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DESIGN AND OPTIMIZATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM OF SITAGLIPTIN

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Key words:

Sitagliptin, Poly vinyl pyrrolidine, polyacrylic acid Gastro retentive floating drug delivery system (GFDDS).

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ABSTRACT: In the present study, Gastro retentive floating drug delivery systems (GFDDS) of sitagliptin, an anti diabetic drug, have been designed to increase the therapeutic efficacy & gastric residence time and to reduce frequency of administration. Therefore a sustained release medication was advantageous so as to achieve the prolonged therapeutic effect and to reduce peak and valley effect in plasma concentration. This can be achieved by formulating modified gastro retentive sustained release dosage forms which resides in the stomach for sufficient time to release the drug in vicinity of the absorption zone. The tablets were prepared by direct compression method, by employing polymers like HPMCK100, Poly vinyl pyrrolidine and polyacrylic acid respectively in various concentrations. The prepared granules were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio and results obtained were satisfactory compressed formulations were further evaluated for thickness, friability, hardness, swelling index and in-vitro dissolution studies. All the formulations showed good results which were compliance with pharmacopoeial standards. In vitro dissolution study was carried out in pH 1.2 buffers. From in vitro dissolution studies, the cumulative % drug release of all formulations ranged from 92.96% – 99.28% at the end of 12 hrs. The in vitro drug release data was fitted into various mathematical model.

INTRODUCTION: High level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of the dosage form. A lot of advancements have been seen in oral sustained drug delivery system in the last few decades. But still oral sustained drug delivery system is complicated by limited gastric residence time. Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine.

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To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract like floating drug dosage systems (FDDS). Gastroretentive systems can remain in the gastric region for several hours and hence can significantly prolong the gastric residence time of drugs that offer numerous advantages; improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment of small intestine [1].

The main objective of the study is to formulate Gastroretentive dosage forms (GRDFs) of sitagliptin in order to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. This technology has

generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome. Gastroretentive dosage form (GRDFs) are designed on the basis of various approaches like, formulating high density (sinking) system that is retain in the bottom of the stomach, low density (floating) system that remain buoyant above gastric fluid, mucoadhesive system that cause bioadhesion to stomach mucosa, expandable, unflodable or swellable system which limits the emptying of dosage form through the pyloric sphincter of stomach, super porous hydrogels magnetic systems etc [2].

The gastroretentive tablets results in release of the drug in to the more absorptive regions of the GIT, is in to the stomach and the small intestine rather than into the large intestine where drug absorption is poor or erratic. This is achieved by adjusting the time period of release for the drug so that it is about the same as or less than the retention time of the tablets at the site of absorption. Thus the system is not transported past the "absorption window" prior to releasing the entire drug, and the maximum bioavailability is attained. Sitagliptin is (R)-4-oxo-4-[3-(triflurometh‌yl)-5,6- dihydro [1,2,4] triazolo[4,3-a] pyrazin -7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine. Sitagliptin blocks dipeptidyl peptidase-4 (DPP-4) activity and it increasesincretin levels (GLP-1 and GIP) which inhibit glucagon release, in turn decreases blood glucose, but more significantly increases insulin secretion. Sitagliptin is for people with type-II diabetes (non-insulin-dependent) and sometimes used in combination with other diabetes medications, but is not for treating type-I diabetes[3].

In the present study Gastro retentive drug delivery system containing Sitagliptin was formulated which would remain in stomach for prolonged period of time in view to maximize bioavailability of the drug and increased patient compliance.

MATERIALS AND METHODS:

Materials:

Sitagliptin as gift sample from DR Reddy's Laboratories, India, polymers from Hi Media Laboratories Pvt. Ltd, Mumbai, India, All the other materials used were of analytical grade.

Pre-Compression Parameters:

The various Pre-compression parameters are Angle of repose, Bulk density, Tapped density, compressibility index, Hausner's ratio and Carr's index were studied.

Bulk Density (Db):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in G/CC and is given by

$$Db = \text{Mass powder}/\text{Volume}$$

Tapped density (Dt):

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in G/CC and is given by

$$Dt = M/Vt$$

Where, M - Mass of the powder
V t – Tapped volume of the powder

Angle of Repose:

The accurately weighed quantities of granules were taken in to funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the granules. The granules were allowed to flowfreely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the formula.

$$\text{Tan}(\theta) = h/r$$

Where h and r are the height and radius of the powder cone.

Carr's index (I) & Hausner's ratio:

Carr's index and Hausner's ratio measure the propensity of granule to be compressed and the flow ability of granule. Carr's index and Hausner's ratio were calculated using following formula.

$$C.I = (Dt - Db)100/Dt$$

Where, Dt – Tapped density of the powder
Db – Bulk density of the powder

Preparation of Sitagliptin tablets by direct compression method:

All the ingredients were passed through sieves separately and weighed as per the formula given in **Table 1**. Weighed ingredients were transferred into polythene bag and mixed for 15 minutes. After mixing thoroughly the powder is subjected for compression. The powder was evaluated for various pre-compression parameters like bulk volume, tapped volume, bulk density, tapped density and angle of repose. After compression they were evaluated for appearance, diameter, tablet weight, thickness, hardness, and friability, uniformity of dispersion, weight variation, and content uniformity. The *in vitro* dissolution profile and stability studies were also carried out [4].

TABLE 1: FORMULATIONS CONTAINING & VARIOUS CONCENTRATIONS OF EXCIPIENTS

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sitagliptin	25	25	25	25	25	25	25	25	25
HPMC K100M	25			25	50			25	50
Polyacrylic acid		25		25	50	25	50		
PVP			25			25	50	25	50
Sodiumbicorbonate	20	20	20	20	20	20	20	20	20
MagnesiumStearate	03	03	03	03	03	03	03	03	03
Talc	02	02	02	02	02	02	02	02	02
Lactose	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total	200	200	200	200	200	200	200	200	200

Evaluation of sitagliptin controlled release tablets:

The matrix tablets prepared were evaluated for the following parameters:

Weight Variation Test:

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Hardness and Friability:

For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the Roche friabilator (Campbell Electronics, Mumbai, India) respectively.

Drug Content:

Five tablets were weighed and triturate, from that transfer an accurately weighed portion of the powder equivalent to about 100mg of sitagliptin in a 100ml volumetric flask containing buffer solution and then concentration is measured at λ max 271 nm.

***In-Vitro* Dissolution Studies:**

The *in-vitro* dissolution studies were performed using the USP-II (Paddle) dissolution apparatus at 50 rpm. The dissolution medium consisted of 900ml of phosphate buffer pH 6.8, maintained at 37±0.50C. An aliquot (5ml) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrometer at 271nm. The study was performed in triplicate.

Kinetic Analysis

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

Zero- order Kinetic model – Cumulative % drug released versus Time.

First- order Kinetic model – Log cumulative % drug remaining versus Time.

Higuchi's model- Cumulative percent drug released versus square root of time.

Korsmeyer equation / Peppa's model- Log cumulative percent drug released versus log time.

Stability Studies:

Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications throughout its shelf life.

Method:

The optimized formulation was subjected for two month stability study according to ICH guidelines**.** The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were then stored at 40ºC / 75% RH for 2 months. Then samples were evaluated for their content and *in vitro* dissolution studies.

RESULTS AND DISCUSSIONS:

FT-IR Analysis:

The compatibility studies revealed both drugs and excipients were compatible after FT IR studies, the results shown in **Fig. 1**

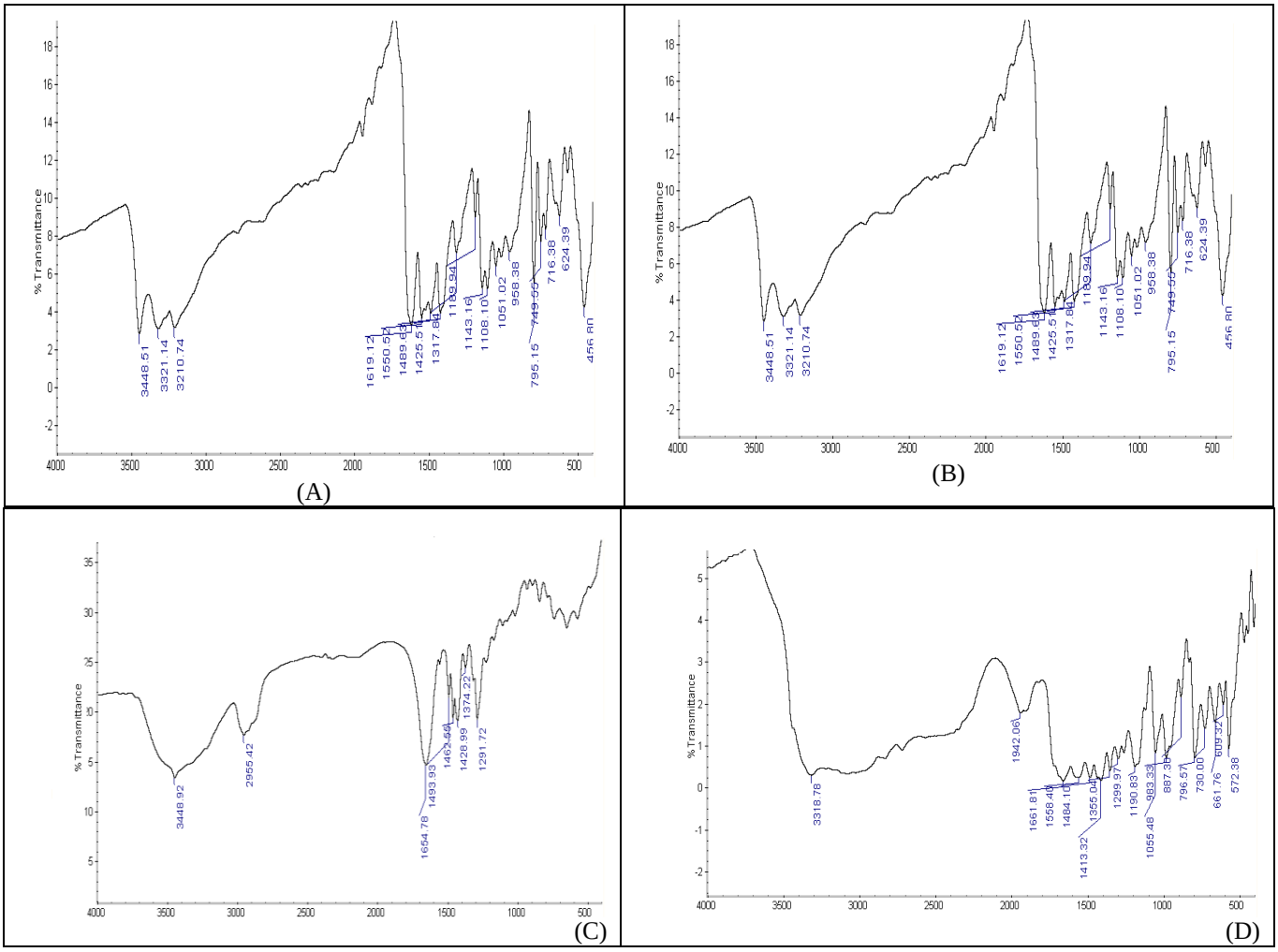

FIG.1: FTIR STUDIES OF DRUG AND EXCIPIENTS, (A) PURE DRUG, (B) DRUG WITH HPMC K100 M, (C) DRUG WITH PVP, (D) DRUG WITH POLY ACRYLIC ACID

Pre-compression evaluation parameters:

For each type of formulation the active pharmaceutical ingredients and excipients was formulated and evaluated for various pre-compression parameter as explained earlier. The Bulk density was found in the range of 0.286 to 0.439G/CC and the tapped density was found to be in the range of 0.338 to 0.514 G/CC. Using the above two density data, the Carr's compressibility index were calculated, the compressibility index was found to be in the range of 11.69 to 21.09% the compressibility and flow ability data indicated good flow properties for all the blended formulation. The better flow property of all powder blends was also evident from angle of repose. The angle of repose was range of 16.04 to 21.04^0. Angle of repose below 30º indicates good flow property. In the present study all powder blends showed good flow property. The results are shown in the **Table 2**.

TABLE 2: PRE-COMPRESSION PARAMETERS

Formulation	Bulk Density G/CC	Tapped Density G/CC	Compressibility Index %	Angle of Repose (^{0})
F1	0.31±0.094	0.408±0.120	14.64±0.03	20.96±0.04
F2	0.286±0.101	0.341±0.034	12.14±0.094	17.64±0.067
F3	0.338±0.074	0.392±0.069	17.89±0.065	16.93±0.051
F4	0.294±0.089	0.338±0.091	16.72±0.074	18.14±0.079
F5	0.309±0.093	0.416±0.113	14.51±0.093	21.04±0.084
F6	0.414±0.112	0.495±0.108	11.69±0.034	20.19±0.099
F7	0.439±0.107	0.514±0.072	19.47±0.107	17.59±0.021
F8	0.326±0.099	0.396±0.074	20.14±0.099	18.69±0.044
F9	0.319±0.094	0.372±0.043	21.09±0.102	16.04±0.042

Post- Compression evaluation parameters:

Weight Variation:

All the formulations were evaluated for their uniformity of weight according to the procedure and they show maximum weight of 200.8mg in F5 and the minimum weight of 199.4 mg in F9 formulations were observed. The maximum allowed percentage weight variation for tablets 200 mg by Indian pharmacopoeia is 7.5%, and no formulations were exceeded the limit. Thus all the formulations were found to be complying with the given standards, and the results are shown in **Table 3.**

Hardness:

All the tablet formulations were evaluated for their hardness as per procedure and all the formulations have an average hardness in the range5.5±0.07 Kg/cm^2 and 5.3±0.009 Kg/cm^2. Which was found to be acceptable and the results are shown in the **Table 3**.

Friability:

The Gastro retentive tablets were evaluated for their percentage friability as per the standards the average percentage friability for all the formulations were found be0.299% to 0.899%, which is observed to be within the limit as per the standard and the results were tabulated in the **Table 3.**

Drug Content:

All the formulations were evaluated for their uniformity of drug content according to the procedure to determine the amount of drug in all the formulation. The percentage of drug was found to be in the range of 91.09 to 98.07% w/w. The maximum drug content of 98.07% w/w for F4 and the minimum of 91.09% w/w for F2 formulations was observed. The results are tabulated in the **Table 3**.

TABLE 3: POST COMPRESSION PARAMETERS

Formulation	Weight Variation (mg)	Hardness(kg/cm^2)	Friability (%)	Drug Content (%)
F1	199.5±0.046	5.5±0.07	0.299±0.014	94.24±0.069
F2	199.6±0.074	5.0±0.143	0.461±0.079	91.09±0.014
F3	200.4±0.084	5.4±0.074	0.341±0.096	93.08±0.056
F4	200.1±0.104	5.9±0.007	0.286±0.0074	98.07±0.074
F5	200.8±0.096	5.1±0.139	0.490±0.0014	98.48±0.089
F6	199.9.±0.034	5.4±0.079	0.578±0.0019	94.57±0.015
F7	200.6±0.097	5.6±0.094	0.699±0.034	98.07±0.045
F8	199.8±0.067	5.1±0.047	0.786±0.047	92.94±0.036
F9	199.4±0.024	5.3±0.009	0.899±0.0014	98.06±0.047

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

The drug release pattern was studied for all the formulations for 12 hours by using paddle type dissolution apparatus in both stimulated gastric fluid and intestinal fluid of pH (1.2)& (6.8) respectively. The percentage cumulative drug release profile was found to be in the range of 92.9% to 99.28%.The maximum release was found to be 99.28% from F9 and minimum release of 92.9% in F5 formulation. From the above studies it was concluded that the formulation F5 & F9 containing HPMC K1OOM, poly vinyl pyrrolidone and Polyacrylic acidwith increasing concentration has shown maximum release when compared to

other formulation. The results are shown in the **Fig.2**.

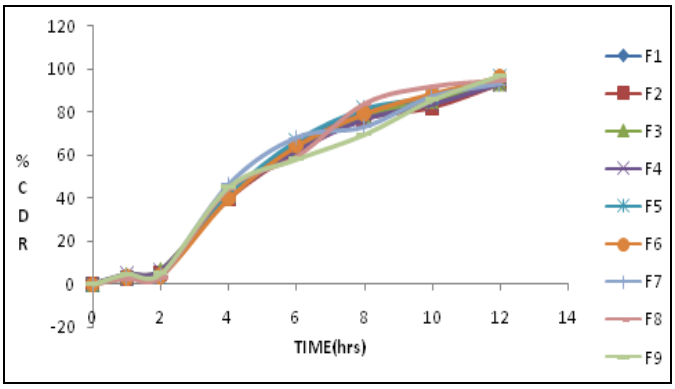

FIG. 2: *IN-VITRO* RELEASE STUDIES

Release kinetics:

The examination of the correlation coefficient 'r' indicated that the drug release followed dissolution controlled mechanism from the cumulative drug release, as the values of 'r' for first order (ranged from 0.9591 to 0.9842) found to be more in comparison to zero order (ranged from 0.9282 to 0.9438) and Higuchi's square root of time (ranged from 0.9390 to 0.9770). It was understood to be predominant first order release pattern. Further, to understand the drug release mechanism, the data were fitted into Peppas exponential model $M^t/M^\infty=Kt^n$, where M^t/M^∞ is the fraction of drug released after time 't' and 'K' is kinetic constant and 'n' is release exponent which characterizes the drug transport mechanism.

The values 'n' were in the range of 0.2951 to 1.7016. The formulation F2 indicating fickian release mechanism ('n' values are less than 0.45) and the other formulations like F1, F3, F4, F5, F6, F7, F8 andF9 is following super II release ('n' values are more than 0.89).

Stability study:

The selected formulation F5 and F9 were subjected to accelerated stability studies for 60 days at 25ºC / 60% RH, 30ºC / 65% RH, 40^0C / 75% RH, *in-vitro* release study was performed on every 30 days and showed negligible change in release profile. The formulation subjected for stability studies was found to have no change in the physical appearance and drug content. The result is shown in the **Table 4.**

TABLE 4: STABILITY STUDIES

Sl No.	Time	Drug content (%)		Cumulative drug release (%)	
		F_5	F_9	F_5	F_9
1	1 Month	98.01	97.89	99.52	99.28
2	2 Month	97.79	97.02	99.31	99.15
3	3 Month	97.12	96.99	99.11	99.09

CONCLUSION*:* From the above study it can be concluded that the polymer plays a major role in the design of oral controlled release of gastro retentive tablet. The study reveals that the release of drug was good when the gastro retentive tablet contained polymers of Poly vinyl pyrolidone and Poly acrylic acid and also shows anomalous diffusion kinetics. Hence it clearly manifestates the necessity of combining different classes of polymer to get an acceptable pharmacokinetic profile in the fluctuating *in-vivo* environment.

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REFERENCE:

1. Choi B.Y., Park H.J., Hwang S.J. and Park J.B. 2002. Preparation of alginate beads for floating drug delivery system: effects of CO2 gas-forming agent. *Int. J. Pharm.*239, 81-91.
2. Dave B.S., Amin A.F. and Patel M.M. 2004. Gastroretentivedrug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. *AAPS Pharm. Sci. Tech.* **5**, 30-34.
3. Chen RN, Hsiu-O Ho, Chiao-Ya Yu. Development of swelling/floating gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose for Losartan and its clinical relevance in healthy volunteers with CYP2C9 polymorphism. European Journal of Pharmaceutical Sci. 2010; 39: 82–89
4. Vinod KR, Santhosh Vasa, Anbuazaghan S. Approaches for gastrotentive drug delivery systems.2010; 1(2): 589-601.
5. Tina Zerilli, Eunice Y Pyon.Sitagliptin phosphate: a DPP-4 inhibitor for the treatment of type 2 diabetes mellitus.Clinical Therapeutics, 2007; 30 (4): 2614-2634
6. Lachman Leon, Lieberman Herbert A. Pharmaceutical Dosage forms: Tablets. In: The Theory and practice of industrial pharmacy. 3rd Ed, USA: Lea and Febiger; 1991. P.293-345.
7. Subrahmanyam CVS. Textbook of Physical Pharmaceutics. 2nd Ed. Delhi: vallabaPrakashan; 2003. P.180-234.
8. ICH Q1A (R2) Stability testing guidelines: Stability Testing of new drug substances and products.[online]. [Cited 2008 Nov 10]; Available from:

URL:http://www.tga.health.gov.au/docs/pdf/euguide/inch/273699r2en.pdfean Helliwell M., The use of bioadhesive in targeted drug delivery within the gastrointestinal tract. Adv Drug Deliv Rev., 1993; 11: 221-251

9. Zate SU, Kothawade PI, Mahale GH. Gastro Retentive Bioadhesive Drug Delivery System: A Review. Int. journal of pharm. research. 2010; 2: 1227-1235.
10. Zaware SR., Gaikwad PD., Bankar VH. Pawar S.P. A Review on Floating Drug Delivery System. Int journal of pharm. Sci. 2010; 2(3):834-847.
11. Vinod KR, Santhosh Vasa, Anbuazaghan S. Approaches for gastrotentive drug delivery systems.2010; 1(2): 589-601.
12. Praveen N, Sheefali M, Deepika S. Floating systems: a novel approach towards gastroretentive drug delivery systems. Int. journal of pharmacy and phram. Sci. 2010; 2(3):2-7.
13. Klusner EA, Lavy E, Barata M, Cserpes E, Friedman M., Hoffman A. Novel gastro retentive dosage form: evaluation of gastro retentivity and its effects on levodopa absorption in humans. Pharm Res 2003:20(9):1466-73.
14. Brahma N, Singh, Kwon H. Kim. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of controlled release. 2000; 63: 235-259.
15. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery System: a review. Int. J. Pharm Tech Res. 2009; 1(3): 623-633.Jain NK, Progress in controlled.

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