablets were evaluated for physical characteristics had shown that all of them comply with specifications of official pharmacopoeias. An optimized tablet formulation (F7) had less buoyancy lag time of 37 sec, total floating time of >12 hrs and higher the drug content of 100.16% and release of Nateglinide was 97.27 % after the end of 12 hours. From the kinetic modeling results, the drug release was Fickian diffusion controlled and followed zero order kinetics.

KEYWORDS: Buoyant tablet, Nateglinide, Chitosan, Wet granulation.

INTRODUCTION

Most of the oral dosage forms posses several physiological limitations such as variable gastrointestinal transit time because of variable gastric emptying leading to no uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach[1]. This leads to incomplete absorption of drugs having absorption window especially in the upper art of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed[2]. However, the short gastric retention time and unpredictable rapid gastric emptying rate can result in incomplete drug release from the dosage form in the absorption zone leading to decrease therapeutic efficacy of administered dose[3]. To increase the gastric residence time of drug a buoyant dosage form can be developed. Nateglinide is an anti-diabetic agent belongs to meglitinides (glinides) class for the management of non-insulin dependent type-2 diabetes mellitus[4]. Nateglinide is majorly absorbed from stomach but poorly soluble in aqueous fluids with shorter biological half life of 2 hours and need of frequent doses per day[5]. Therefore, controlled buoyant drug delivery systems are needed to enhance effectiveness of such drugs and to reduce dose of frequency. In this study an attempt was made to develop buoyant matrix tablet of Nateglinide with naturally occurring chitosan polymer.

MATERIALS AND METHODS

Materials

Nateglinide was obtained as a gift sample from Actiza Pharmaceutical Pvt. Ltd, Surat, India. Chitosan obtained as a gift sample from Medrich Pvt. Ltd. Bangalore. Microcrystalline cellulose, PVP, and Citric acid were procured from Reachem laboratory chemicals Pvt. Ltd. Chennai, India. Magnesium stearate and talc were procured from S.D. Fine chemicals Pvt. Ltd. Mumbai, India. All chemicals and solvents used were of analytical grades.

METHODS

Compatibility

To study the various excipients of formulation with Nateglinide compatibility, a solid admixture were prepared by mixing the drug with all excipients of formulation at the ratio of 1:1 and stored in air tight container at 45±2ºC / 75±5% RH using stability chamber (Labtop, Skylab instrument and engineering Pvt. Ltd. Thane. India). After a period

of 3 months the solid admixture was characterized using FTIR spectroscopy.

Preparation of Standard curve of Nateglinide

50mg of Nateglinide were dissolved in methanol to get stock solution of 1000µg/ml. The above solution was subsequently diluted to get a series of dilutions containing 8-22µg/ml of Nateglinide solutions. The absorbance of the prepared dilutions was measured at 465nm by using UV-Spectrophotometer (Shimadzu UV-1800) using methanol as blank. The standard plotted against Concentration verses absorbance[6].

Preparation of Buoyant tablet

Buoyant tablet of Nateglinide was prepared by conventional wet granulation technique. Each buoyant tablet containing 60mg of Nateglinide was prepared with varying ratio of chitosan as polymer and microcrystalline cellulose (MCC) as diluent, keeping all other excipients as constant in weight as shown in table no.1. A blend of Nateglinide and the required quantity of chitosan, MCC, sodium bicarbonate, citric acid and PVP K30 were mixed with solvent blend of methanol and water (1:1) to get a wet damp mass. The wet damp mass was passed through sieve no. 12 to get wet granules and granules dried at 60ºC for 1 hour. The dried granules was mixed with talc and Magnesium stearate, were compressed into tablet of hardness 4-5kg/sq.cm on a 12 station Cadmic rotary tablet punch machine.

Table 1: Formulations containing various quantities of excipients

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nateglinide	60	60	60	60	60	60	60	60	60
Chitosan	05	10	15	20	25	30	35	40	45
MCC	50	45	40	35	30	25	20	15	10
PVP	10	10	10	10	10	10	10	10	10
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Magnesium stearate	02	02	02	02	02	02	02	02	02
Talc	03	03	03	03	03	03	03	03	03

*All quantities are in milligram (mg)

Characterization

Thickness, Hardness, Weight variation, and Friability determination

Thickness was determined using Vernier calipers, hardness was measured by using a Pfizer hardness tester, weight variation was calculated as per the standards and friability was varied out Roche friabilator (M/s Techno scientific and equipments)[7].

Assay of Nateglinide

10 tablets were selected randomly and powdered, powder were equivalent to 1 tablet was taken and allowed to dissolve on 100ml of methanol by placing in shaker for an hour. The solution was filtered and analyzed at 465nm using UV spectrophotometer after suitable dilutions.[8]

Determination of Swelling Index (S.I)

The swelling behavior of tablet was measured by considering its weight gain, after placing in 100ml of 0.1N HCL in beaker. After time intervals of 1,2,4,6 and 8 hours each tablet was taken out from beaker, blotted with tissue paper to remove excess water and weighed on analytical balance. The experiment was carried in triplicate for each time point. The swelling index was calculated using following formula.[9]

$$S.I = \frac{Wet\ weight\ of\ tablet - Dry\ weight\ of\ tablet}{Dry\ weight\ of\ tablet} x\ 100$$

Buoyancy lag time and total floating time

The time required to float a tablet from the bottom of the medium to the upper surface of the medium after placing in 100ml of 0.1N HCL in a beaker was determined as floating lag time and the duration of time to float a tablet constantly on the dissolution medium was noted as total floating time. The experiment was conducted in triplicate.[10]

In-vitro drug release studies

An 8 station dissolution rate test apparatus–II paddle type (Model– DS 8000, M/s Lab India) was used to study the release of Nateglinide from the tablet. The dissolution test was carried out by placing 1 tablet containing 60mg of Nateglinide in 900ml of 0.1N HCL at 37ºC ± 0.5ºC at a paddle speed of 50 rpm. After each 1 hour a sample of solution of 5ml was withdrawn from dissolution apparatus and same volume of fresh medium was replaced and assayed spectrophotometrically (Shimadzu UV-1800) at 465nm after appropriate dilution. All the experiment was conducted in triplicate.[11]

Kinetic modeling of drug release

The drug release mechanism from a matrix system can be studied using various kinetic models, even though it is complicated but practically evident in the case of matrix system. The order of drug release from matrix was described by using zero

order and first order kinetics. The mechanism of drug release from the matrix was studied by using Higuchi equation and Koresmeyer-Pappa's equation.[12]

RESULTS AND DISCUSSION

Compatibility study

FTIR spectra of Nateglinide and excipients solid admixtures were recorded between 500 to 3000 cm-1. The characteristic peaks of Nateglinide were observed at 1636 and 2932. No significant change observed in the characteristic peaks of Nateglinide in all the solid admixture of drug and excipients. The FTIR spectrum shows in figures1 and 2.

Pre-compression studies

The prepared granules were subjected to various physical studies before compressing into tablets. Bulk density of the granules was found in the range of 0.25 g/cc to 0.39 g/cc and tapped density between 0.28 g/cc to 0.43 g/cc. the calculated Carr's index was between 6.77 to 13.28 %. The flow property of the granules was assures by angle of repose, which was found between 23.56º to 27.39º for all formulation granules. The data is evidence of good flow behavior and compressibility. The results are shown in table no.2.

Table 2: Pre-Compression Parameter results

Formulation	Bulk density g/cm³	Tapped density g/cm³	Compressibility index %	Angle of repose (º)
F_1	0.39	0.43	9.30	23.56
F_2	0.38	0.405	6.862	26.25
F_3	0.33	0.362	8.88	25.93
F_4	0.256	0.286	11.27	26.07
F_5	0.248	0.2861	13.28	27.39
F_6	0.391	0.424	7.78	26.82
F_7	0.309	0.334	7.48	27.07
F_8	0.352	0.382	8.45	25.93
F_9	0.33	0.354	6.77	24.96

Physical properties of compressed tablets

Weight variation for all the formulation was found to be in the range of 150mg ± 0.42mg to 150mg ± 0.31mg. Hardness of the tablet was in the range of 5.03 to 5.91kg/cm². The percentage loss of weight during friability test was 0.21% to 0.62% which is found to be within standard limit and sufficient hardness to withstand mechanical resistance. Thickness of formulated tablets was of between the ranges of 4.35 to 4.88 mm. The drug content varied between 94.29 to 103.02% in all tablets with low standard variation indicating content uniformity of the prepared batches. All the physical properties are within the pharmacopoeial specifications and the above parameters are shown in table no.3.

Table 3: Physical properties of compressed tablets (n = 3)

Formulation	Thickness (mm)	Weight Variation(mg)	Hardness (kg/cm²)	Friability (%)	Drug content (%)
F_1	4.48±0.04	120±0.400	5.15±0.187	0.21±0.04	94.29
F_2	4.45±0.03	120±0.350	5.15±0.237	0.40±0.07	101.06
F_3	4.39±0.1	120±0.317	5.01±0.172	0.34±0.04	96.69
F_4	4.43±0.02	120±0.314	5.03±0.186	0.30±0.02	98.15
F_5	4.53±0.08	120±0.420	5.14±0.135	0.16±0.06	103.02
F_6	4.55±0.06	120±0.320	5.15±0.187	0.43±0.05	99.31
F_7	4.40±0.03	120±0.330	5.11±0.116	0.62±0.1	100.16
F_8	4.35±0.04	120±0.325	5.91±0.231	0.51±0.08	97.25
F_9	4.38±0.05	120±0.423	5.03±0.186	0.38±0.04	98.30

Buoyancy studies

All the formulations shows lag time of between 37 sec to 81 sec. Buoyancy lag and total floating time of all the formulations are expressed in table no.4. Among all formulations F7 has least buoyant lag time of 37 sec. in 0.1N HCL and remained buoyant for 12 hours. The proportionate quantity of sodium bicarbonate (16.66%) to the quantity of chitosan is ideal to be buoyant for long period with the release of appropriate amount of CO_2 when it comes in contact with dissolution fluid. Due to the production of CO_2 from the tablet matrix decrease the density of the tablet below one making that tablet buoyant.

Table 4: Buoyancy lag time. Total floating time of formulation (F1- F9) (n=3)

Formulation	Buoyancy lag time (sec)	Total floating time (hrs)
F_1	55±02	>10
F_2	49±01	>12
F_3	70±03	>11
F_4	74±01	>12
F_5	39±03	>12
F_6	81±02	>11
F_7	37±01	>12
F_8	76±04	>11
F_9	61±02	>10

Swelling Index

From the graphical representation (figure no. 3, 4) and value from the table no.5 swelling behavior of all the formulations is due to the formation of hydrogel by chitosan. The swelling index increases as the concentration of high molecular weight polymer increases. The comparative swelling behavior of all the formulations with respect to time is shown in figure 5.

Table 5: Swelling index studies (n=3)

Time in (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	1.2± 0.1	4.2± 0.18	10.2± 0.56	15.6± 0.35	21.4± 1.02	25.6± 0.97	43.4± 0.85	48.1± 1.32	59.9± 2.01
2	2.5± 0.21	5.6± 0.15	14.6± 0.81	18.3± 0.24	28.3± 0.98	29.7± 1.01	60.1± 0.98	69.4± 2.01	80.3± 2.58
4	3.1± 0.12	7.4± 0.18	18.5± 0.91	21.5± 0.36	34.2± 1.2	30.4± 1.6	84.7± 1.01	93.2± 1.92	117.4 ±1.69
6	3.7± 0.2	8.3± 0.84	20.8± 0.24	28.4± 0.35	32.1± 1.01	35.9± 0.9	107.5 ±1.2	112.3 ±1.36	129.6 ±1.86
8	7.8± 0.15	9.3± 0.91	25.4± 0.34	30.4± 0.65	36.3± 0.91	40.6± 0.82	119.8 ±1.02	130.6 ±1.57	147.5 ±1.58

***In-vitro* drug release studies**

Table no. 6 shows the release of Nateglinide in 0.1N HCL at particular time, which is also represented graphically in figure no. 6 and 7. All the trials performed with three tablets. In all the formulations the initial release of the drug for the first three hours was varied between higher to lower (18 to 42%) depends on amount of chitosan used. The release rate was found to be controlled as the amount of chitosan increased in the tablet formulation. As the chitosan having property to increase the viscosity with exposed to dissolution medium, the release of the drug from the matrix was suppressed. The viscous and gel like structure was recovered at the end of dissolution study. The 'n' value for all the formulations varied from 0.710 – 0.890 which indicating that the release mechanism was non-Fickian. It can be inferred that the release was dependent on both relaxation of polymer and diffusion.

Table 6: Cumulative percentage release of Nateglinide from buoyant matrix tablets (n=3)

Time In Hrs	Percentage release of Nateglinide after each time in (hrs) ± S.D								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F9
0	0	0	0	0	0	0	0	0	0
1	26.63 ±1.3	29.11 ±0.9	22.81 ±1	19.52 ±0.7	22.63 ±1.3	18.25 ±0.8	25.53 ±0.8	25.79 ±1.4	23.40 ±1.2
2	35.72 ±1	42.08 ±1.1	33.44 ±0.8	31.51 ±0.6	33.82 ±0.8	26.54 ±0.7	34.67 ±0.7	37.53 ±1.2	33.37 ±1.5
4	51.65 ±0.8	59.08 ±0.8	50.61 ±0.9	45.42 ±0.6	46.41 ±1.4	38.64 ±0.7	48.86 ±1.8	50.33 ±0.7	46.24 ±0.8
6	71.14 ±1.5	79.83 ±1	69.25 ±1	56.79 ±0.9	60.68 ±1.2	50.57 ±0.6	65.80 ±1.4	70.8 ±2	59.40 ±0.7
8	83.67 ±0.9	92.78 ±0.7	82.45 ±0.9	67.45 ±0.7	76.26 ±1.1	64.88 ±0.8	80.05 ±1.3	87.75 ±1.8	70.39 ±0.7
10	92.29 ±0.7	98.44 ±2.1	91.73 ±0.4	78.27 ±0.8	92.02 ±1.1	77.81 ±0.7	92.10 ±0.7	95.44 ±0.8	82.59 ±1.5
12	96.70 ±0.7		95.53 ±1	88.75 ±0.8	98.52 ±1.7	94.04 ±0.3	97.27 ±1.1		95.50 ±0.8

Drug release kinetics

The *in-vitro* drug release data was subjected to the best fit test by linear regression analysis according to zero order and first order equation. Higuchi and Korsmeyer – Pappas model in order to determine the mechanism of the drug release. The coefficient of correlation (r) is summarized in table no. 7. The 'r' values of zero order and first order plot were compared. The 'r' values of zero order were in the range of 0.95 to 0.997 where as the 'r' values of first order were in the range of 0.93 to 0.996. From the 'r' values of all the formulations indicating that, drug release was found to follow zero order ('r' value near to one). This may be due to poor soluble nature of Nateglinide. The drug release from the prepared buoyant tablets followed Fickian diffusion, since 'n' value of Korsmayer – Pappas plot was found in the range of 0.318 to 0.414. The 'r' values (0.98 to 0.99) from the Higuchi's plot were inferred that the release of drug from matrix tablet was diffusion controlled. Hence the drug release from matrix followed zero order release and Fickian diffusion controlled.

Table 7: Drug release kinetic studies

Formulation	Zero order	First order	Higuchi model	Korsmeyer equation	
	Regression coefficient (r)	Regression coefficient (r)	Regression coefficient (r)	Regression coefficient (r)	Exponential value (n)
F1	0.962	0.962	0.987	0.992	0.318
F2	0.953	0.933	0.981	0.983	0.331
F3	0.962	0.962	0.990	0.992	0.363
F4	0.984	0.984	0.988	0.994	0.340
F5	0.997	0.992	0.983	0.995	0.364
F6	0.996	0.996	0.966	0.995	0.414
F7	0.989	0.989	0.995	0.994	0.367
F8	0.970	0.963	0.982	0.990	0.344
F9	0.992	0.987	0.983	0.996	0.338

CONCLUSION

From the results, we conclude that buoyant drug delivery system offer a practical and suitable approach to prepare controlled release of Nateglinide with chitosan as rate controlling agent to enhance bioavailability and dose reducing frequency. Based on all observations and results, it is conferred that

there is no incompatibility between Nateglinide and all other excipients used in the tablet formulations with required floating time and drug release.

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Figures

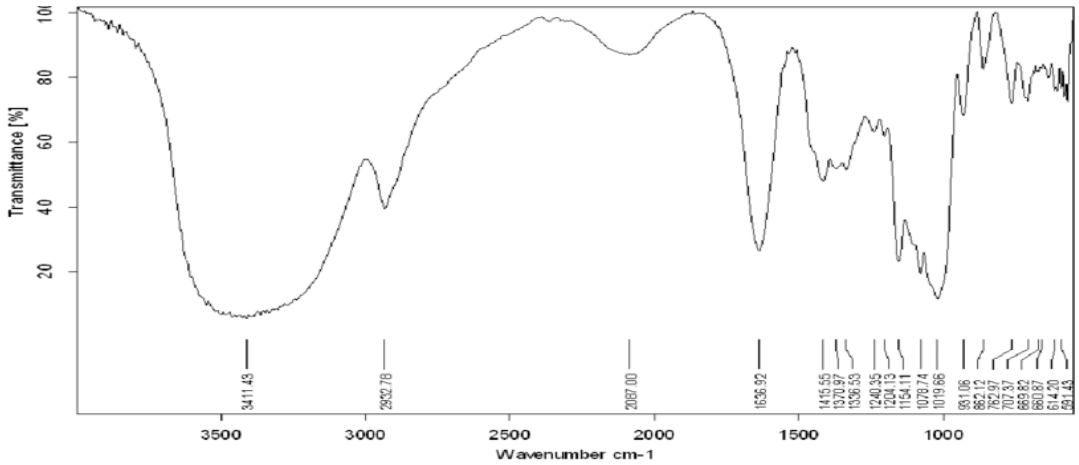

Fig. 1- IR spectrum of Nateglinide

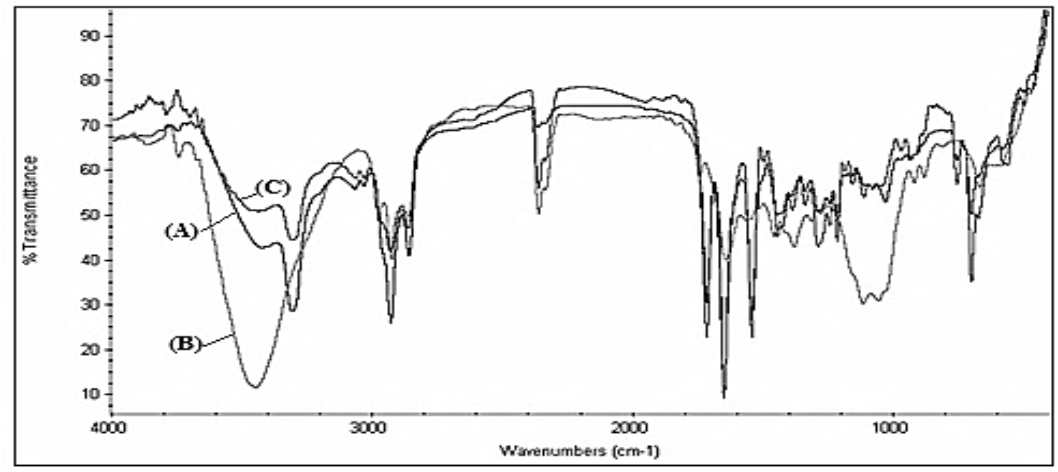

Fig. 2: IR Spectrum of Nateglinide with Excipients

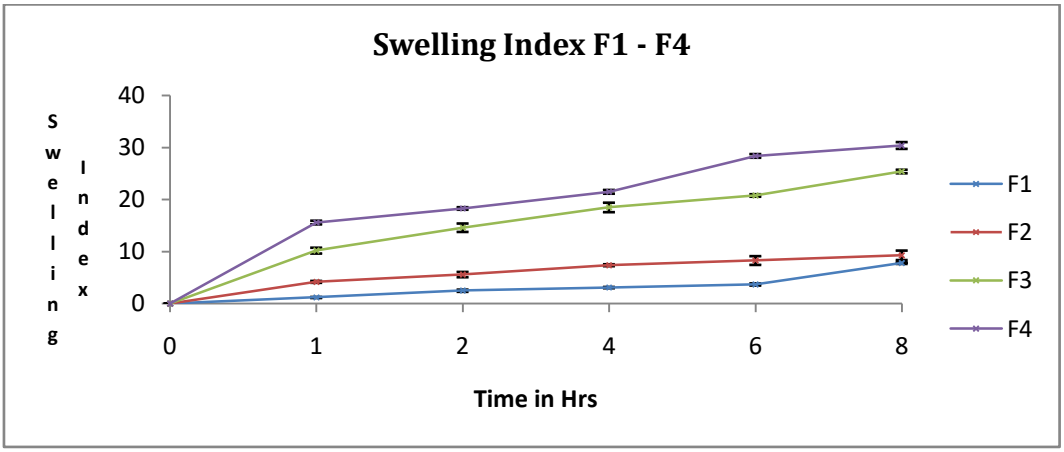

Fig. 3: Swelling Index of formulation F1 – F4

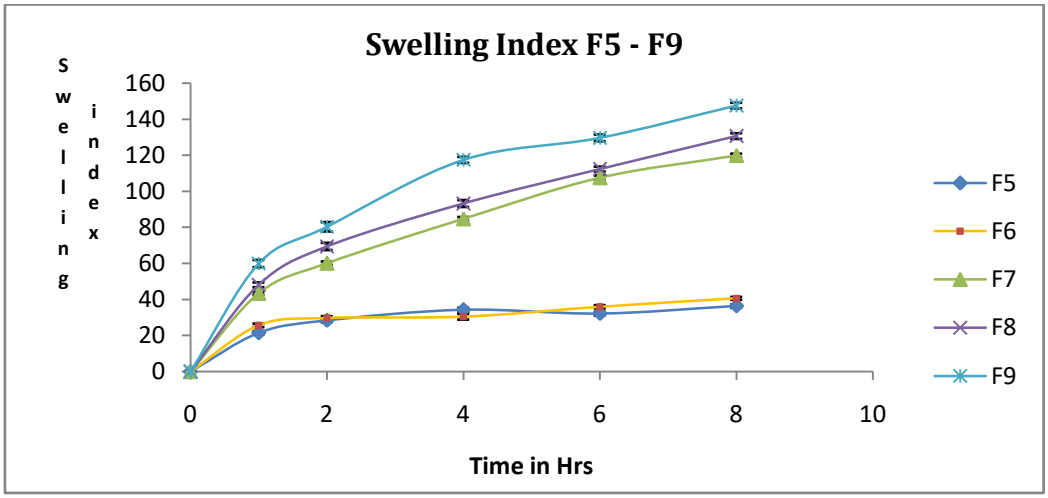

Fig. 4: Swelling Index of formulation F5 – F9

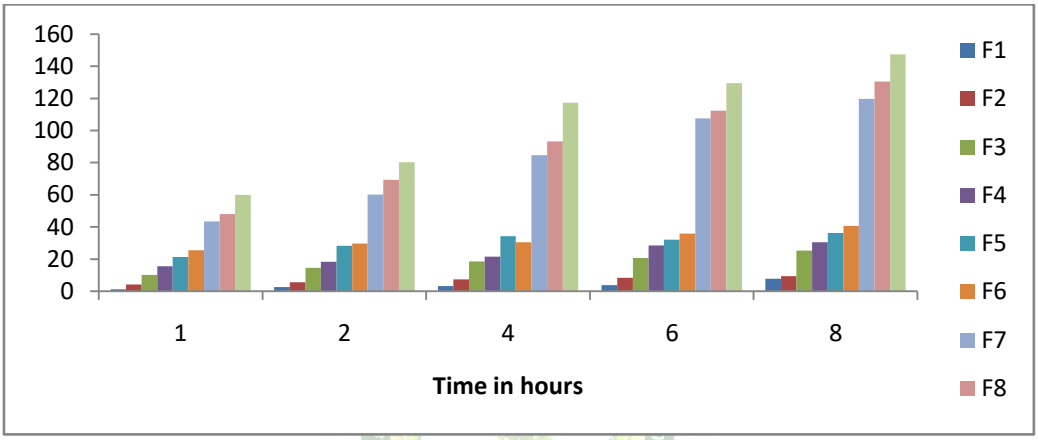

Fig. 5: Swelling behavior

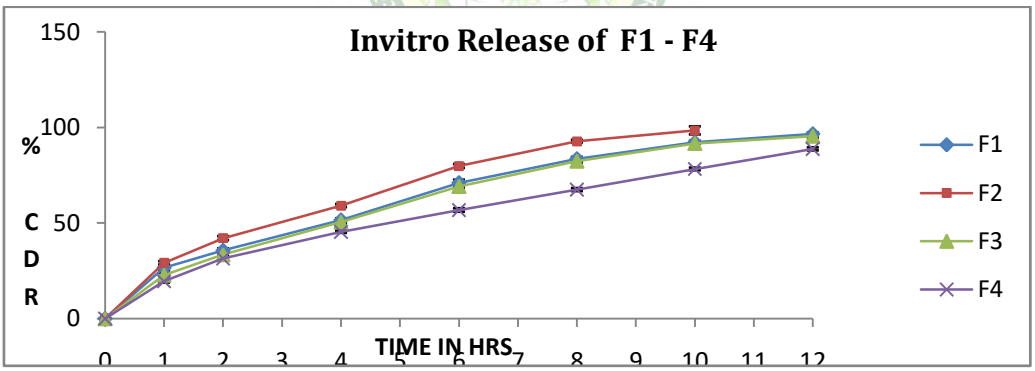

Fig. 6: In-vitro drug release profile. (F1 – F4)

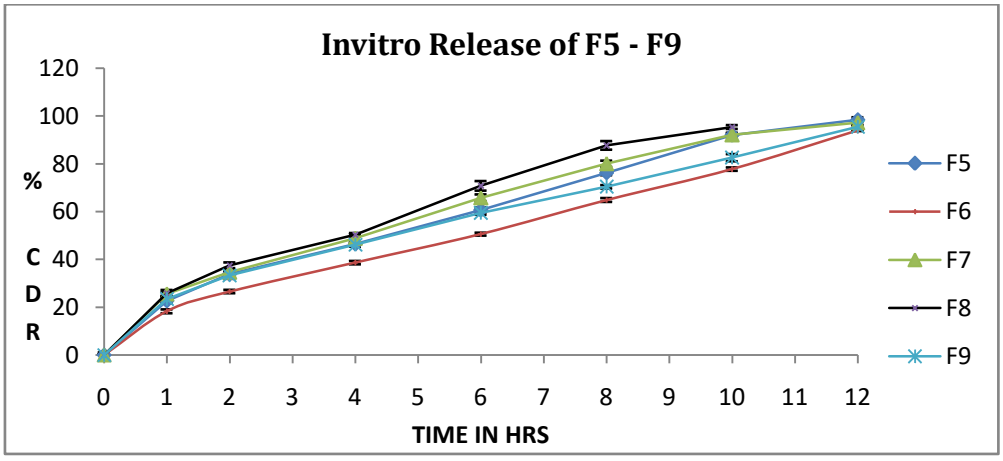

Fig. 7: In-vitro drug release profile. (F5 – F9)