

Research article on Brayophyllum Pinnatum Loaded Sustained Release Tablet

Trupti Harishchandra Karpe, Proff. Smeeta More

Research Scholar (M pharmacy Pharmaceutics)PES MODERN COLLEGE OF PHARMACY (Savitribai PhuleUniversity,Pune)

Submitted: 25-09-2022

ABSTRACT :

The purpose of this study To study antiulcer activity of BrayophyllumPinnatum in the form of floating tablet.

As well to evaluate efficiency of fenugreek gum for developing gastro retentive floating tablets of BrayophyllumPinnatum when used alone or in combination with established polymers. The floating Tablet were prepared wet granulation technique and evaluated for various parameters like physical characterization, hardness, friability, weight variation, drug content uniformity, swelling index and in-vitro buoyancy and drug release. Fenugreek gum was efficient as release retardant and floating agent when used alone or in combinations with HPMC. The results indicated that fenugreek gum effectively sustained release for 12 hrs with parameters such as floating lag time, buoyancy, and floating time in acceptable range. In-vitro drug release kinetics evaluated using the linear regression method was found to follow the Higuchi release kinetics equation. This suggests that fenugreek gum can be a novel hydrophilic polymer in designing of FDDS.

Floating drug delivery system is a gastroprotective drug delivery system, has bulk density less than gastric fluids and so remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.^[1,2,3,4,]

Keywords:Brayophyllumpinnatum fenugreek gum Gastro Retentive Drug Delivery, Floating System, Controlled Release.

I. INTRODUCTION

Brayophyllum Pinnatum (family: Crassulaceae) was widely used in traditional medicine. They are found in especially in tropical Africa, India, China, Tropical America. The physiochemical study shows presence of alkaloid, flavonoid, lipids, organic acids, phenols, triterpene, glycoside and bufadienolides.^[5,6] It is widely used in treatment of haemostatic and wound healing. It is also used in treatment of immunomodulatory, Accepted: 06-10-2022

_____ CNS depressant, analgesic, anti-inflammatory, antidiabetic, anticonvulsant, anticancer, antiallergic, nephroprotective, hepatoprotective, antileishmanial, antiulcer activity. From this review of plant, it highlight the chemical constituent and medicinal uses of plant.First of all, Davis et al. investigated the floating systems to utilize the problem of swelling of dosage forms and have given an advanced gastroretentive system to the pharmaceutical field which is now-a-days one of the most effective controlled release dosage form.^[16] In spite of fewer limitations such as gastric motility, pH, and presence of food the floating delivery system still have advantages such as improved bioavailability of the drug, prolonged release, and local action which contribute in therapeutics of any disease significantly.[7,8]



Bryophyllumpinnatum is a perennial, succulent and corpulent vegetable with glabrous and tuberous stem. This species can reach up to 150 cm in height. The oldest stalks have a light color while the youngest ones are reddish with defilements. Its leaves are variable and decussates, being the lowest ones generally simple or sometimes imparinates. The leaves are 30 cm long, the upper are 3-5-7 foliated, long petiolate, thick, fleshy and dark with crenate borders. Drugs obtained from the plant source are easy to extract



and get the product also these are less expensive, safe and efficient and produces very less side effects. According to the study of World Health Organization (WHO), medicinal plants in future will be the best source to procure a large variety of the drugs. In this modern era there are still many countries which depend on the traditional practitioners and herbal medicines for their primary care and treatment. Medicinal plants are plants which consists of the one or more beneficial substances that can be used for therapeutic purposes or which can as a precursor for the synthesis of useful drugs. An extensive literature review was conducted in different scientific databases such as PubMed, Web of Science, Scopus. The study covered several aspects of the vegetal species like botany, phytochemistry, traditional uses, pharmacology and toxicology. In addition, the scientific names, synonyms and popular names of major species identified by the botanical databases "Flora do Brasil", Tropicos, International Plant Names Index and The Plant List were included. The common names found in the book "Coletâneacientífica de plantas de uso medicinal" (Amaral et al., 2005) were also used. The data were updated in April 2018.

Gastric ulcer is a common disease that develops complications such as hemorrhages and perforations when not properly treated. Extended use of drugs in the treatment of this pathology can provoke many adverse effects. Therefore, finding medicinal plants with gastroprotective and mucosal healing properties has gained increasing interest

Material Method:

Brayophy llumPinnatum obtain from Pune (rural) Maharashtra. fresh leaves of brayophy llumpinnatum other ingredients are obtained from collage laboratory. All the other chemicals were used as received and were of analytical reagent grade.

METHOD: The parameter of authentication and preformulation is caried out.

Drug Profile:

Chemical constituents: B.Pinnatum is rich in alkaloids, triterpenes, glycosides, flavonoids, cardienolides, steroids, bufadienolides and lipids^[9,10,11,12]. The leaves contain a group of chemicals called bufadienolides which are very active. Bufadienolides like bryotoxin A, B, C which are very similar in structure and activity as two other cardiac glycosides, digoxin and digitoxin and possesses antibacterial, antitumorous, cancer preventative and insecticidal actions^[12, 13, 14].

Bufadienolides-Bryophyllin A (bryotoxin)^[15]; Bryophyllin B (Fig. 1); Bryophyllol (Fig. 2); Bryophollone (Fig. 3); Bryophollenone (Fig. 4); Bryophynol (Fig. 5); Bersaldegenin (fig. 6).







Authentication Parameter

The parameters like melting point,FTIR spectra, angle of repose, bulk density, tapped density, Hausner's ratio were determined as the part of preformulation studies.11



FIG. 5: BRYOPHYNOL

Solubility Studies

The Term Solubility is defined as maximum amount of solute that can be dissolved in a given amount of solvent to form a homogenous system at specified temperature and Specific Pressure to from Saturated Solution.^[16]

Sr.No.	Medium	Concentration of drug soluble (mg/ml)
1	Water	15.99
2	pH1.2 Acidic Buffer	7.89
3	pH6.8Phosphate Buffer	4.28
4	pH7.4Phosphate Buffer	3.17

Procedure

To Prepare a different solutions Water, PH 1.2 Acidic Buffer, PH 6.8 Phosphate Buffer, PH 7.4 Phosphate Buffer.

• The drug material is added in to above solutions till Supersaturated Solution is from The Mixture Placed in Orbital Shaker for 24 hrs. After 24 hrs. Filter the mixture TakeFiltrate and Give Absorbance. To detect the Concentration of Drug is Soluble in Different Solutions.

Mechanism of floating systems:

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (Fig.: 1) the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object.

The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations¹⁷.

 $F = F_{buoyancy} - F_{gravity} = (Df - Ds) gV$ Where, F = total vertical force, Df = fluid density,Ds = object density, V = volume and g = acceleration due to gravity.^[17,18,19]



Calibration Curve of BrayophyllumPinnatum

Calibration Curve is determined by using UV Spectrophotometric methods. In which 10 mg drug is added in 100 ml of water (100 μ g/ml Solution). To Prepared different Dilutions (0, 2, 4,

• Water (H₂O)

Conc.	abs
0	0
2	0.228
4	0.439
6	0.652
8	0.85
10	1.061
12	1.25

• 0.1N HCL

Concentration	Absorbance
0	0
2	0.012
4	0.19
6	0.22
8	0.38
10	0.49

pH 1.2 ACETATE <u>BUFFER</u>

concentration	abs
0	0
2	0.09
4	0.121
6	0.125
8	0.135
10	0.211

1. Calibration curve in water (H₂O)

6, 8, 10, 12) of above solution (100 ug/ml Solution). Take Absorbance in respective a 200-400 nm

U.V Absorbance.









3. pH 1.2 ACETATE BUFFER



Drug excipient compatibility studies

Drug is an active part of dosages form and it is mainly responsible for therapeutic value and Excipient substances which are included along with drugs being formulated in a dosage form so as to impart specific qualities to them. It is important for determination of Stability of the dosage forms. It's also used for development of new drug delivery system as well as investigation of new drug Product.

PROCEDURE:

DRUG and polymer in a dryer to make it moisture-free. The dry sample of powders was

separately mixed and triturated with dry potassium bromide. This mixture was placed in a DRS assembly sample holder. The infrared spectrum was recorded and the spectral analysis was done (Shimadzu, 8400S, Japan).^[15]

Fourier transform infrared spectrum.

Drug-excipient compatibility studies: Compatibility studies were carried out to know the possible interactions between Bryophy llumpinnatum and excipients used in the formulation. Physical mixtures of drug and excipient.^[20,21]



Formulations	F1	F2	F3	F4	F5	F6
Drug	67%	67%	67%	67%	67%	67%
Gum powder	10%	10%	8.30%	6.60%	11.66%	11.30%
HPMC K4M	10%	6.60%	8.30%	10%	5%	5.33%
Sodium bicarbonate	4%	4%	4%	4%	4%	4%
PVP K90	1.33%	1.33%	1.33%	1.33%	1.33%	1.33%
aerosil	3.33%	3.33	3.33	3.33	3.33	3.33
Lactose	4%	4%	4%	4%	4%	4%
Magnesium stearate	0.33%	0.33%	0.33%	0.33%	0.33%	0.33%
Talc	0.33%	0.33%	0.33%	0.33%	0.33%	0.33%

FORMULATION TABLET

TABLE 1.1

PREPARATION OF GRANNULES

BRAYOPHYLLUM Preparation of PINNATUM n floating tablet: All the ingredients (except glidants and lubricant) as shown in Table1 were weighed separately, mixed thoroughly in poly bag for 10 minutes to ensure uniform mixing and the mixture was passed through sieve no.60. Granulation was done with a solution of calculated quantity of PVP K90 in sufficient isopropyl alcohol. The wet mass was passed through sieve no. 12, and dried at 75°C for 2 hours.

TABLET PUNCHING

The dried granules were sized by sieve no. 18 and mixed with magnesium stearate and talc. The blend thus obtained was compressed (8 mm diameter, flat punches) using a single station tablet press machine

EVALUATION OF GRANULES:

The granules were evaluated for their flow properties. Angle of repose of granules was determined by the funnel method.

Loose bulk density (LBD) and tapped bulk densities (TBD) were determined, according to the method reported by Raghuram, The Carry index (compressibility index) and Hausner ratio determined from the LBD and TBD.^[13,23,25,27]

Formulation Code	Bulk density (gm/cm ³) ±S.D	Tapped density (gm/cm ³) ±S.D	Carr's index (±S.D %)	Hausner's ratio (±S.D %)	Angle of repose (θ)
F1	0.486±0.011	0.562±0.041	13.58±0.71	0.864 ± 0.031	23.71 ±S 0.51
F2	0.468±0.005	0.564±0.013	15.29±0.56	0.829±0.014	21.52 ±S 0.59
F3	0.483±0.114	0.569±0.096	16.72±0.32	0.848±0.052	25.32 ±S 0.38
F4	0.446±0.032	0.567±0.038	17.60±0.27	0.786±0.031	26.42 ±S 0.72
F5	0.453±0.147	0.534±0.025	15.64±0.13	0.848 ± 0.041	24.75 ±S 0.34
F6	0.550±0.025	0.592±0.012	17.26±0.24	0.929±0.036	25.29 ±S 0.12

EVALUATION OF GRANNULES :



aluation of po	luation of post compression parameters for formulations F1-F6							
Formulation Code	Thickness (mm)	Diameter (mm)	Hardness (kg/cm ²)	Friability (%)	Weight variation (mg)	Floating lag time(sec)	FLOATING TIME(hrs.)	Drug content (%)
F1	2	8	5	24	300±25	7	21	98±45
F2	2	8	4	22	300±5	6	21	97±89
F3	2	8	5	13	299±08	7	23	99±56
F4	2	8	5	14	301±10	8	22	99±08
F5	2	8	4	15	300±09	5	24	99±87
F6	2	8	4	19	298±10	8	23	98±78

EVALUATION OF TABLET

TABLE1.3

Prepared tablet were evaluated for quality control tests like weight variation test, hardness test, friability test and content uniformity study.^[14-15]

1. Uniformity of weight: Twenty tablets were weighed individually and the average weight was determined. The percentage deviation was calculated and checked for weight variation as per IP14. Deviation of weight variation is given in table 2.

DEVIATION FOR WEIGHT VARIATION TABLE

Average Weight of tablet (mg)	% Deviation
80mg or less	10
80 mg to 250 mg	7.5
250 mg or more	5

TABLE 1	.4
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- 1. Hardness: Hardness or tablet crushing strength (fc), is the force required to break a tablet in a diametric Compression. This compression force was measured using Monsanto tablet hardness tester for all the batches15. It is expressed in kg/cm².
- 2. Thickness: Thickness of tablets is for uniformity of tablet size. important Thickness was measured using Vernier Calipers on 3 randomly selected samples.^[16]
- 3. Friability test: Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes, the tablets were weighed and the percentage loss



in tablet weight was determined using the below given formula.^[17]

%Loss=<u>initial wt. of tablets (W1)- final wt. of</u> tablets(W2) X 100

Initial wt. of tablets

- 4. Floating lag time: The lag time was carried out in beaker containing 250 ml of pH 1.2 buffer solution as a testing medium maintained at 37°C. The time required for the tablet to rise to the surface and float was determined as floating lag time in minutes.^[18]
- 5. Floating Time (Buovancy Time): Drugs that exhibit poor solubility in the intestinal tract. Floating drug delivery in systems (FDDSs) are one of the most prominent approaches of GRDDs, characterized by the capacity of the formulation to float in and over the gastric contents. FDDSs are low density systems, which allows them to remain buoyant in the stomach for a prolonged period. In the development of FDDSs based on the mechanism of buoyancy the widely employed technology is effervescent systems. In effervescent systems, carbon dioxide gas production occurs due to the reaction of carbonates and bicarbonates present in the formulation with gastric fluid. The gas that forms is entrapped in the polymers, which allows the system to remain buoyant. The FDDSs are effectively used to design sustained drug delivery systems and improve the overall oral bioavailability of drugs.^[21,22,27,26]
- 7. Drug content: Five tablets were weighed individually, and powdered. FLOATING TABLETS were ground using a mortar and pestle and transferred into a 50 mL volumetric flask containing 0.1 N HCl and the volume was made up to 50 ml. The mixture was sonicated for 10 min to ensure complete extraction of the drug. The solution was filtered through Whatman filter paper and assayed spectrophotometrically (Shimadzu 1700, Japan) at 273 nm to determine the percent drug content.^[16,17,24,28]
- 8. In vitro drug release studies Drug release studies of The dissolution studies were carried out with 900 mL of 0.1 N HCl as dissolution medium at 37±0.5°C and at 50 rpm. A 10 mL aliquot was withdrawn and immediately replaced by the same volume of fresh medium to maintain sink condition. The aliquot was

filtered through Whatman filter paper and absorbance was measured at $\underline{-n}$ m using a UV spectrophotometer (Shimadzu 1700, Japan) to determine the drug release.^[16,18,29,30]

9. Dissolution studies: The release rate of BrayophyllumPinnatum from floating tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of pH 1.2 buffer solution, at $37 \pm 0.5^{\circ}$ C and 50 rpm. Aliquot volume was withdrawn from the dissolution apparatus hourly for 12h, and the samples were replaced with fresh dissolution medium. After filtration and suitable dilution the amount of drug release by the determination of calibration curve. ^[20]

Details of Dissolution Test:

- 1. Apparatus : USP Type II
- 2. Volume of medium : 900 ml
- 3. Temperature : 37 °C
- 4. Paddle Speed : 50 rpm
- 5. Dissolution medium used: pH 1.2 buffer solution
- 6. Aliquot taken at each time interval: 5 ml
- 10. Stability studies of the standard formulations: Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess the drug and formulation stability, the stability studies were carried out on the one most satisfactory formulation as per ICH guidelines Q1C.^[21] The most satisfactory formulation F3 was sealed in aluminum packaging and was kept in humidity chamber maintained at $35 \pm 2 \text{ °C} / 60 \pm 5 \text{ \% RH}$ and 40 \pm 2 °C / 75 \pm 5 %RH for 3 months. It was then evaluated for various parameters to check the stability and efficacy of the product.

11. Swelling Study

Determination of Swelling Index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 hrs. The swelling index (SI), expressed as a percentage, and was calculated from the following equation. The percentage weight gain by the tablet was calculated by the formula.^[7,8,31,32,33]



Swelling index $=\frac{wt-w0}{w0} \times 100$

Where, S.I. = Swelling index Wt = Weight of tablet at time t Wo = Weight of tablet before immersion

II. RESULT AND DISCUSSION

The floating tablet of Brayophy llumPinnatum was successfully prepared by using fenugreek gum powder and HPMC .formulation 6 has shows best sustain release activity and which has good floating properties. The release profile of optimized formula has R² value is 0.9894.It has good stability at storage condition.

1 Calibration curve

Conc.	abs
0	0
2	0.228
4	0.439
6	0.652
8	0.85
10	1.061
12	1.25

2 0.1N HCL

Concentration	Absorbance
0	0
2	0.012
4	0.19
6	0.22
8	0.38
10	0.49

3 pH 1.2 ACETATE BUFFER

concentration	abs
0	0
2	0.09
4	0.121
6	0.125
8	0.135
10	0.211



1. Calibration curve in water (H₂O)



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2 0.1 N HCL
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3 pH 1.2 ACETATE BUFFER



2. Fourier transform infrared spectrum.

Drug-excipient compatibility studies: Compatibility studies were carried out to know the possible interactions between Bryophyllumpinnatum and excipients used in the formulation. Physical mixtures of drug and excipient.^[20,21]



2. Pure Drug



4 Mixture of Drug and fenugreek

3. Mixture of drug and excipients.



5.SWELLING INDEX

The tablets were weighed individually (W1) and placed separately in glass beaker containing 200 mL of 0.1 N HCl maintained at $37^{\circ}C\pm1^{\circ}C$. At regular 1-h time intervals until 24 h,

tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then re-weighed (W2) and swelling index (SI) was calculated using the following formula.

DOI: 10.35629/7781-0705897915 | Impact Factor value 7.429 | ISO 9001: 2008 Certified Journal Page 907



SI = (W2-W1)/(W1)

TIME	F1	F2	F3	F4	F5	F6
1hr	20.27	26.43	19.21	18.48	20.11	18.06
2hr	36.09	44.60	34.12	30.12	33.16	29.18
3hr	51.02	60.57	49.56	47.23	48.32	42.70
4hr	62.47	72.22	60.89	54.42	60.06	53.04
6hr	72.09	85.11	70.06	63.15	71.51	59.56

Table 21:% swelling index of formulated floating tablets









Batch F1 & F2 after 9 hrs.



Batch F3 & F4 after 9 hrs.



Batch F5 & F6 after 9 hrs.



• Floating behaviour of tablet

The tablets were floated and remained buoyant without disintegration thus it, maintains its dimensional stability during floating. The formulation F1,F2 , F3,F4,F5,F6 containing FENUGREEK,HPMC AND Their buyoncy lag time is 5,6,7,8,4,8 sec respectively of 1114minutes and TFT from 11-14 hrs respectively shown in the Table 4. The total buoyancy / floating time of batch containing plain cfenugreek gum shows good floating behavior. When fenugreek used it shows better floating behavior. Increased in concentration of fenugreek increases floating time as shown in table 4.

Physicochemical Properties of Fenugreek gum table

Parameter	Result				
Solubility	Slightly soluble in cold water, But quickly dissolves in				
	warm water, forms viscous colloidal solution,				
	insoluble in ether, acetone, chloroform, methanol,				
	ethanol.				
pH (1% solution)	6.23±0.2				
Specific gravity (0.01%	$1.0005\pm2.3X10^{-4}$				
solution) g/ml					
Water content (%)	71±5.2				
Total ash	0.967±0.015				
Water soluble ash	0.847±0.015				
Melting point	232°-240°C				
Acid insoluble ash	0.01±0.005				
Swelling index	8±0.2				

Table 2.1

htly soluble in cold water, But quickly
olves in warm water, 0.1NHCL
±.21
± 0.015
7 ± 0.015
°-240°C
±0.005

Table 2.2

Dissolution study

Hour	F1	F2	F3	F4	F5	F6
1	0.211	0.209	0.220	0.23	0.233	0.293
2	0.278	0.26	0.283	0.29	0.293	0.299
3	0.373	0.32	0.339	0.36	0.367	0.398
4	0.395	0.385	0.398	0.389	0.389	0.389
5	0.599	0.587	0.499	0.498	0.488	0.487



6	0.639	0.599	0.59	0.599	0.598	0.59
7	0.808	0.695	0.69	0.698	0.697	0.69
8	0.908	0.789	0.791	0.799	0.787	0.79
9	0.985	0.899	0.897	0.899	0.904	0.887
24	1.346	1.446	1.389	1.486	1.358	1.346



CUMMULATIVE DRUG RELEASE(F1-F6)

PERCENT DRUG RELEASE OF OPTIMIZED BATCH (F5)

TIME (Hrs.)	Absorbance	B-0.2718	C/0.0489	D*900	E/100	F/200	% Drug release
1	0.233	-0.0388	-0.793456	-714.11043	-7.1411043	-0.0357055	-3.5705521
2	0.293	0.0212	0.43353783	390.184049	3.90184049	0.0195092	1.95092025
3	0.367	0.0952	1.94683027	1752.14724	17.5214724	0.08760736	8.7607362
4	0.389	0.1172	2.39672802	2157.05521	21.5705521	0.10785276	10.7852761
5	0.488	0.2162	4.42126789	3979.1411	39.791411	0.19895706	19.8957055
6	0.598	0.3262	6.67075665	6003.68098	60.0368098	0.30018405	30.0184049
7	0.697	0.4252	8.69529652	7825.76687	78.2576687	0.39128834	39.1288344
8	0.787	0.5152	10.5357873	9482.20859	94.8220859	0.47411043	47.4110429

DOI: 10.35629/7781-0705897915 | Impact Factor value 7.429 | ISO 9001: 2008 Certified Journal Page 911



9	0.904	0.6322	12.9284254	11635.5828	116.355828	0.58177914	58.1779141
24	1.358	1.0862	22.2126789	19991.411	199.91411	0.99957055	99.9570552



Kinetic Studies

Kinetic modelling of drug release

To analyze the mechanism of drug release from the floating tablets, the in vitro dissolution data of the formulations were fitted to the zero order, first order, Higuchi model and Korsmeyer- Peppas model.







III. RESULT AND CONCLUSION:

The floating tablet of BrayophyllumPinnatum was successfully prepared by using fenugreek gum powder and HPMC .formulation 6 has shows best sustain relese activity and which has good floating properties. The release profile of optimized formula has R 2 value is 0.9056.It has good stability at storage condition.

Conclusion: The floating drug delivery system was prepared in an effort increase the gastric retention time of the dosage form and to control drug release. One of the most feasible approaches for achieving a prolonged and predictable dug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastro-retentive dosage forms that will provide us with new and important therapeutic options. Floating matrix tablets are designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique.

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DOI: 10.35629/7781-0705897915 | Impact Factor value 7.429 | ISO 9001: 2008 Certified Journal Page 914



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