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Design and Evaluation of Valacyclovir Hydrochloride Floating Microsphere

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Keywords: Gastro retentive system, Valacyclovir HCl, Eudragit S100, Ethyl Cellulose, Floating microspheres, Non-aqueous Solvent Diffusion Method.

ABSTRACT

In the present study, an attempt has been made to prepare floating microspheres by Non-aqueous solvent evaporation method. Valacyclovir HCl, having short biological half-life of < 30 minutes (Acyclovir 1.5-2 h) and its rapid elimination from the body, is ideally suited to be delivered through floating multiunit dosage form. Biocompatible polymers, Eudragit S100 and Ethyl cellulose were used along with drug in different proportions. The prepared six formulations (F1-F6) were characterized for their micromeritic properties, particle size, percentage yield, morphology, buoyancy studies, drug encapsulation efficiency, and *in-vitro* drug release studies. The formulated microspheres were found free floating. The optical microscopic studies revealed that the particles were of the size range of 95.03-152.48 μm with porous and almost spherical in shape. The prepared floating microspheres were found to produce the percentage yield of 65.6-79.8%, with 74.70-85.06% drug encapsulation efficiency and 71.5-79.1% buoyancy. *In-vitro* drug release studies showed cumulative % of drug release between 85.15-93.03%. The data obtained in this study thus suggests that a micro particulate floating dosage form of Valacyclovir HCl can be successfully designed to give prolonged release of drug and hence improved bioavailability.

INTRODUCTION:

Recently in the field of pharmaceutical technology, great efforts have been directed towards the prefabrication of existing drug molecules in a fashion, capable of solving problems related to poor water solubility, poor bioavailability, dosing problem, stability, toxicity, etc. This trend of working has led to development of new drug delivery systems.

Even today, conventional drug-delivery systems have primary pharmaceutical products commonly seen in prescriptions with 'over the counter' marketplace. They provide prompt discharge of the drug, but in order to achieve with maintain drug concentration by way of in therapeutically achieved range, it is often necessary to administer it several times a day. Conventional drug therapy results in significant fluctuations of drug concentration in systemic circulation causing either lethal effect or no therapeutic action.

Essential goal of drug therapy is to give therapeutic quantity of drug to good site in body to promptly achieve with then uphold desired drug concentration. This idealized objective points to two aspects the majority important to the drug delivery, namely spatial placement as well as temporal delivery of drug. Spatial placement relates to targeting a drug to specific organ or else tissue even as temporal delivery refers to controlling rate of drug delivery to that specific organ or tissue. Despite marvelous progression in drug delivery, oral route leftovers preferred route for administration.

Oral controlled RDF has been made more than past three decades. These drug delivery systems have a huge potential of solving problems associated by way of conventional multiple dosing system like strict adherence to timely dosing, flip-flop plasma concentration, associated side effects due to systemic accumulation of drug. Thus, there have numerous advantages for instance improved efficacy, reduced toxicity, improved patient compliance with convenience, reduction in health care cost, etc.

However, this approach is faced by way of several physiological difficulties, for instance, inability to restrain with locating controlled drug-delivery system by way of in the desired region of Gastrointestinal Tract, due to variable gastric emptying with motility. Furthermore, the relative brief gastric emptying time in humans which normally averages 2-3 h through major absorption zone i.e. stomach with upper part of intestine able to result in incomplete drug-discharge from drug delivery system leading to low bioavailability with thus reduced efficacy of administered dose.

Efforts to get better oral drug and its bioavailability have grown in parallel by way of pharmaceutical industry. As the number with chemical variety of drugs has greater than before, novel strategies have required developing orally active therapeutics. The precedent 2 decades have been characterized by an increased understanding of causes of low bioavailability with great deal of innovation in oral delivery technologies, noticeable by an unparalleled increase of drug-delivery industry.

It is evident from the recent scientific with patent literature that an increased interest in new dosage forms that have retained in stomach for prolonged with expected phase of time subsist in the present day in academic with industrial research groups. One of the majority possible moves toward for achieving a prolonged with predictable drug delivery profile in Gastrointestinal Tract is to control gastric residence time.

Control of placement of drug-delivery system in specific region of Gastrointestinal Tract offers advantage for variety of important medicines characterized by narrow absorption window in Gastrointestinal Tract or medicines by way of stability problem. These considerations have to lead development of unique oral controlled discharge dosage form by way of gastro retentive properties i.e. dosage form could be retained in the stomach for several hours with discharge the medicine there in a controlled with prolonged manner so that medicine could be supplied continuously to its absorption site in the upper Gastrointestinal Tract.

To understand the contemplation taken in drawing of gastro retentive dosage forms with to evaluate their performance, the relevant anatomy with physiology of Gastrointestinal Tract must be fully understood.

The Gastrointestinal Tract is fundamentally a cylinder about 9 meters long that runs through middle of body from mouth to anus with comprising first throat (pharynx), second part oesophagus, then stomach, second last small intestine (consisting of duodenum, jejunum with ileum) with lastly large intestine (consisting of cecum, appendix, colon with rectum). In the living person, it is shorter because the muscles along walls of gastrointestinal tract organs have in state of tone (sustained contraction).

Wavelike contractions of smooth muscle in wall of Gastrointestinal Tract propel the food along the tract from esophagus to anus.

MATERIALS AND METHODS

VALACYCLOVIR HCl

Valacyclovir HCl is the HCl salt of the L-valyl ester of the antiviral drug acyclovir.

Structure:

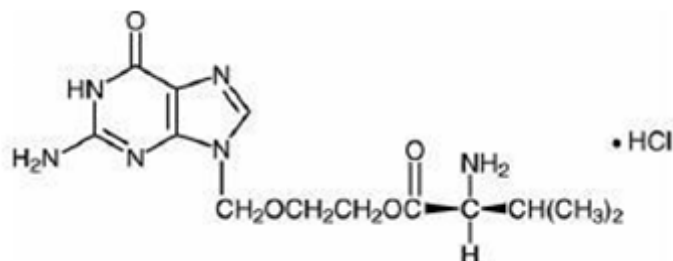


Figure 1: Chemical structure of Valacyclovir HCl

Category	:	Oral antiviral drug
Chemical name	:	(S)-2-[(2-amino-6-oxo-6,9-dihydro-3H-purin-9yl)methoxy]ethyl 2-amino-3-methylbutanoate
Mol. wt	:	360.8 g/mol
Molecular formula	:	C ₁₃ H ₂₁ N ₅ O ₄
Physical appearance	:	White to off white crystalline powder
pH	:	4.0 – 6.0
Melting point	:	170 - 172°C
Solubility	:	Soluble in water, methanol with ethanol. Insoluble in Chloroform
Storage/Stability	:	Store at controlled room temperature 13 - 30°C.

Mechanism of action:

Valacyclovir has a prodrug, an esterified version of aciclovir that has greater oral bioavailability (about 55%) than aciclovir (10–20%). It has converted by esterases to the active drug aciclovir, with the amino acid valine, via hepatic first-pass metabolism. Aciclovir has selectively converted into a monophosphate form by viral thymidine kinase, which has far more effective (3000 times) in phosphorylation than cellular thymidine kinase. Subsequently, the monophosphate form has further phosphorylated into the active triphosphate form, aciclo-GTP, by cellular kinases. Aciclo-GTP has a very potent inhibitor of

viral DNA polymerase; it has approximately 100 times higher affinity to viral than cellular polymerase. Its monophosphate form also incorporates into the viral DNA, resulting in chain termination. It has also been shown that the viral enzymes cannot remove aciclo-GMP from the chain, which results in inhibition of further activity of DNA polymerase. Aciclo-GTP has fairly rapidly metabolized by way of in the cell, possibly by cellular phosphatases.

Dosage:

Shingles:

1000mg three times a day.

Genital Herpes:


Initial dose: 1000mg two times a day

Recurring herpes: 500 mg two times a day

Cold Sores:

2000mg orally two times a day

Pharmacokinetics:

Bioavailability (%)	 55%
Protein binding (%)	: 13–18%
Elimination half life	: <30 minutes (valaciclovir); 2.5-3.6 hours (aciclovir)

Absorption:

After oral administration, Valacyclovir HCl has rapidly absorbed from the gastrointestinal gut with nearly completely converted to acyclovir with L-valine by first-pass intestinal as well as/or hepatic metabolism. It has absorbed in the lower parts of stomach with upper parts of small intestine.

Metabolism:

Valacyclovir has converted to acyclovir with L-valine by first-pass intestinal as well as/or hepatic metabolism. Acyclovir has converted to a small extent to inactive metabolites by aldehyde oxidase with by alcohol with aldehyde dehydrogenase. Neither valacyclovir nor acyclovir has metabolized by cytochrome P450 enzymes. Plasma concentrations of unconverted valacyclovir are low with transient, generally becoming non-quantifiable by 3

hours after administration. Peak plasma valacyclovir concentrations are generally less than 0.5 mcg/mL at all doses.

Distribution:

Valacyclovir HCl has a protein bounding around 13 – 18%

Excretion:

40 – 50% has excreted through renal route with around 47 % has excreted through the feces.

Precautions:

Should be taken care of patients contraindicated by way of hypersensitivity reactions by way of valacyclovir or acyclovir formulations earlier.

Drug interactions:

No clinically significant drug-drug interactions or drug-food interactions are present.

Side effects:

Common adverse drug reactions ($\geq 1\%$ of patients) associated by way of valaciclovir therapy are the same as for aciclovir, its active metabolite, with include: nausea, vomiting, diarrhea with headache. Infrequent adverse effects (0.1–1% of patients) include agitation, vertigo, confusion, dizziness, edema, arthralgia, sore throat, constipation, abdominal pain, rash, weakness as well as/or renal impairment. Rare adverse effects ($< 0.1\%$ of patients) include coma, seizures, neutropenia, leukopenia, tremor, ataxia, encephalopathy, psychotic symptoms, crystalluria, anorexia, fatigue, hepatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis well as/or anaphylaxis.

Polymer Profile

Polymethacrylates

Synonym: Eudragit; Methacrylic acid.

Non-proprietary Names:

NF: Methacrylic acid copolymer; polymeric methacrylates.

Chemical Name:

Copolymer synthesized from dimethyl aminoethyl methacrylate with other neutral methacrylic esters.

Functional category: Film former, tablet binder.

Density: 12.5; 0.825 g/cm³.

Structural formula:

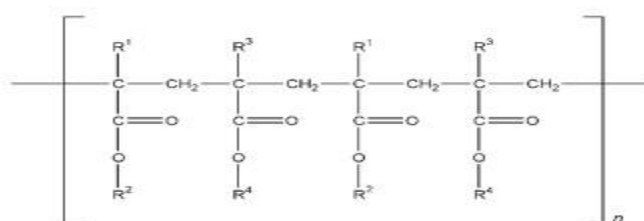


Figure 2: Structure of Eudragit

Type S with Type L

R1 = -CH₃

R3 = -CH₃

R2 = -H

R4 = CH₃



Molecular Weight: ≥100,000 with approximately 135,000.

CAS Registry Number: 9065-11-6

Description:

Polymethacrylates are film coatings with matrix structures based on polymeric methacrylates. They are synthetic cationic with anionic polymers of dimethylamino ethyl methacrylates, methacrylic ratios.

Type L (easily soluble in intestinal fluid) has 50% methacrylic acid with Type S (barely soluble in intestinal fluid) has 30% methacrylic acid; both are anionic polymers of methacrylic acid with methacrylic acid esters in different ratios available as 12.5% solution in isopropanol by way of out plasticizer (L 12.5, S 12.5); with as 12.5% ready to use solution in isopropanol by way of 1.25% dibutyl phthalate as plasticizer (L 12.5p, S 12.5p); colorless, by way of the characteristic odor of the solvent.

Solubility:

1g of Eudragit L100 or Eudragit S100 dissolves in 7g methanol, ethanol, in aqueous isopropyl alcohol with acetone, with in 1 N sodium hydroxide to give clear to slightly cloudy solutions. Eudragit L100 with Eudragit S100 are practically insoluble in ethyl acetate, methylene chloride, petroleum ether with water.

Viscosity:

Eudragit L100: 18 mm²/s

Eudragit S100: 29 mm²/s

Acid Value: Eudragit L100: 316 mgKOH/gDS

Eudragit S100: 190 mgKOH/gDS

Incompatibilities:

Incompatibilities occur by way of acid as well as/or alkaline conditions depending upon which polymer has being used.



Stability with Storage Conditions:

Dry powder forms appear to be stable at room temperature. Dispersions are stable for about 1 year after manufacturing with stored at room temperature in tight containers protect against moisture.

Applications:

Eudragit L100 with Eudragit S100 are employed as film coating agents resistant to gastric fluid by way of different solubilities (L<pH 6, S> 7).

Ethyl Cellulose³⁸

Synonyms: Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical Name with CAS Registry Number: Cellulose ethyl ether [9004-57-3].

Empirical Formula: C₁₂H₂₃O₆ (C₁₂H₂₂O₅)_nC₁₂H₂₃O₅

Structural Formula:

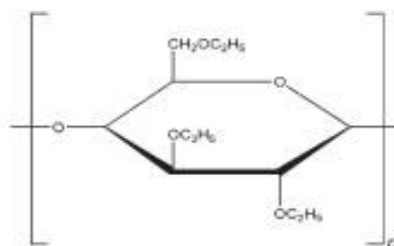


Figure 3: Structure of Ethyl Cellulose Functional Category:

Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity increasing agent.

Description: Tasteless, free flowing, white in color.

Solubility:

Practically insoluble in glycerin, propylene glycol, with water, but soluble in certain organic solvents, depending upon ethoxy content.

Softening point: 158-162°.

Incompatibilities: Incompatible by way of paraffin wax with microcrystalline wax.

Regulatory acceptance: NFXVI.

Pharmacopeial Specifications:



Assay (of ethoxyl groups)	44.0–51.0%
Lead	≤ 10 ppm
Arsenic	≤ 3.0 ppm
Heavy metals	≤ 40 ppm
Residue on ignition	≤ 0.4%
Loss on drying	≤ 3.0%

Safety: Essentially non-toxic.

Stability with Storage Conditions:

It has chemically resistant to alkalis, both dilute with concentrated, with to salt solutions, although it has more sensitive to acidic materials than are cellulose esters. However, the material can by way of with dilute acids for a limited period of exposure. Ethylcellulose has subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This might be prevented by the use of antioxidant with chemical additives that absorb light in the 230–340 nm range. Ethylcellulose should be stored at a temperature not

exceeding 32°C (90°F) in a dry area away from all sources of heat. Store in a well closed container.

Applications in Pharmaceutical Formulation or Technology:

1. Binder in tablets. Ethyl cellulose might be blended dry with wet granulated by way of a solvent for instance alcohol. Tablets made by way of ethyl cellulose as a binder tend to exhibit poor dissolution with poor drug absorption.
2. Coating material for tablets. Ethylcellulose by itself forms a water insoluble film coating. It is commonly used by way of HPMC to alter the solubility of the film. Other materials might be used for this as well.
3. Coating material for stabilization with taste masking.
4. Slow drug-release from film. Caffeine with salicylic acid incorporated into ethylcellulose films have been shown to exhibit diffusion controlled release.
5. Coating for drug microcapsules. Ethylcellulose has been used to coat particles of drugs to form microcapsules. This type of microcapsule slows dissolution of the drug as a function of microcapsule wall thickness.

RESULT AND DISCUSSION



Table 1: Physico-chemical properties of valacyclovir

Color	:	White to almost white crystalline powder
Odor	:	Odorless
Taste:	:	Bitter

Solubility

Solubility studies of Valacyclovir have been done in various solvents such as water, Chloroform, Ethanol, Methanol, and 0.1N HCL solution. We were found that a solubility of valacyclovir is good in a Methanol solution.

Table 2: Solubility studies of Valacyclovir in different solvent

S. No.	Solvent used	Solubility
1.	Water	Slightly Soluble
2.	0.1 N HCL	Soluble
3.	Ethanol	Slightly Soluble
4.	Methanol	Freely Soluble
5.	0.1N NaOH	Soluble

Melting Point determination:

Melting point determination of the obtained drug sample was done because it is a good first indication of purity of the sample since the presence of relatively small amount of impurity can be detected by a lowering with widening in the melting point range.

The melting point of the drug sample range of the drug is 196-200°C.

Partition Coefficient measurement:

The partition coefficient (P) is defined as the ratio of the equilibrium concentrations of a dissolved substance in a two-phase system consisting of two largely immiscible solvents. In the case Chloroform and water:

$$P_{o/w} = C_{\text{chloroform}}/C_{\text{water}}$$

The partition coefficient (P) therefore is the quotient of two concentrations and is usually given in the form of its logarithm to base 10 (log P).

The **partition coefficient** is a ratio of concentrations of un-ionized compound between the two solutions. To measure the **partition coefficient** of ionizable solutes, the pH of the aqueous phase is adjusted such that the predominant form of the compound is un-ionized. The logarithm of the ratio of the concentrations of the un-ionized solute in the solvents is called **log P**:

$$\log P_{\text{oct/wat}} = \log \left(\frac{[\text{solute}]_{\text{octanol}}}{[\text{solute}]_{\text{water}}^{\text{un-ionized}}} \right)$$

Loss on Drying (LOD):

Procedure: Loss on drying directly measuring by IR moisture balance. Firstly calibrate the instrument by knob then take 1 gm sample (powder) and set the temp at 100°C to 105°C for 5 minutes and constant reading set the knob and check % moisture.

Result: The percentage of loss on drying of Valacyclovir was found to be 0.87% w/w respectively.

Determination of pH (1% w/v solution in water):

The pH of Valacyclovir was determined by Digital pH meter and found to be 4.9

Flow property of valacyclovir powder:

Bulk density:

A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, V_0 , to the nearest graduated unit. Calculate the bulk density, in gm/ml gm/cc, by the formula

$$\text{Bulk density} = \text{Bulk Mass} / \text{Bulk Volume}$$

Results: Bulk density of powder was found to be 0.0715g/cc.

Table 3: Bulk Density of valacyclovir

S. No.	Density	Valacyclovir
1	Untapped Density	0.0715 g/cc
2	Tapped Density (after 50 tapping)	0.0893g/cc

Compressibility Index (%)

$$\text{C.I.} = \frac{100 (V_0 - V_f)}{V_0} \quad \text{OR} \quad \text{C.I.} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Result: The compressibility index of Valacyclovir was found to be 20.224%.

Hausner ratio:

$$\text{Hausner Ratio} = \text{Tapped density} / \text{Bulk Density}$$

Result: The Hausner ratio of Valacyclovir was found to be 1.244.

Angle of Repose

Procedure: The angle of repose is a relatively simple technique for estimating the flowability of a powder through a funnel and fall freely onto a surface. The height and diameter of the resulting cone are measured and using the following equation, the angle of repose can be calculated. Weigh 10 gm of Valacyclovir powder accurately, and pass through the funnel height up to 10 cm from surface and measure the height and diameter by scale.

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

Where h, r is the relatively height and radius of the powder cone.

Result: The Angle of repose of Valacyclovir is 40.57 degree.

Result: Particle size pass through 40# is 100 (% w/w).

Moisture by Karl-Fischer Apparatus (KF)

Result: The Moisture content of valacyclovir is 0.76%

Determination of λ_{\max} by UV-visible spectroscopy

Procedure:

Accurately weighed 10mg of Valacyclovir separately and dissolved in 10ml of 0.1N HCL in 10ml of volumetric flask and prepared suitable dilution to make it to a concentration of 10 μ g/ml make adequate of sample with concentration range of 5-25 μ g/ml Valacyclovir and calculate the spectrum of this solution was run in 200-400nm range in U.V spectrophotometer.

Result: The λ_{\max} found for Valacyclovir is 256.0nm as shown in Figure.



Evaluation of Valacyclovir floating microspheres:

Particle size analysis:

Particle size was determined by Optical microscopy method. It plays important role in floating ability and release of drug from Microsphere. If size of Microspheres is less than 500 μ m release rate of drug will be high and floating ability will reduce, while Microspheres ranging between 200 μ m - 500 μ m, the floating ability will be more and release rate will be in sustained manner. The mean particle size of Valacyclovir microsphere was in range 210 - 264 μ m as shown in Table 4.

Table 4: Mean particle size of different batches of Valacyclovir microsphere

Sr. No.	Formulation code	Mean particle size (μm)
1.	F ₁	212 \pm 12
2.	F ₂	225 \pm 21
3.	F ₃	264 \pm 23
4.	F ₄	236 \pm 25
5.	F ₅	242 \pm 24
6.	F ₆	244 \pm 40
7.	F ₇	210 \pm 23

Floating behavior of microsphere:

Valacyclovir microsphere was dispersed in 0.1 HCl as simulate gastric fluid. Floating ability of different formulation was found to be differed according to EC and HPMC ratio. F₁-F₄ formulations showed best floating ability (91.47-72.97%) in 6 h. F₅-F₈ formulation showed less floating ability (66.12-45.09%) as showed in Table-6.8. The floating ability of microsphere is decreased by increasing the HPMC ratio.

Drug Entrapment:

The drug entrapment efficacies of different formulations were in range of 48.47 - 74.19 % w/w as shown in Table No-6.9. Drug entrapment efficacy slightly decreases with increase HPMC content and decreased EC ratio in Microspheres. This is due to the permeation characteristics of HPMC that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of Valacyclovir microspheres.

CONCLUSION:

Drug absorption in the gastrointestinal tract is a highly variable process. Floating microspheres are promises to be a potential approach for gastric retention enhances the bioavailability and controlled delivery of various therapeutic agents. Significant attempts

have been made worldwide to explore these systems according to patient requirements, both in terms of therapeutic efficacy and compliance.

Floating microspheres as gastro-retentive dosage form precisely control the release rate of target drug to a specific site and facilitate an enormous impact on health care. These systems also provide tremendous opportunities in the designing of new controlled and delayed release oral formulations, thus extending the frontier of futuristic pharmaceutical development. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of these promising drug delivery systems.

In-vitro data obtained for floating microspheres of Valacyclovir showed good incorporation efficiency, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. From the results, it can be concluded that the drug release from the floating microspheres controlled by the polymer proportion. Prepared formulation showed best appropriate balance between buoyancy and drug release rate.

REFERENCES



1. Chien YW. Concepts and system design for rate controlled drug delivery in novel drug delivery system. 2nd ed., New York: Marcel dekker Inc. 1992; 50:1-42.
2. Chiao CS, Robinson JR. Sustained release drug delivery system. In: Longor MA, Robinson JR (editors). Remington: The science and practice of industrial pharmacy. 19th edn. Eastern Pennsylvania. Mack Publication Company 1995; 2: 1660-75.
3. Tortora GJ, Grabowski SR. Principles of Anatomy and Physiology. 10th edn., New York: John Wiley and Sons 2002; 866-73.
4. Ross, Wilson. Anatomy and Physiology in health and illness. 9th edn., London: Churchill Livingstone 1996; 294-8.
5. Brahmanekar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics a treatise. 1st ed. VallabhPrakashan. 2002; 337.
6. Martindale. The complete drug reference. Edited by Parfitt K. 36th edn; (I):218.1.
7. The Merck Index. An encyclopedia of chemicals, drugs and biological. 13th edn: 1925.
8. Drug facts and comparisons. 50th edn. 1996:2018-19.
9. Shinde AJ, Harinath MN. Gastroretentive Drug Delivery System: An
10. Gapa P, Gaba M, Garg R, Gupta GD. Floating microspheres: a review 2008; 6(5). Available from URL: <http://www.pharmainfo.net/reviews/floatingmicrospheres-review>.
11. Lalla JK. Introduction to controlled release and oral controlled drug delivery systems. The Eastern pharmacist 1991; 45:25-8.
12. Gadad AP, Naduvnamani SN, Patil MB, Dandagi PM, Manvi FM. Floating alginate beads: A novel approach to prolong gastric residence, an overview. Int J PharmaExcip 2008; 7(1):5-11.
13. R Garg, GD Gupta. Progress in Controlled Gastroretentive Delivery Systems. Trop J Pharm Res 2008; 7 (3):1055-1066.

14. Patel GM, Patel HR, Patel M. Floating Drug Delivery System: An Innovative Approach to Prolong Gastric Retention. *Pharmainfo.net* 2007;5(6). Available from URL:<http://www.pharmainfo.net/reviews/floating-drug-delivery-system-innovative-approach-prolong-gastric-retention>.
15. Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating drug delivery systems: A review. *AAPS PharmSciTech* 2005; 6(3):E372-E390.
16. Davis SS. Formulation strategies for absorption windows. *Drug Dev Tech* 2005; 10(4):249-57.
17. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A review. *Research J Pharm. and Tech.* 2008; 1(4):343-48.
18. Singh BN, Kim KH. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. *J control release* 2000; 63:235-59.
19. Shirwalkar AA, Kumar SMR and Jacobs. Recent developments in floating drug delivery systems for gastric retention of drugs. An overview. *Indian drugs* 2006; 43(9):697-704.
20. JM Patil, RS Hirlekar, PS Gide, VJ Kadam. Trends in floating drug delivery system. *Journal of scientific and industrial research* 2006; 65:11-21.
21. Shah S.H., Patel J.K., Patel N.V. Stomach specific Floating drug delivery system: A review. *Int.J. PharmTech Res.*2009, 1(3):623-33.
22. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. *Pharm. Res.* 1997; 14(6):815-9.
23. Nayak A, Maji R, Das B. Gastroretentive drug delivery systems: a review. *Asian Journal of Pharmaceutical and Clinical Research* 2010; 3(1):1-10.

