

Available online on 15.04.2019 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-18, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited

Open  Access

Research Article

Formulation and Evaluation of Torsemide Granules (Sustained Release)

Satya Prakash Singh, Navneet Kumar Verma*

Kailash Institute of Pharmacy and Management, GIDA, Gorakhpur Affiliated to Dr. A.P.J. Abdul Kalam Technical University, Lucknow, U.P., India

ABSTRACT

The aim of study was to design development and optimize a controlled release system of Torsemide. to increase its bioavailability by increasing the residence time in the stomach without contact with the mucosa, and was achieved through the preparation of floating granules by melt granulation techniques. Torsemide; a loop diuretic used in the treatment of congestive heart failure and edema was chosen as the drug candidate to be formulated as gastro retentive multiparticulate system as it is a weakly basic drug with a short half-life of 2-3 hrs. Gelucire 43/01 was selected as a lipid carrier in different ratio (1:0.5, 1:1, 1:1.5) along with drug. The formulation F₁ to F₆ were prepared and evaluated for dependent variable (in vitro floating ability) and formulations F₄ to F₆ were selected as preliminary optimized formulation. The preliminary optimized formulation F₄ to F₆ were evaluated for micromeritic properties, drug content and percentage yield, *in-vitro* drug release, percentage *in-vitro* floating ability and formulation F₄ was selected as optimized formulation that exhibited good floating ability and zero order drug release (85.95 %) at the end of 8 hours. Aging effect on storage was evaluated using *In-vitro* drug release. The *In-vitro* drug release study of the aged sample showed increase in release behaviour, it may be due to phase transformation of Gelucire. In conclusion, hydrophobic lipid, Gelucire 43/01 can be considered as an effective carrier for design of a multi-unit floating drug delivery system of Torsemide.

Keywords: Torsemide, Floating granules, Gelucire, In-vitro release study.

Article Info: Received 22 Feb 2019; Review Completed 09 April 2019; Accepted 14 April 2019; Available online 15 April 2019



Cite this article as:

Singh SP, Verma NK, Formulation and evaluation of torsemide granules (Sustained release), Journal of Drug Delivery and Therapeutics. 2019; 9(2-s):480-485 <http://dx.doi.org/10.22270/jddt.v9i2-s.2581>

*Address for Correspondence:

Navneet Kumar Verma, Kailash Institute of Pharmacy and Management, GIDA, Gorakhpur Affiliated to Dr. A.P.J. Abdul Kalam Technical University, Lucknow, U.P., India

INTRODUCTION

Buccal route is measured as the most auspicious route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day¹. This results in a significant fluctuation in drug levels. Recently, several technical advancements have led to the development of several novel drug delivery systems (NDDS) that could revolutionize method of medication and provide a number of therapeutic benefits². The most important objectives of these new drug delivery systems are: First, it would be single dose, which releases the active ingredient over an extended period of time. Second, it should deliver the active entity directly to the site of action, thus, minimizing or eliminating side effects. To overcome the limitations of conventional drug delivery system, floating tablets have been developed. Drugs that have narrow absorption window in the gastrointestinal tract (GIT) will have poor absorption. For these drugs, gastroretentive drug delivery systems offer the advantages in prolonging the gastric emptying time. To formulate a successful stomach specific or gastroretentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug

delivery system³, low density systems⁴⁻⁶, raft systems incorporating alginate gels⁷⁻⁹, bioadhesive or mucoadhesive systems¹⁰, high density systems¹¹⁻¹³, super-porous hydrogels¹⁴ and magnetic systems¹⁵⁻¹⁷. Swellable, floating and sustained release tablets are developed by using a combination of hydrophilic polymer (hydroxypropyl methylcellulose), swelling agents (croscopolldone and croscarmellose) and effervescent substances (sodium bicarbonate and citric acid). Oral Controlled release drug delivery systems (OCRDDS) that can be retained in the stomach for a long time have many advantages over sustained release formulations. Controlled drug delivery system release the drug in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption site in the upper gastrointestinal tract. Development of controlled release oral drug delivery system (CRDDS) by overcoming physiological adversities like short gastric residence times and unpredictable gastric emptying times. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. controlled release gastro retentive dosage form (CRGRDFS or GRDDS).¹⁸ Controlled release Gastro retentive drug delivery systems (GRDDS) are the systems which are retained in the stomach for a prolonged period of time and thereby improved the

bioavailability. GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form ¹⁹.

MATERIALS AND METHODS

Materials and Equipments

Torsemide, Gelucire 43/01 (Gattefosse St Priest, Cedex, France). Acetone (Sd fine-chemicals). Potassium chloride (Sd fine-chemicals). Hydrochloric acid, Potassium dihydrogen phosphate, Sodium hydroxide pellets, Ethanol (Sd fine-chemicals), Dissolution rate test apparatus (Electrolab Pvt. Ltd. Mumbai), pH /mill voltmeter (Century instrument Pvt. Ltd.), UV-VIS spectrophotometer (Shimadzu Corp. Japan), Standard test sieves (HICON, Grover Enterprises, Delhi),

Digital oven (Science tech Pvt. Ltd. India), Digital Electronic Balance (Shinko Denshi corp. Japan), Digital M. P. apparatus (Jindal Scientific instruments, Ambala), Single Pan Electronic Balance (Contech instrument pvt. Ltd. Mumbai), Magnetic Stirrer with Hot Plate (B.D. Scientific Industries, Delhi).

Preparation of granules of torsemide

Melt granulation technique (MG)

Lipid was melted at 50 - 60 °C, and the drug was added, mixed well, and cooled to room temperature. The mass was passed through a 710-µm (22 mesh) sieve to obtain uniform-sized granules. ^{20, 21}

The formulation codes of the granules prepared are listed in Table 1.

Table 1: Formulation codes of Torsemide granules

Method of preparation	Formulation code	Drug	Gelucire 50 /13	Gelucire 43/01
Melt granulation method	F ₁	1	0.5	-
	F ₂	1	1	-
	F ₃	1	1.5	-
	F ₄	1	-	0.5
	F ₅	1	-	1
	F ₆	1	-	1.5

Selection of preliminary optimized formulations

Formulations F₁ to F₆ were prepared and evaluated for dependent variable like percentage floating ability. On the basis of dependent variable the optimized formulations were selected having good floating ability. ²⁰

Determination of floating behavior

Twenty unit granules were placed in 900 ml of distilled water and pH 6.8 phosphate buffers in a vessel maintained at 37°C ± 0.5°C and stirred at 100 rpm in USP 24 type II dissolution test apparatus. The percentage of floating granules up to 8 hours was determined and the floating times were measured by visual observation. ²⁰

Evaluation of preliminary optimized formulations ²⁰

Micromeritic properties

Determination of bulk and tapped density

2g of different optimized formulations was subjected into 10 ml graduated measuring cylinder separately and the volume was noted down. The graduated cylinder was tapped 50 times using bulk density apparatus. The bulk density and tapped density was determined using following formula (Aulton et al 2002).

$$\text{Bulk density} = \frac{\text{weight of floating granules}}{\text{initial volume}}$$

$$\text{Tapped density} = \frac{\text{weight of floating granules}}{\text{final volume after tapping}}$$

Determination of granule density

Granule density of different formulation was determined by liquid displacement method (Martin et al 1999) by suspending the granules in a solvent in which the granules were insoluble.

Determination of hausner's ratio

The density determinations were used to determine the Hausner's ratio and could be determined using following formula. ²²

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Determination of Carr's compressibility index

The density determinations were used to determine the carr's compressibility index and could be determined by following formula. ²²

$$\text{Carr's compressibility index} = \frac{\text{Tapped density} - \text{Fluff density}}{\text{Tapped density}} \times 100$$

Determination of angle of repose (θ)

The angle of repose of different formulation was determined by fixed funnel method and could be determined by using following formula. ²²

$$\text{Angle of Repose } (\theta) = \tan^{-1}(h / r)$$

Where,

h and r are height of pile and radius of the base of the pile respectively.

Determination of drug content and percentage yield

Ten milligrams of floating granules were added to 10 ml of pH 6.8 phosphate buffer, heated to 60 °C to 70 °C, and allowed to cool to room temperature. The lipid was solidified and the drug solution was filtered through whatman no. 1 paper (whatman plc, middlesex, uk). The sample was analyzed for drug content by UV spectrophotometry at 290 nm after suitable dilutions. Determinations were performed in triplicate. Percentage yield of each formulation was calculated. ²⁰

Determination of *in-vitro* floating ability

Twenty unit granules were placed in 900 ml of pH 6.8 phosphate buffers in a vessel maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ and stirred at 100 rpm in USP 24 type II dissolution test apparatus. The percentage of floating granules up to 8 hours was determined and the floating times were measured by visual observation.²⁰

$$\% \text{ of floating ability} = N_f / (N_f + N_s) \times 100$$

Where, N_f and N_s are numbers of the floating and settled granules respectively.

In-vitro drug release studies

Dissolution of Torsemide from different formulations were studied in 900 ml of pH 6.8 phosphate buffer using a USP apparatus 2 (paddle type) dissolution rate test apparatus. Samples equivalent to 50 mg of Torsemide was used in each test at 100 rpm and temperature $37 \pm 0.5^{\circ}\text{C}$. Samples (5 ml) were withdrawn at predetermined time intervals till 8 hours, immediately replaced with fresh dissolution medium and analyzed for Torsemide content at 290 nm after suitable dilution. Percent of Torsemide dissolved at various time intervals was calculated from the regression equation generated from the suitably constructed calibration curve. The release studies were conducted in triplicates.²⁰

Model Fitting

Values obtained from drug release from different formulations in pH 6.8 phosphate buffer were subjected for model fitting parameters (zero order, first order, Higuchi, Hixson- Crowell and Peppas).

Selection of Optimized Formulation

The optimized formulation was selected on the basis of model fitting parameters shown by the formulation.

Effect of Aging

The optimized was stored upto one month at room temperature (25°C) in order to detect physical changes.

(structural or polymorphic) on aging associated with glyceride bases. The effect of aging on optimized formulation was studied by *in-vitro* drug release.²⁰

RESULTS AND DISCUSSION

Selection of Preliminary Optimized Formulations

Formulations F_1 to F_6 were prepared and evaluated for dependant variable (Table 2) like percentage floating ability. On the basis of percentage floating ability formulations F_4 , F_5 and F_6 were selected as optimized formulations as it exhibited good floating ability. Formulations F_1 , F_2 and F_3 were rejected based on low value of percentage floating ability.

Table 2: Observation table of invitro floating ability in distilled water and pH 6.8 phosphate buffer

Formulation Code	<i>In-vitro</i> floating ability	
	Distilled Water	pH 6.8 phosphate buffer
F₁	Sink (within 1 hour)	Sink (within 1 hour)
F₂	Sink (within 1 hour)	Sink (within 1 hour)
F₃	Sink (within 1 hour)	Sink (within 1 hour)
F₄	Float (8 hours)	Float (8 hours)
F₅	Float (8 hours)	Float (8 hours)
F₆	Float (8 hours)	Float (8 hours)

Evaluation of Preliminary Optimized Formulations

All the preliminary optimized formulations (F_4 - F_6) were evaluated for variable parameters and the optimized formulation was selected.

Micromeritic properties

Determination of bulk density and tapped density

The bulk density and tapped density was determined using bulk density apparatus (Aulton et al 2002) and represented in Table 3. The bulk density and tapped density of

preliminary optimized formulations (F_4 - F_6) were found to be in the range of 0.276- 0.292g/cm³ and 0.323- 0.334g/cm³.

Determination of granule density

The granule density, measured by liquid displacement method by suspending the granules in a solvent in which the granules were insoluble like liquid paraffin, ranged from 0.695 - 0.781 g / cm³, which is less than 1.004 g / cm³ (Vyas and Khar 2002), the specific gravity of the gastric fluid, substantiating the buoyant properties of the granules.

Table 3: Determination of hausner's ratio

Formulation code	Bulk density $\pm$ S.D (g/cm ³)	Tapped density $\pm$ S.D (g/cm ³)	Granule density $\pm$ S.D (g/cm ³)	Hausner's ratio $\pm$ S.D	Carr's compressibility index $\pm$ S.D	Angle of repose (θ) $\pm$ S.D
F₄	0.276 $\pm$ 0.0015	0.331 $\pm$ 0.0030	0.753 $\pm$ 0.0021	1.199 $\pm$ 0.0014	16.61 $\pm$ 0.023	17.21 $\pm$ 0.015
F₅	0.284 $\pm$ 0.0021	0.323 $\pm$ 0.0026	0.781 $\pm$ 0.014	1.137 $\pm$ 0.0019	12.07 $\pm$ 0.030	15.63 $\pm$ 0.029
F₆	0.292 $\pm$ 0.0020	0.334 $\pm$ 0.0028	0.695 $\pm$ 0.010	1.143 $\pm$ 0.0018	11.59 $\pm$ 0.19	16.26 $\pm$ 0.040

The Hausner's ratio of different formulations were determined and found to be in the range of 1.137 – 1.199 and indicated good flow property.

Determination of Carr's compressibility index

The Carr's compressibility index of different formulations were determined and found to be in the range of 11.59-16.61% which indicated fair to passable flow property.

Determination of angle of repose (θ)

The angle of repose of different formulations were determined and found to be in the range of 15.63- 17.21° indicated excellent flow property.

Determination of drug content and percentage yield

The percentage yield and drug content of different formulations were determined and represented in Table 4. The percentage yield and drug content was found in the range of 89.36 - 92.54 and 97.28 - 98.17%. Low values of standard deviation indicated the uniformity in drug content.

Table 4; Observation table of percentage yield and percentage drug content

Formulation code	Percentage yield	Drug content(%) $\pm$ S.D.
F ₄	92.54	97.28 $\pm$ 0.545
F ₅	90.36	98.17 $\pm$ 0.676
F ₆	89.36	97.41 $\pm$ 0.496

Determination of *in-vitro* floating ability

The percentage *in-vitro* floating ability of different formulations were determined and represented in Table 5. Formulations F₄ – F₆ exhibited 90 to 100 % floating ability at the end of 8 hours in pH 6.8 phosphate buffer. This is due to the lower bulk density of the formulations and hydrophobic nature of Gelucire 43/01 used in granules.

Table 5: Observation table of percentage *in-vitro* floating ability in pH 6.8 phosphate buffer.

Formulation code	Percentage <i>in-vitro</i> floating ability
	pH 6.8 phosphate buffer
F ₄	100
F ₅	100
F ₆	100

In-vitro drug release studies

The *in-vitro* drug release profiles of the granules prepared by melt granulation (F₄-F₆) were compared with that of pure drug. In the fed state gastric pH ranges from more than pH 2.0 – pH 6.5 (Arora et al 2005), therefore pH 6.8 was selected as fed state gastric pH. In fed state, at pH 6.8, the pure drug showed 99.79 % while formulation F₄, F₅ and F₆ showed 85.95 %, 79.95 % and 77.83 % drug release after 8 hours respectively.

As the Gelucire 43/01 ratio was increased in the formulations F₄ to F₆ prepared by melt granulation technique, the release rate was lowered due to hydrophobic nature of Gelucire 43/01. The analysis of data was done using PCP Disso v2.08 software.

Release Kinetics of Preliminary Optimized Formulations

Regression coefficient, n and k values were obtained for zero order, first order, Higuchi, Hixson Crowell and peppas from the values obtained from % drug release. The *in-vitro* drug release profiles were clarified by the data obtained from model fitting. Model dependent parameters showed zero order models as the best fit model. It was concluded that formulation F₄ prepared by melt granulation with Drug: Gelucire 43/01 ratio 1:0.5 followed zero order release kinetics as the best fit model.

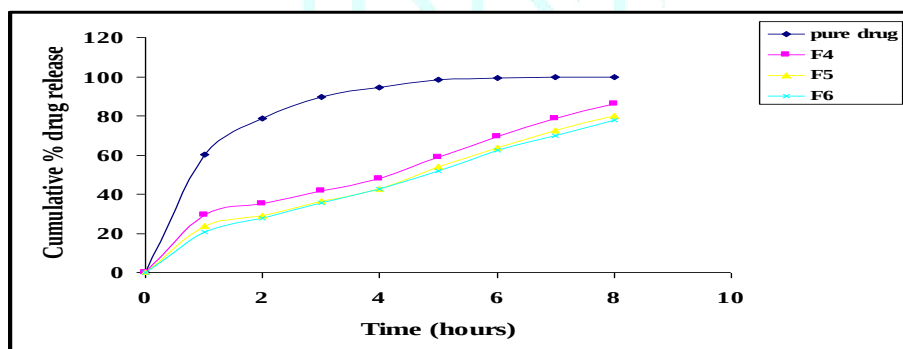


Figure 1: Comparative % drug release profile in pH 6.8 phosphate buffer

Selection of Optimized Formulation

The formulations F₄ to F₆ were evaluated for different evaluation parameters like micromeritic properties, percentage *in-vitro* floating ability, percentage yield and drug content and in vitro drug release. Model dependent parameters were calculated. It was concluded that formulation F₄ prepared by melt granulation with Drug: Gelucire 43/01 ratio 1:0.5 followed zero order release kinetics as the best fit model.

Effect of Aging

In-vitro drug release

In-vitro drug release profiles of granules on aging (after 10 and 30 days) were shown in Figure 2. Drug release increased on aging, which might be attributed to the phase transformation. The floating ability of the granules was not affected by aging. The zero order kinetics shown by aged granule so the drug release kinetics were not affected by aging.

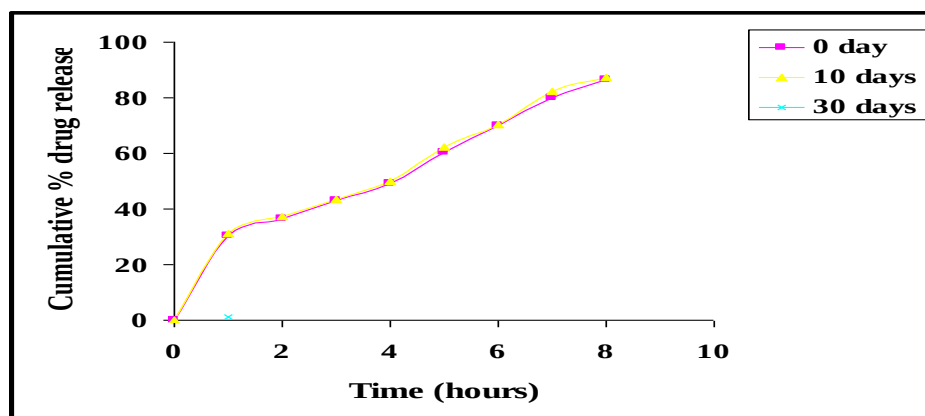


Figure 2: Release profile of Torsemide from formulation F₄ showing effect of aging

CONCLUSION

The present study was aimed to prepare floating granular delivery system with an objective to control the release rate of Torsemide. The performance of the formulations was evaluated and the floating ability of the granules and the release rate of the drug (Torsemide) from the granules can be controlled by changing the composition ratio of Gelucire 43/01. Formulation F₄ (Drug: Gelucire 43/01 ratio 1:0.5) exhibited good buoyancy and drug release (85.95%) with zero order release pattern selected as optimized formulation. The study demonstrated that hydrophobic lipid Gelucire 43/01, can be as an effective carrier for the design of a multi unit floating drug delivery system of Torsemide. Torsemide, is a loop diuretics that prevent that the body from absorbing too much salt, allowing the salt to instead be passed in urine. It is used in treatment of congestive heart failure and odema. Torsemide belongs to the biopharmaceutical classification system class IV i.e. Torsemide has low permeability and low solubility. Its oral bioavailability is 40-60%. The poor aqueous solubility and poor dissolution rate of the drug may have negative impact on its bioavailability. Estimation of Torsemide was carried spectrophotometrically by UV method at 290nm. The pre-formulation study involving FTIR shows that no interaction between drug and polymer. The stability study indicates that there is no degradation of drug in the formulation. Hence the Torsemide was selected for the formulation. As it was important the overall bioavailability of Torsemide, its absorption throughout the intestine was also focused. The sustained release floating granules of the Torsemide is made by the melt granulation technique. Such formulation achieves sustained release of drug in the intestine, so that sustained absorption can be achieved. The drug release profile of the developed formulation in comparison with the marketed formulation indicated a definite improvement in the drug release pattern throughout the gastrointestinal pH. The main aim of the design and optimization of controlled release system of Torsemide is to increase the bioavailability by increasing residence time in the stomach without contact with mucosa. The Torsemide is formulated as a gastro retentive multiparticulate system as it is a weekly basic drug with a short half-life of 2-3 hrs. The gelucire 43/01 and 50/13 was selected as lipid carrier in different ratios (1:0.5, 1:1, and 1:5) along with drug. There were six formulations developed (F1, F2, F3, F4, F5, F6) in which F1-F6 are dependent variables while F4-F6 were selected as preliminary optimized formulations. Thus by adopting the principle of solubility enhancement and sustained release floating granules was obtained in order to improve the bioavailability of drug. Gastro retentive systems can remain in the gastric region for several hours and hence significantly

prolong the gastric residence time of drug. Prolong gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has application also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The multi-unit dosage such as floating granules may be more suitable because of slow release of drug at desired rate system. The expulsion of the floating system from stomach after complete release of drug. The reduction of dosing frequency may also be found. It is an increase in gastric residence time. Instead of it having a low dose and no first pass hepatic metabolism. The Torsemide drug is soluble in acetone, ether and sparingly soluble in ethyl alcohol. Its melting point is 210°C. There has been excretion found: renal 66%, biliary 33%. The major site of action is the thick ascending limb loop of Henle where Torsemide inhibits Na⁺-K⁺-2Cl⁻ co-transport. A minor component of action on proximal tubule has been indicated. It is secreted in proximal tubule by organic anion transport and reaches ascending limb loop of Henle where it acts on the luminal side of the membrane. It metabolizes the corticomedullary osmotic gradient and blocks positive as well as negative free water clearance, which is increased mainly due to high Na⁺ load reaching distal tubule. Torsemide has weak carbonic anhydrase inhibitory activity on acid-base balance of the body and it causes a little distortion of the same; mild alkalosis occurs at high doses. It may interact with Indomethacin, Lithium, aspirin and other salicylates. It has a lot of side effects like Hypokalemia, Acute saline depletion, hearing loss etc.

REFERENCES

1. Agyilrah GA, Green M, Ducret R. Evaluation of the gastric retention properties of a cross linked polymer coated tablet versus those of a non-disintegrating tablets. *Int J Pharm* 1991; 75:241-247.
2. Hoffman F, Pressman JH, Code CF. Controlled entry of orally administered drugs, physiological considerations. *Drug Dev Ind. Pharm* 1983; 9:1077-1085.
3. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. *Pharm. Res.* 1997; 14:815-819.
4. Kawashima Y, Niwa T, Takuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. *J. Pharm. Sci.* 1992; 81(2):135-140.
5. Ichikawa M, Watembla S, Miyake VA. Multiple unit oral floating dosage systems I: Preparation and in-vivo evaluation of floating and sustained release characteristics. *J. Pharm. Sci.* 1991; 80:1062-1066.
6. Sato Y, Kawashima Y, Takenchi H. "In vitro and in vivo evaluation of riboflavin containing microballoons for floating

- controlled delivery system in healthy humans." *Int. J. Pharm.* 2004; 275:75-82.
7. Washington N, "Investigation into the barrier action of an alginate gastric reflux suppressant, Liquid Gaviscon", *Drug Invest* 1987; 2:23-30.
 8. Foldager J, Toftkjor H, "Antacid composition." US Patent 1991; 5068109.
 9. Fabrcgas JL, Cucala CG, Pous J, Sites RA. In vitro testing of an antacid formulation with prolonged gastric residence time. *Drug Dev. Ind. Pharm.* 1994; 20:1199-1212.
 10. Ponchel G, Irache JM. Specific and nonspecific bioadhesive particulate system for oral delivery to the gastrointestinal tract. *Adv. Drug Del. Rev.* 1998; 34:191-219.
 11. Redniek AB, Tucker SJ. Sustained release bolus for animal husbandry. US Patent 1970; 3:507,952.
 12. Bechgaard H, Ladefoged K. Distribution of pellets in the gastrointestinal tract: The influence on transit time exerted by density or diameter of pellets. *J. Pharm. Pharmacol.* 1978; 30:690- 692.
 13. Davis SS, Stockwell SF, Taylor MJ, Hardy JG, Whelley DR. The effect on density on the gastric emptying of single and multiple-unit dosage form. *Pharm. Res.* 1986; 3:208-213.
 14. Hwang SJ, Park H. Gastric retentive drug delivery systems. *Cri. Rev. Ther. Drug Carr. Syst.* 1998; 15:234-284.
 15. Ito R, Mchida Y, Sannan T, Nagai T. Magnetic granules: a novel system for specific drug delivery to oesophageal mucosa in oral administration. *Int. J. Pharm.* 1990; 61:109-117.
 16. Fujimori J, Machida Y, Nagai T. Preparation of magnetically responsive tablet and confirmation of its gastric residence in beagle dogs. *STP Pharm. Sci.* 1994; 4:425-430.
 17. Griming R, Berntgen M. "Estimation of the gastric residence time magnetic dosage forms using the Heidelberg capsule." *Pharmazie.* 1996; 51:328-331.
 18. Chein YW. Novel drug delivery systems, Marcel Dekker, New York; 1992; 2:185- 210.
 19. Lalla JK. Introduction to controlled release and oral controlled drug delivery systems. *The Eastern Pharmacist* 1991; 45:25-28.
 20. Patel D. M., Patel N. M., Patel V. F., Bhatt D. A., Floating Granules of Ranitidine Hydrochloride-Gelucire 43/01: Formulation Optimization Using Factorial Design' *AAPS Pharm. Sci. Tech.*, 2007; 8(2):08- 14.
 21. Shimpi S., Chauhan B., Mahadik K.R. and Paradkar A. Preparation and evaluation of diltiazem HCl-Gelucire43/01 floating granules prepared by melt granulation', *AAPS Pharm. Sci. Tech.*, 2004; 5(3):43.
 22. Dixit N., Floating drug delivery system. *Journal of current Pharmaceutical Research*, 2011; 7(1):6-20.

