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Preparation and evaluation studies on sustained release of furosemide using lipid excipient

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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.

INTRODUCTION

The oral route is considered as the most promising 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 day [1]. 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 benefits [2]. 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 system [3], low density systems [4-6], raft systems incorporating alginate gels [7-9], bioadhesive or mucoadhesive systems [10], high density systems [11-13], super-porous hydrogels [14] and magnetic systems [15-17]. Swellable, floating and

sustained release tablets are developed by using a combination of hydrophilic polymer (hydroxypropyl methylcellulose), swelling agents (crospovidone and croscarmelose) 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 USED

Furosemide (Sanofi Aventis Pharma Mumbai), 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 FUROSEMIDE

Melt granulation technique (MG)

Lipid was melted at 50 - 60 ^{o}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.

Procedure:

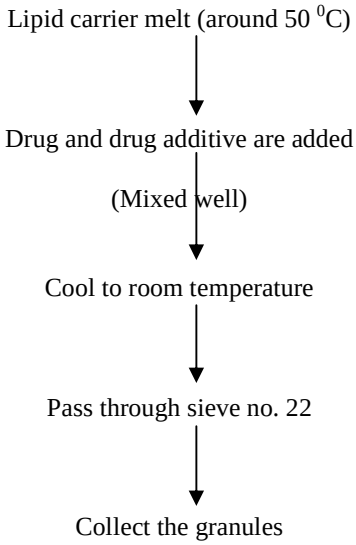

Chart 1; Flow chart for preparation of floating granules by melt granulation technique

Table 1; Formulation codes of Furosemide 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 F_1 to F_6 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 5.8 phosphate buffer in a vessel maintained at $37^oC \pm 0.5^oC$ 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).

Bulk density = weight of floating granules / initial volume

Tapped density = weight of floating granules / 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]

Hausner's ratio = Tapped density / 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 5.8 phosphate buffer, heated to 60 ^{o}C to 70 ^{o}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 271 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 5.8 phosphate buffer in a vessel maintained at 37^{o}C ± 0.5^{o}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]

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

Where,

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

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

Dissolution of Furosemide from different formulations were studied in 900 ml of pH 5.8 phosphate buffer using a USP apparatus 2 (paddle type) dissolution rate test apparatus. Samples equivalent to 50 mg of Furosemide was used in each test at 100 rpm and temperature 37 ± 0.5 °C. Samples (5 ml) were withdrawn at predetermined time intervals till 8 hours, immediately replaced with fresh dissolution medium and analyzed for Furosemide content at 271 nm after suitable dilution. Percent of Furosemide 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 5.8 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 a 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 5.8 phosphate buffer

Formulation Code	*In-vitro* floating ability	
	Distilled Water	pH 5.8 phosphate buffer
F_1	Sink (within 1 hour)	Sink (within 1 hour)
F_2	Sink (within 1 hour)	Sink (within 1 hour)
F_3	Sink (within 1 hour)	Sink (within 1 hour)
F_4	Float (8 hours)	Float (8 hours)
F_5	Float (8 hours)	Float (8 hours)
F_6	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/cm^3 and 0.323- 0.354g/cm^3.

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 / cm ^{3} , which is less than 1.004 g / cm ^{3} (Vyas and Khar 2002) , the specific gravity of the gastric fluid, substantiating the buoyant properties of the granules.

Table3; Determination of hausner's ratio

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 11.51-22.033% 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- 17.21^0 indicated excellent flow property.

Formulation code	Bulk density±S.D (g/cm^3)	Tapped density±S.D (g/cm^3)	Granule density±S.D (g/cm^3)	Hausner's ratio±S.D	Carr's compressibility index±S.D	Angle of repose (θ) ±S.D
F_4	0.276±0.0015	0.331±0.0030	0.7533±0.0021	1.199±0.0014	16.61±0.023	17.21^0±0.015
F_5	0.284±0.0021	0.323±0.0026	0.781±0.014	1.137±0.0019	12.07±0.030	15.63^0±0.029
F_6	0.292±0.0020	0.334±0.0028	0.695±0.010	1.143±0.0018	11.59±0.19	16.26^0±0.040

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 89.54 - 92.54 and 96.97 - 98.28%. 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(%) ± S.D.
F_4	92.54	97.28± 0.545
F_5	90.36	98.17± 0.676
F_6	89.36	97.41± 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 F_4 – F_6 exhibited 90 to 100 % floating ability at the end of 8 hours in pH 5.8 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 5.8 phosphate buffer

Formulation code	Percentage *in-vitro* floating ability
	pH 5.8 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 (F_4-F_6) 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 5.8 was selected as fed state gastric pH.In fed state, at pH 5.8, the pure drug showed 99.79 % while formulation F_4, F_5 and F_6 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 F_4 to F_6 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 model as the best fit model. It was concluded that formulation F_4 prepared by melt granulation with Drug: Gelucire 43/01 ratio 1:0.5 followed zero order release kinetics as the best fit model.

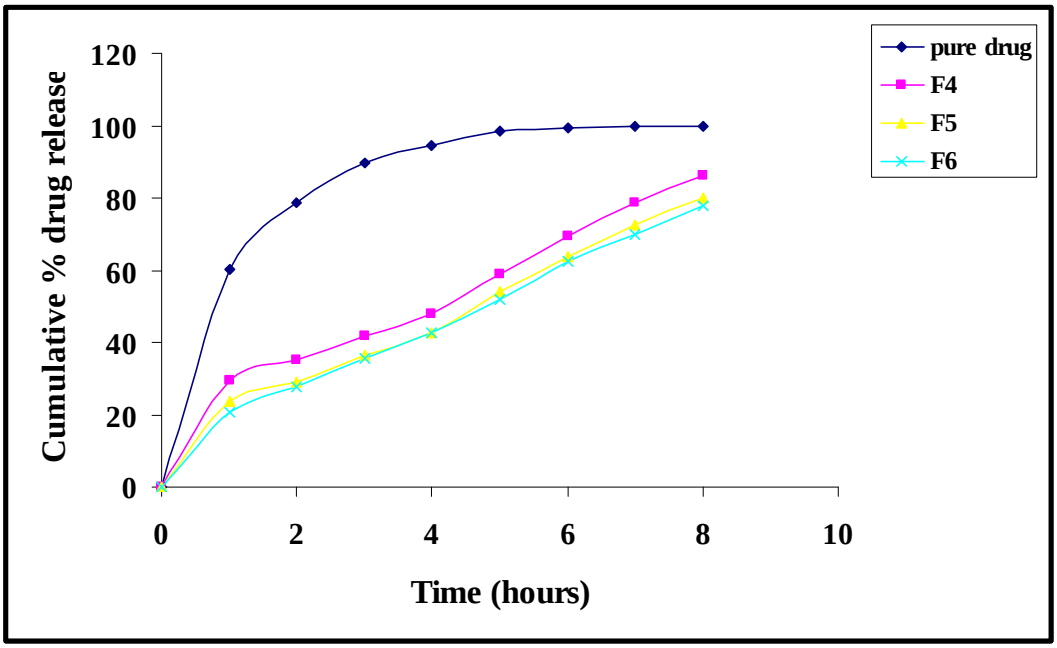

Figure 1; Comparative % drug release profile in pH 5.8 phosphate buffer

SELECTION OF OPTIMIZED FORMULATION

The formulations F_4 to F_6 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 F_4 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.

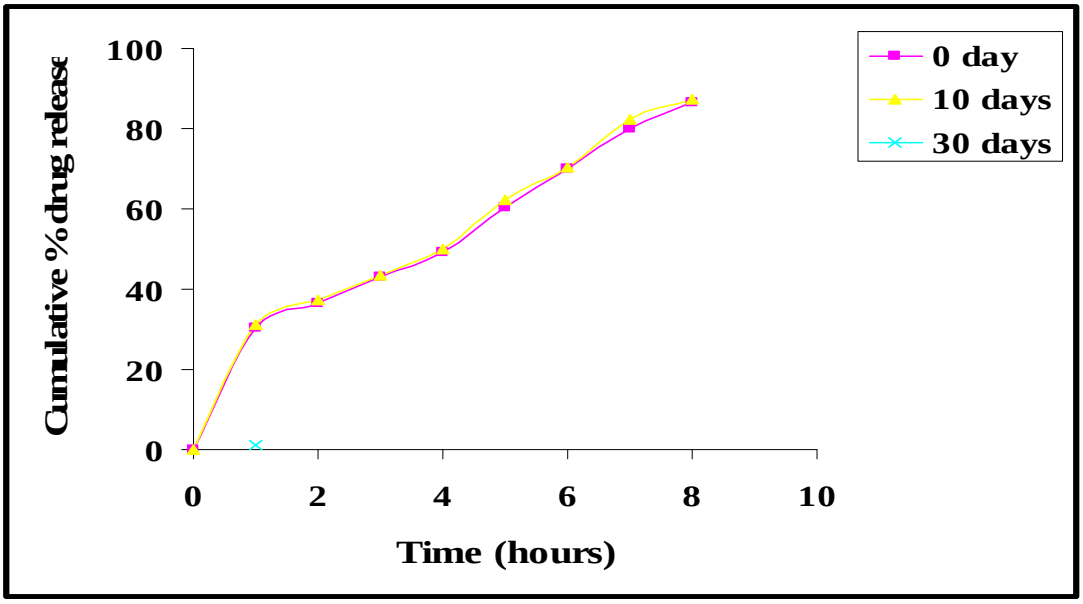

Figure 2; Release profile of Furosemide from formulation F_4 showing effect of aging

Summary and conclusion

Summary

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. 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 improve bioavailability ,reduces drug waste, and improve solubility for drug 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 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 found. It is increase in gastric residence time. Instead of it have low dose and no first pass hepatic metabolism. The furosemide drug has soluble in acetone, ether and sparingly soluble in ethyl alcohol. It melting point has 210c.There excretion was found renal 66%,bilary 33%. The major site of action is the thick ascending limb loop of Henle where furosemide inhibits Na+-K+-2Cl- cotransport.A minor component of action on proximal tubule has been indicated. It secreted in proximal tubule by organic anion transport and reaches ascending limb loop of Henley where it on act luminal side of the membrane.metabolishes the

corticomedullary osmotic gradient and block positive as well as negative free water clearance+ is increased mainly due to high Na+ load reaching distal tubule. Furosemide has weak carbonic anhydrase inhibitory on acid base balance of the body and it causes the little distortion of the same; mild alkalosis occurs at high doses. It may inter act with the Indomethacin, Lithium, aspirin and other salicylate. It has lot of side effect like Hypokalemia, Acute saline depletion, hearing loss etc. The bulk density tapped density of preliminary optimized formulation Were found to be in range of 0.027-0.292 and 0.323-0.354.Instead of there Hauser's ratio was found to be 1.137-1.199.which indicate good flow property. The percentage yield drug content was found in range of 89.54-92.54 and 96.97.-98.28% the low value of standard deviation indicated The formulation F4-F6 exhibited 90 to 100%floating ability at the end of 8 hrs. in PH5.8 phosphate buffer. This is due to the lower bulk density of the formulation and hydrophobic nature of Gelucire 43/01 used in granules. IN the fed state, at PH5.8,the pure drug showed 99.79% while formulation F4,F5andF6 showed85.95%,79.95%and77.83% drug release after 8 hours respectively. As the Gelucire 43/01 ratio was increased in the formulation F4toF6 prepared by melt granulation technique The release rate was lowered due to hydrophobic nature of gelucire 43/01.

CONCLUSION

The present study was aimed to prepare floating granular delivery system with an objective to control the release rate of Furosemide. The performance of the formulations was evaluated and the floating ability of the granules and the release rate of the drug (Furosemide.) from the granules can be controlled by changing the composition ratio of Gelucire 43/01. Formulation F_4 (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 Furosemide.

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