IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 10, Issue 3 Series. I (March 2020), PP. 44-51
www.iosrphr.org

Preparation and Evaluation of Sustained Release Floating Granules of Furosemide

Sanatan Kumar Verma
Department of Pharmaceutics
Hygia Institute of Pharmaceutical Education & Research, Lucknow (U.P)
Received 24 March 2020; Accepted 10 April 2020

ABSTRACT: The objective of study was to design and optimize a controlled release system of Furosemide. 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. Furosemide; 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 F_1 to F_6 were prepared and evaluated for dependent variable (in vitro floating ability) and formulations F_4 to F_6 were selected as preliminary optimized formulation.
The preliminary optimized formulation F_4 to F_6 were evaluated for micromeritic properties, drug content and percentage yield, *in-vitro* drug release, percentage *in-vitro* floating ability and formulation F_4 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 Furosemide.
Keywords: Furosemide, Floating granules, Gelucire, In-vitro release study.

I. INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents, that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in detail. In vivo/in vitro evaluation of FDDS has been discussed by scientists to assess the efficiency and application of such systems. Several recent examples have been reported showing the efficiency of such systems for drugs with bioavailability problems.

II. MATERIALS AND METHODS

MATERIALS AND EQUIPMENTS USED

List of materials

Chemicals/Materials	Supplier
Furosemide	Sanofi Aventis Pharma Mumbai.
Gelucire 43/01	Gattefosse(St Priest,Cedex),France.
Acetone	Sd fine-chemicals.
Potassium chloride	Sd fine-chemicals.
Hydrochloric acid	Sd fine-chemicals.
Potassium dihydrogen phosphate	Sd fine-chemicals.
Sodium hydroxide pellets	Sd fine-chemicals.
Ethanol	Sd fine-chemicals.

List of equipments

S. No.	Equipments	Manufacturers/Suppliers
1.	Dissolution rate test apparatus	Electrolab Pvt. Ltd. Mumbai
2.	pH /mill voltmeter	Century instrument Pvt. Ltd.
3.	UV-VIS spectrophotometer	Shimadzu Corp. Japan
4.	Standard test sieves	HICON, Grover Enterprises, Delhi
5.	Digital oven	Science tech Pvt. Ltd. India.
6.	Digital Electronic Balance	Shinko Denshi corp.Japan
7.	Digital M. P. apparatus	Jindal Scientific instruments, Ambala
8.	Single Pan Electronic Balance	Contech instrument pvt. Ltd.Mumbai
9.	Magnetic Stirrer with Hot Plate	B.D. Scientific Industries, Delhi

III. RESEARCH ENVISAGED

AIM – Preparation and evaluation studies on sustained release floating granules of Furosemide using lipid excipients.

Reason for selection of project

Rapid gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to diminished efficacy of the administered dose, therefore different approaches have been proposed to retain the dosage form in the stomach.

The multi unit dosage forms such as granules may be more suitable because they claim

- Slow release of drug at a desired rate from the system.
- Expulsion of the floating system from stomach after complete release of drug.
- Reduction in dosing frequency.
- Increase in gastric residence time (g. r. t).
- Increased patient compliance.
- Reduction in fluctuations in plasma drug concentration.
- Controlled administration of the therapeutic dose at a desired delivery rate.

Reasons for the selection of furosemide as a drug candidate

- Short half life (2-3 hours).
- Absorption in gastric region.
- Low dose (20-80 mg).
- No first pass hepatic metabolism.

Reasons for selection of excipients

Selection of lipid carriers was based on following criteria:

- Sustain the release of drug.
- being compatible with the drug
- does not decompose on storage or during the shelf life of the dosage form

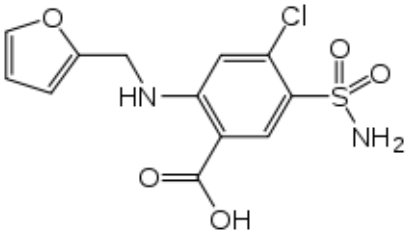
DRUG PROFILE

Drug : Furosemide.

Category : High sealing Diuretic (Loop Diuretic).

Molecular Formula : $C_{12}H_{11}ClN_2O_5S$

Structural Formula



IUPAc Name :4-chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid.
Molecular weight : 330.745 g/mol.
Dose : 20 to 80 mg.
Identification
UV absorption : λ_{max}- 271nm (medium- 0.02n NoaH).

Chemical test : dissolve about 5mg drug in 10 ml of methanol. Transfer 1 ml of this solution to a flask and add 10 ml of 2.5n HCLl. Reflux on a steam bath for 15 minutes. Cool and add 15 ml of 1n naoh and 5 ml of $nano_2$ (1 in 1000 ml). Allow the mixture to stand for 3 minutes. Add 5 ml of freshly prepared n-(1- naphthyle) ethylene diamine hydrochloride solution (1 in 1000 ml). Red to violet color produced.
Assay : weight accurately about 0.5 gm of drug. Dissolved in 40 ml of dimethyl formamide (dmf) and titrate with 0.1m naoh using bromothymolblue solution as

indicator. Perform a blank determination and make any necessary correction.
Each ml of 0.1m NaOH is equivalent to0.03307 gm of furosemide.

Description-
Color: White**.**
Solubility: Soluble in acetone, sparingly soluble in ethyl alcohol, soluble in ether, practically soluble in water, dissolves in dilute solution of alkali hydroxide.
Melting point: 210ºC.
Pharmacokinetics
Bioavailability :43-69%.
Metabolism :Hepatic and renal glucoronidation.
Half life :100 minutes
Excretion :Renal66%, Biliary 33%.

Mechanism of action:

The major site of action is the thick ascending limb of loop of Henle where furosemide inhibits Na^+-K^+-$2Cl^-$ cotransport. A minor component of action on proximal tubule has also been indicated. It is secreted in proximal tubule by organic anion transport and reaches ascending limb of loop of Henle where it acts from luminal side of the membrane. It abolishes the corticomedullary osmotic gradient and blocks positive as well as negative free water clearance. K^+ secretion is increased mainly due to high Na^+ load reaching distal tubule.

Furosemide has weak carbonic anhydrase inhibitory action and increase HCO_3^- excretion as well; urinary P^H may rise but the prominent urinary action is Cl^-; acidosis does not develop. Its action is independent of acid-base balance of the body and it causes the little distortion of the same; mild alkalosis occurs at high doses.

Interactions:
- Aminoglycoside antibiotics such as Gentamicin (produce additive ototoxicity).
- Aspirin and other salicylates (diminishes the action of furosemide).
- Indomethacin.
- Lithium (serum lithium level rises).
- Synergistic effects with other antihypertensives (e.g. Doxazosin).
- Sucralfate.

Contra indication:
- Severe Na and water depletion.
- Hypersensitivity to furosemide.

- Hypokalemia.
- Hyponatremia.
- Precomatose states associated with liver cirrhosis.
- Anuria or renal failure.
- Addison's disease.

Adverse effects:
- Hypokalemia.
- Acute saline depletion.
- Dilutional hyponatremia.
- GIT and CNS disturbances.
- Hearing loss.
- Allergic manifestations.
- Hyperuricaemia.
- Magnesium depletion.

Precautions:
- Prostatic hyperplasia.
- Hepatic or renal impairment.
- Gout.
- Diabetes.
- Impaired micturition.
- Pregnancy and lactation.
- Infusion rate should not exceed 4 mg/min to reduce the risk of ototoxicity.
- Monitor fluid and electrolyte balance and renal function.
- May lower serum levels of calcium and magnesium, so serum level should be monitored.

Uses:
- Edema.
- Acute pulmonary edema (acute lower ventricular failure, following myocardial infarction).
- Cerebral edema.
- Forced dieresis.
- Hypertension.
- Along with blood transfusion in severe anaemia, to prevent vascular overload.
- Hypercalcaemia and renal calcium stones.

EXCIPIENTS PROFILE

GELUCIRES

Gelucires are a family of vehicles derived from mixtures of mono-, di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids.

Gelucires are available with a range of properties depending on their Hydrophilic-lipophilic balance (HLB 1-18) and melting point (33^0C-65^0C) range.

Gelucires containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in preparation of sustained release formulations.

The major problems affecting design of any dosage form are related with the solubility and stability of drug substances. And hence to solve these problems carriers like polyethylene glycol (PEG), polyvinyl pyrollidone (PVP), polozxamers, polyols, organic acid and hydrotropes helping the dissolution enhancement of poorly soluble drugs are used.

But now a days new type of excipients which are polyethylene glycol glycerides compossed of mono-, di-and triglycerides and mono- and diesters of polyethylene glycol (PEG) called as gelucire are used. They are group of inert semi-solid waxy ampiphilic excipients, which are surface active in nature and disperse or soluvilize in aqueous media forming micelles, microscopic globules or vesicles. They have been widely studied as controlled release matrices as well as for improvement of physicochemical properties of drug. They are identified with respect to their melting point and HLB value

PLAN OF WORK

- Identification of drug
- U.V spectroscopic method
- Melting point determination
- FTIR spectrophotometric method
- Preformulation studies
- Particle size analysis
- Bulk density
- True density
- Granule density
- Solubility analysis

- Selection of granulation technique
- Melt granulation technique
- Melt solidification technique
- Formulation development
- Selection of lipid as a carrier
- Optimization of formulation
- Formulation of floating granules
- Evaluation of formulation
- Primary evaluation

a. Floating ability
b. Drug release ability

- In-vitro (dissolution according to G.I fluid)
- Stability study

IV. RESULTS AND DISCUSSION

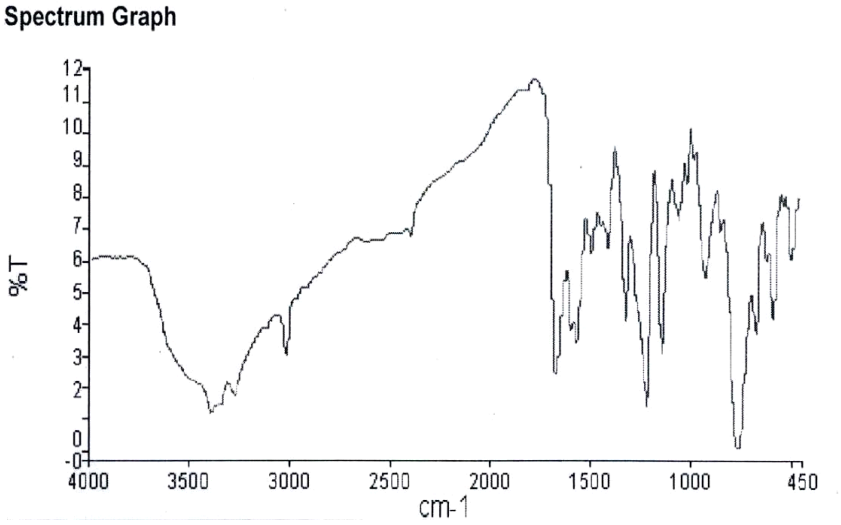
DRUG IDENTIFICATION TESTS

Melting point determination

On calibration of the melting point apparatus with L - ascorbic acid AR (observed melting point 150 ^{o}C, reported melting point 141 -145 ^{o}C)
and sodium bicarbonate AR (observed melting point 275 ^{o}C ,reported melting point 270 ^{o}C), a correction factor of -5 ^{o}C was documented. The correcting melting point of the drug was found to be 209 ^{o}C, which corresponds to the literature value of 206 - 210 ^{o}C (B.P 2003), and proves the identity and purity of drug.

FTIR

The IR spectrum was found concordant with the IR spectrum of furosemide reported in official monograph (B.P 2005) .



IR spectra of furosemide

UV spectrophotometric study

Spectrophotometric study was carried out in order to determine the λ_{max} of Furosemide in pH 5.8 phosphate buffer. 10 µg / ml solution of Furosemide in the test medium when scanned for absorption maxima in the range of 200 - 400 nm, exhibited the results tabulated in Table 3.1 on three consecutive days.

Scanned λ_{max} and the absorbance values of same sample of Furosemide prepared in pH 5.8 phosphate buffer at three consecutive days.

Day	Strength	Scanned λ_{max}	Absorbance
1	10 µg / ml	271 nm	**1.300**
2	10 µg / ml	271 nm	**1.298**
3	**10 µg / ml**	**271 nm**	**1.305**

The scanned λ_{max} were found to be similar as that of reported λ_{max} (271 nm, reference) and the difference in absorbance value for three determinations was found to be insignificant at 95 % confidence interval.

CALIBRATION CURVE

Selection of media

Fasting state pH is usually steady and approximates 2 and food buffers, neutralizes gastric acid, thus increasing the pH up to about 6.5 (Dressman et al 1990). Floating drug delivery systems are usually administered in fed state, as during the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Therefore, pH values in fed state conditions for preparation of calibration curves was selected.

V. CONCLUSION

Furosemide, 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 . Furosemide belongs to the biopharmaceutical classification system class IV i.e. furosemide has low permeability and low solubility. It oral bioavailability is 40-60%.The poor aqueous solubility and poor dissolution rate of the drug may have negative impact on it bioavailability.

Estimation of furosemide was carried spectrophotometric ally by UV method at271nm.the pre - formulation study involving FTIR show that no interaction between drug and polymer. The stability study indicates that there is no degradation of drug in the formulation. Hence the furosemide was selected for the formulation .As it was important the overall bioavailability of furosemide. it absorption throughout the intestine was also focused. The sustain release floating granules of the furosemide is made by the melt granulation technique. Such formulation is achieve sustained released of drug in intestine, so that sustain absorption can be achieve. The drug released profile of the developed formulation in compression with the marketed formulation indicated a definite improvement in the drug release pattern throughout gastro intestine PH.

The main aim of the design and optimize controlled release system of furosemide is to increase the bioavailability by increasing residence time in the stomach without contact with mucosa. The furosemide is formulated as a gastro retentive multiparticulate system as it is a weekly basic drug with sort half-life of 2-3 hrs. The gelucire 43/01 and50/13was selected as lipid carrier in different ratio (1:05, 1:1, and 1:5) along with drug. There were six formulation are developed (F1, F2, F3, F4, F5, F6) in which F1-F6 are dependent variables while F4-F6 where selected as preliminary optimized formulation. Thus by adopting the principle of solubility enhancement and sustain release floating granules was obtained in to improve the bioavailability of drug.

ACKNOWLEDGEMENT

I have taken efforts in this project. However, it would not have been possible without the kind support and help of many individuals and organizations. I would like to extend my sincere thanks to all of them. I am using this opportunity to express my gratitude to everyone who supported me throughout the course of this **M.Pharm**, project.

Firstly, I would like to express my sincere gratitude to my advisor **Mr. Santosh Kumar** Associate Professor, Department of Pharmaceutics, Hygia Institute of Pharmaceutical Education and Research, Lucknow for the continuous support of my M.PHARM study and related research, for his patience, motivation, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my **M.PHARM.** thesis.

My sincere thanks also go to **Mr. Ali Jafri (kaku sir)**, Chairman of Hygia Institute of Pharmaceutical Education and Research (HIPER, Lucknow) for providing all the necessary facilities required for my research work.

I would like to thank **Mr. Jiteendra Madan**, Associate Professor, Departmant of pharmaceutics, HIPER, Lucknow for their support in instrumentation and other lab works.
Besides my advisor, I would like to thank Assistant Professor **Mr.Arvind Kumar**, Department of Pharmaceutical Chemistry, HIPER, for the support in pharmaceutics study and research.

REFERENCES

[1]. Amighi K., Goole J. and Vanderbist F. (2007) 'Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms' *Int. J. Pharm.*, Vol. 334, pp. 35-41.
[2]. Amin A. F., Dave B. S., Patel M. M., (2004). Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. *AAPS Pharm Sci Tech*, Vol. 26, Issue 7, pp 78- 84.
[3]. Aulton M.E., (2002) '*Pharmaceutics: The science of Dosage form design'*, Edn Second, Churchill Livingstone, London, pp. 113-115.
[4]. Ali J., Arora S., Ahuja A., Babbar A. K., Sharma R. K., Khar R. K., (2007). Formulation and development of hydrodynemically balanced system for metformin: In vitro and in vivo evaluation. *Eur J Pharmaceutics Biopharm*, Vol. 67, pp 196-201.
[5]. Asmussen B, Cremer K, Hoffmann HR, Ludwig K, Roreger M., (2001). Expandable gastroretentive therapeutic system with controlled active substance release in gastrointestinal tract. *US patent 6*290989.
[6]. Bardonnet P.L., Faivre V., Pugh W.J., Piffaretti J.C. and Falson F. (2006) '*Gastroretentive dosage forms: Overview and special case of Helicobacter pylori*' J. Control Release, Vol 111, pp.1-18.
[7]. *British Pharmacopoeia* (2004).,vol.I,Stationaryoffice,The department of health,Great Britain,pp.481.
[8]. Barthelemy P., (1999). Compritol 888 ATO: an innovative hot melt coating agent for prolong release drug formulation. Eur J Pharm Biopharm, Vol. 47, Issue 1, pp 87-90.
[9]. Bomma R., Swamy Naidu R. A., Yamsani M. R., Veerabrahma K., (2009). Development and evolution of gastro retentive norfloxacin tablets. *ActaPharma*, Vol. 59, pp 211-21.
[10]. Burns S.J., Attwood D. and Barnwell S.G. (1998). 'Assessment of a dissolution vessel designed for use with floating and erodible dosage', *Int. J. Pharm*., Vol.160, pp.213-218.
[11]. Bulgarelli E, Forni F, Bernabei MT. (2000). Effect of matrix composition and process conditions on casein gelatin beads floating properties. *Int J Pharm*. Vol. 198, pp157-165.
[12]. Carstensen J.T. and Rhodes C.T. (2000) '*Drug stability: Principles and Practices*', Edn Third, Vol. 107, Marcel Dekker, Inc., New York, pp. 358-368.
[13]. Chen G.L. and Hao W.H. (1998) 'In vitro performance of floating sustained-release capsule of verapamil', Drug Delv. *Ind. Pharm*., Vol.24, No.11, pp.1067-1072.
[14]. Choia B. Y., Park H. J., Hwangb S. J., Parkc J. B., (2002). Preparation of Alginate Beads for Floating Drug Delivery System: Effects of CO2 Gas- Forming Agents. Int J Pharmaceutics. Vol. 4, pp 113-117.
[15]. Chen P.J., Shih C.Y. and Tai Y.C. (2006) 'Design, fabrication and characterization of monolithic embedded parylene micro channels in silicon substrate', Lab chip Vol.6, No.6, pp.803-810.
[16]. Chien W.Y. (2005) '*Novel drug delivery systems'*, Edition 2, *Marcel Dekker Inc*., New York, pp.160-161.
[17]. Craig D.Q.M., Sutananta W. and Newton J.M., (1994) 'The effects of ageing on the thermal behaviour and mechanical properties of pharmaceutical glycerides', *Int. J. Pharm*., Vol. 111, pp. 51-62. doi:10.1016/*j.ijpharm*.2007.09.009
[18]. Dave B.S., Amin A.F. and Patel M. (2004) 'Gastro retentive drug delivery system of ranitidine HCl formulation and *in vitro* evaluation', *AAPS Pharm. Sci. Tech., Vol.5, Article34.*
[19]. Deshpande A.A., Shah N.H., Rhodes C.T. and Malick W. (1997) '*Development of a novel controlled release systems for gastric retention*', Pharm. Res., Vol.14, pp.815-819.
[20]. Dressman J.B., Berardi R.R., Dermentzoglou L.C., Russel J.L., Schmaltz S.P., Barnett J.L. and Jarvenpaa K.M. (1990) 'Upper gastrointestinal pH in young, healthy men and women', *Pharm. Res.*, Vol.7, No.7, pp.756-761.
[21]. El-Kamel A. H., Sokar M. S., Al Gamal S.S., Naggar V. F., (2001). Preparation and evaluation of ketoprofen floating oral delivery system. *Int J Pharmaceutics* , Vol. 220, pp 13-21.
[22]. Franz MR, Oth MP. (1993) Sustained release, bilayer buoyant dosage form. *US patent 5*232704.
[23]. Garg S. and Sharma S. (2003) '*Gastro retentive drug delivery systems, Business Briefing'*, Pharma Tech., pp.160-166.

[24]. Gines J.M.,Veiga M.D., Arias M.J. and Rabasco A.M.(1995) 'Elaboration and thermal study of interactions between cinnarizine and geluire 53/10 physical mixtures and solid dispersions', *Int. J. Pharm.,* Vol. 126, pp. 287-291.
[25]. Gupta R. and Pathak k., (2008) 'Optimization Studies on Floating Multiparticulate Gastroretentive Drug Delivery System of Famotidine', *Drug Dev.Ind. Pharm.,* Vol. 1, pp.1-8.

Sanatan Kumar Verma. "Preparation and Evaluation of Sustained Release Floating Granules of Furosemide." *IOSR Journal of Pharmacy (IOSRPHR),* 10(3), 2020, pp. 44-51.