



FORMULATION AND EVALUATION OF PHOSPHOLIPID DISPERSED FLOATING TABLETS OF FUROSEMIDE

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ABSTRACT

Oral administration is the most convenient and preferred means of any drug delivery to the systemic circulation. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable and controlled rate required for therapeutic effect. To improve the solubility and bioavailability of poorly water soluble drugs, solid dispersions is the most frequently used. Amongst solid dispersions, lipid based carriers had a higher success rate in enhancing the bioavailability of Class II drugs (Furosemide), one such promising group of carrier is Phospholipid (soyalecithin). The aim of the present work was to prepare phospholipid solid dispersion of Furosemide (PLD) with soy lecithin in different ratios using solvent evaporation method. The prepared PLD4 was used to prepare core tablets (F1-F5) using polymers HPMC K4M & E15, which were further subjected to compressed coat (C1-C5) using sodium bicarbonate, PVP K 30 and HPMC E5. Post-compression parameters of Furosemide tablets were evaluated. Formulation F4 core tablet was optimized having drug release of 93.31% in 12 hrs, drug content was 99.50%, floating lag time 16sec with floating time 12 hrs. Among compressed coated floating tablets of Furosemide, C3 has shown 93.31% release with zero order release pattern.

KEYWORDS: Solid dispersion, soyalecithin, floating lag time, Higuchi equation, compressed coated

INTRODUCTION

Gastroretention drug delivery systems are designed to be retained in the stomach for extended periods of time and release their active ingredients, thereby allowing sustained and prolonged entry of the drug into the upper gastrointestinal tract¹.

Floating drug delivery systems have a bulk density less than gastric fluids and thus remain in the stomach without affecting the rate of gastric emptying for longer periods of time. While the system floats on the stomach contents, the drug is slowly released from the system at the desired rate. This results in increased retention time in the stomach and control of fluctuations in plasma drug concentration².

Solid dispersions have been defined as “dispersion of one or more active ingredients in an inert carrier or matrix in a solid state by a melting (fusion) method, a solvent, or a melting solvent” (S. Qi *et al.*, 2010). Among the available technologies, the solid dispersion (SD) method is often considered a promising strategy, which significantly increases solubility and bioavailability by reducing the particle size to the micromolecular level³.

Among solid dispersions, lipid-based carriers have been more successful in increasing the bioavailability of class II drugs (furosemide), one such promising group of carriers is phospholipid (soyalecithin). Furosemide is a high ceiling loop diuretic. It is primarily used to treat hypertension; it is the drug of first choice in congestive heart failure edema. In this study, phospholipid dispersed floating tablets of furosemide were prepared and evaluated to increase the bioavailability of furosemide when administered orally.

METHODOLOGY

Materials

Materials used in the study were Furosemide (Yarrow chemicals), Soya lecithin, HPMC K4M, HPMC E15, HPMC E5, Stearyl alcohol, PVP K30, Magnesium stearate, Microcrystalline cellulose, octadecanol were from Himedia, Sodium bicarbonate, Sodium hydroxide A.R., Hydrochloric acid, Orthophosphoric acid were from S.D. Fine-Chem. Ltd, India. Potassium dihydrogen orthophosphate, Methanol (HPLC grade) were from Merck, India.

Methods

Standard graph of Furosemide in pH 1.2 hydrochloric acid

About 100 mg of furosemide was accurately weighed and dissolved in 100 ml of methanol (stock solution - A, 1000 µg/ml). 10 ml of this solution was diluted to 100 ml with hydrochloric acid of pH 1.2 (stock solution - B, 100 µg/ml). From this stock solution-B, dilutions were made with pH 1.2 HCl to obtain solutions of different concentrations (5, 10, 15, 20, 25 and 30 µg/ml). The absorbance of these prepared furosemide solutions was measured with a UV-Visible spectrophotometer at A-max 280 nm using a pH 1.2 hydrochloric acid solution as a reference/blank. A standard graph has been drawn.

Formulation of phospholipid solid dispersion⁴

A solid dispersion of furosemide phospholipid (FPD) was prepared using soy lecithin in different ratios such as 1:1, 1:1.5, 1:2 and 1:3. FPD was prepared by the solvent evaporation method, which is schematically shown in Table 1. Furosemide 40 mg was taken and dissolved in 15 mL of methanol. The required amount of phospholipid was added to the drug solution. This solution was transferred to a round bottom flask, attached to a rotary flash evaporator and evaporated at 45°C, maintained at 30 rpm for 10 minutes. The phospholipid dispersion was obtained, collected and dried in a desiccator until completely dry.

Preparation of Core tablets

Core tablets of Furosemide formulated using phospholipid dispersion (1:3 ratio) equivalent to 40mg of drug along with remaining ingredients as shown in Table 2. The mixtures were compressed into core tablets with an average total weight of 358 mg per tablet.

Compression coating of core tablet⁷

Among the core tablets, F4 formulation showing good pre-compression parameter, less floating lag time and increased *in-vitro* release of the drug further used for the coating by compression coating using ingredients shown in Table 3. The average total weight of coated tablet C1 to C5 was found 630mg with 358mg core tablet inside.

Table1 : Formulation of solid dispersion with phospholipid

Formulation code	Furosemide (mg)	Soya lecithin (mg)	Ratio
PLD 1	40	40	1:1
PLD 2	40	60	1:1.5
PLD 3	40	80	1:2
PLD 4	40	120	1:3

Table2 : Composition of Core tablets

Ingredients (mg)	F1	F2	F3	F4	F5
Dispersion	160	160	160	160	160
Octadecanol	30	30	30	30	30
Sodium bicarbonate	30	30	30	30	30
Polyvinylpyrrolidone K30	16	16	16	16	16
HPMC K4M	120	100	80	60	40
HPMC E15	-	20	40	60	80
Magnesium stearate	2	2	2	2	2

Table 3: Composition of the compressed coated tablets

Ingredients(mg)	C1	C2	C3	C4	C5
HPMC E5	120	140	160	180	200
Octadecanol	35	35	35	35	35
Sodium bicarbonate	25	25	25	25	25
PVP K30	80	60	40	20	-
Microcrystalline cellulose	10	10	10	10	10
Magnesium stearate	2	2	2	2	2

EVALUATION⁵

Solubility Studies of Furosemide and Phospholipid dispersion

Excess furosemide and PL dispersion were placed individually in distilled water, 0.1 N HCl, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer and methanol (10 mL) to determine solubility. Saturation solubility studies were performed for 48 hours at 36°C and solubility was determined by analyzing the samples in a UV-visible spectrometer.

Compatibility studies

Differential scanning calorimetry (DSC) is a thermoanalytical technique that measures the difference in the amount of heat required to raise the temperature of a sample and a reference as a function of temperature.

X-ray powder diffraction (XRD) is a rapid analytical technique primarily used for phase identification of a crystalline material and can provide information on unit cell dimensions. The analyzed material is finely ground, homogenized and the average bulk composition is determined.

Pre-compression parameters

The flow properties of the drug molecules are the important factor in the selection of manufacturing process of formulation.

Bulk density

Both bulk density and shaken bulk density were determined. Weighed amounts of the PhosphoLipid dispersion were placed in a 10 ml graduated cylinder each. The initial volume was observed, the cylinder was dropped by its own weight onto a hard surface from a height of 2.5 cm at 2 second intervals. Tapping continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas (Bhagawat *et al.*, 2012).

$$\rho_b = M/V_o$$

ρ_b = Apparent Bulk density

M = weight of the sample

V_o = apparent volume of powder

Tapped density

The test powder sample was sieved through a No. 18 sieve and a sample weight equivalent to 2 g was filled into a 10 ml measuring cylinder. Mechanical tapping of the cylinder was performed using a tap density tester at a constant speed for 100 times. Volume was considered as the swept volume of fVT (shobit *et al.*, 2011; Chaitanya P *et al.*, 2014). The shaking density was calculated in g/cm³ according to the formula

$$\text{Tapped density } (\rho_t) = M/V_f$$

Where, M = weight of the Sample powder taken

V_f = tapped volume.

Angle of repose

The PL dispersion angle of repose was determined by the funnel method. An accurately weighed sample was taken into a funnel. The height of the funnel was adjusted so that the tip of the funnel was just touching the top of the PhosphoLipid dispersion powder pile. The powder was allowed to flow freely through the funnel onto the surface. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation (More *et al.*, 2004).

$$\tan \theta = h/r$$

Where h = height of funnel and r = radius of pile.

Compressibility Index

Compressibility is the ability of the powder to decrease in volume under pressure. The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed (Shobit *et al.*, Chaitanya *et al.*, 2014). It is determined by bulk and tapped densities. In theory, less compressible a material the more flowable it is. As such, it is the measure of the relative importance inters particle interactions. In a free-flowing powder, such interactions are generally significant, and the bulk and tapped densities will be closer in value for poor flowing materials, there are frequently greater interparticle interactions, and the greater difference between bulk and tapped densities will be observed. Those differences are reflected in the compressibility Index which is calculated by using following formula.

$$\text{Carr's compressibility Index (\%)} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of powder or granular material.

$$\text{Hausner's ratio} = \text{TBD/LBD.}$$

EVALUATION OF CORE AND COATED TABLETS⁶

Weight variation

Twenty tablets from each batch were individually weighed. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight.

Thickness test

The thickness in millimeters (mm) was measured individually for 10 pre-weighed tablets by using vernier calipers. The average thickness and standard deviation were reported.

Hardness test

Tablet hardness was measured using a Pfizer hardness tester. The crushing strength of the 10 tablets with known thickness and weight of each was recorded in kg/cm² and the hardness and the standard deviation was reported.

Friability test

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. The initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as a percentage. It should be preferably below 1.0%.

$$\% \text{ Friability} = [(W_1 - W_2) / W_1] \times 100$$

Where, the W_1 = weight of tablets before the test, W_2 = weight of tablets after the test.

Drug content

Ten tablets from each formulation were taken and powdered. The powdered sample equivalent to 100 mg of drug was transferred to a volumetric flask and dissolved in methanol, mixed and filtered. The required amount of 0.1 N Hydrochloric acid was added to the filtrate suitably diluted with media and drug content was analyzed against blank by UV spectrophotometer at 280 nm. The percentage of drug present in the tablets was calculated.

Floating lag time and total floating time determination

The time between the introduction of the tablet into the medium and its rise to the top of the dissolution vessel is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. These tests are usually performed in simulated gastric fluid or 0.1 N HCl maintained at 37°C, by using USP dissolution apparatus containing 900 mL of 0.1N HCl as the dissolution medium.

In-vitro drug release studies

The *in-vitro* dissolution study was carried out in the USP dissolution test apparatus, type II (paddle). One tablet was placed in each of the six dissolution flasks containing 900 mL of dissolution medium, maintained at $37 \pm 0.5^\circ\text{C}$. After completion of each specified time interval, a 5 mL was replaced by dissolution media from a zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1 cm from the vessel wall and filtered through 0.45 μm membrane filters. The samples were collected at specified time intervals and diluted to required volume with dissolution medium. Finally percentage drug dissolved was calculated.

Dissolution conditions:

Medium: 0.1 N Hydrochloric acid

Volume: 900 mL

Temperature: 37°C ± 0.5°C Apparatus

USP Type-II (Paddle): 50 rpm

Time interval: 1, 2, 4, 6, 8, 10 and 12 hours.

Drug release kinetic studies

The dissolution data were fitted to kinetic models such as zero-order, first-order, Higuchi, and Peppas-Korsmeyer equation models. The order of drug release from floating systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppas-Korsmeyer equation.

RESULTS AND DISCUSSION**Preparation of standard graph of Furosemide in 0.1N Hydrochloric acid**

Different concentrations of Furosemide were prepared in 0.1N HCl. Estimation of Furosemide was performed by using UV spectrophotometer at the maximum wavelength 280 nm, in Figure 1.

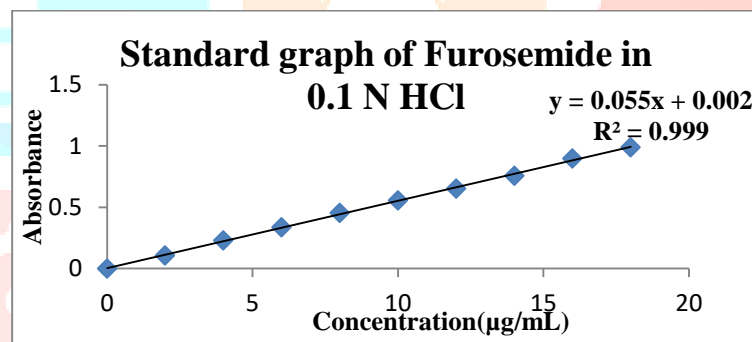


Figure 1: Standard graph of Furosemide in 0.1N HCl at λ_{\max} 280nm

Solubility studies of Furosemide and Phospholipid dispersion

The solubility studies was determined by analyzing the samples in UV Visible spectrometer and shown in Table 4 and 4.1.

Table 4: Solubility studies of the Furosemide

Media	Solubility(µg/mL)
Distilled water	73±1
0.1 N HCl	22±1
pH 7.4	140±3
pH 6.8	4,205±230

Table 4.1: Solubility studies of Phospholipid dispersion in 0.1N HCl

Ratio (Furosemide : Soya lecithin)	Solubility in 0.1 N HCl (µg/mL)
Pure Furosemide drug	22±1
1:1	126±5
1:1.5	163±9
1:2	208±13
1:3	244±10

Compatibility studies

Differential scanning calorimetry (DSC) of Furosemide and PL dispersion

The DSC thermogram of Furosemide and PL dispersion showed an exothermic peak at a temperature of 206°C in Figure 2 & 2.1 respectively, indicating that the drug is compatible with phospholipid.

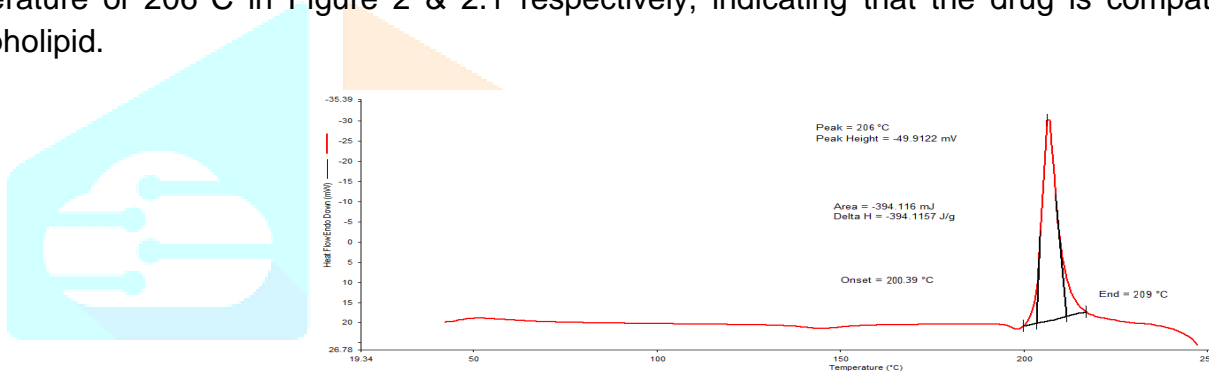


Figure 2: Furosemide pure drug

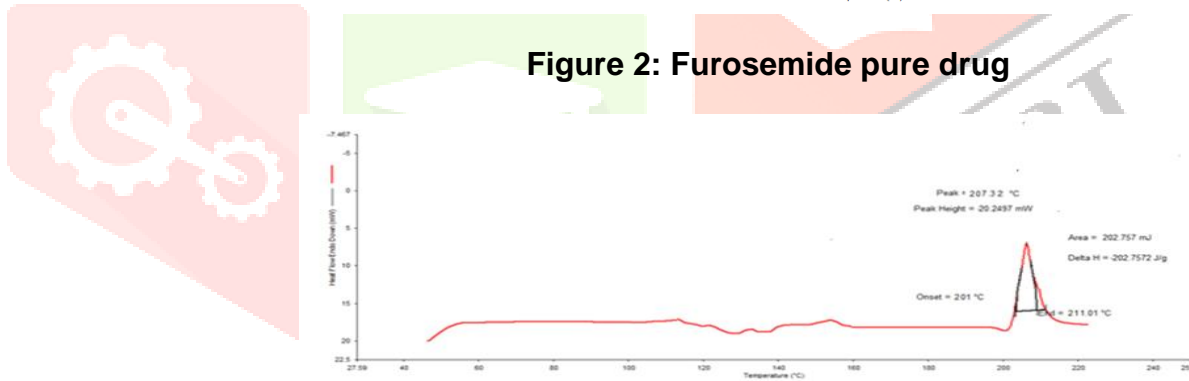


Figure 2.1: DSC Thermogram of phospholipid dispersion

X-ray powder diffraction (XRD)of Furosemide and PL dispersion

The pure drug showed numerous high intensity diffraction peaks at 2θ of $15-30^\circ$ demonstrating the crystalline nature of the drug, shown in Figure 3.

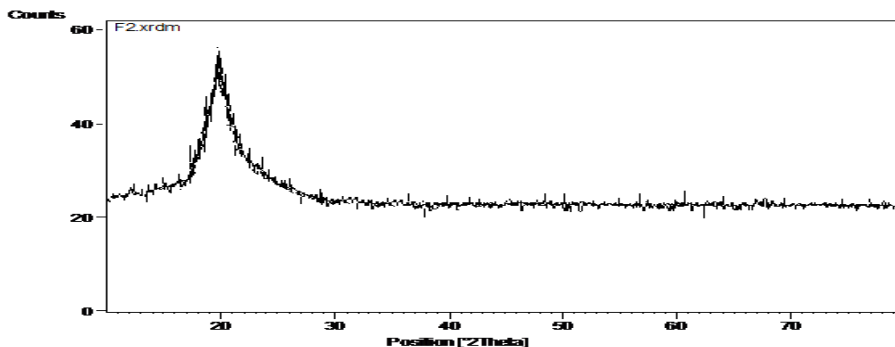


Figure 3: XRD of pure Furosemide drug

The pure drug showed numerous high intensity diffraction peaks at 2θ exhibited diffuse peaks, an indicative amorphous state and disappearance of characteristic peaks of the drug. The PXRD studies reveal the formation of dispersion, shown in Figure 3.1.

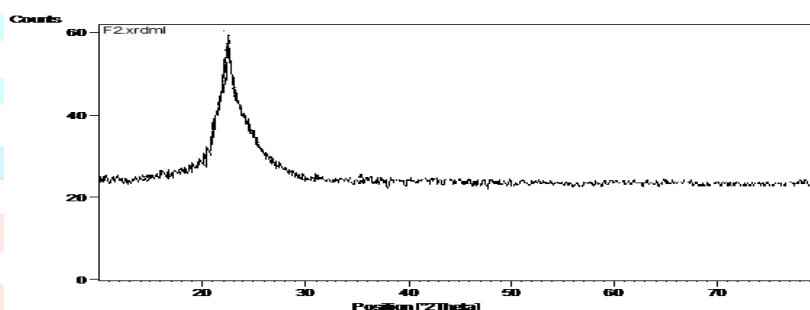


Figure 3.1: XRD of Phospholipid dispersion

Percentage yield and drug content (%) of the Solid dispersion

The content of drug was determined by UV Spectrophotometric method. A yield of solid dispersions from 96% to 98 % as shown in Table 5. The percentage loss of solid dispersion was found to be 2.5-1.3%. The assay values were found to be within pharmacopoeial limits.

Table 5: Determination of yield and drug content of the dispersion

Formulation	Ratio	% Yield	% Drug Content
PLD1	1:1	98.7	99.5
PLD2	1:1.5	97.5	99
PLD3	1:2	97.5	98.5
PLD4	1:3	97.5	97.2

Pre-compression parameters

It was observed that all the formulations prepared were found to be having good flow properties and shown in Table 6&7.

Table 6: Pre compression parameters of core tablets

Formulation code	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index	Hausner's ratio	Angle of repose
F1	0.62	0.66	6.06	1.06	28.2
F2	0.57	0.62	8.06	1.08	29.1
F3	0.52	0.57	8.77	1.09	29.5
F4	0.50	0.54	7.40	1.08	29.7
F5	0.48	0.51	5.88	1.06	28.1

The values of bulk density and tapped density of various formulations were found to be in the range of 0.48 to 0.62 (gm/mL) and 0.51 to 0.66 (gm/mL) respectively. Carr's index of the prepared blend falls in the range of 5.88 to 8.77. The Hausner's ratio falls in the range of 1.06 to 1.09. The values of angle of repose were found in the range of 28.1° – 29.7°. From these results, it was concluded that the powder blends had good flow properties and can be used for tablet manufacturing.

Table 7: Pre compression properties of coating material

Formulation code	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index	Hausner's ratio	Angle of repose
C1	0.58	0.62	5.16	1.03	28.4
C2	0.54	0.57	5.26	1.04	29.1
C3	0.50	0.54	7.40	1.08	29.5
C4	0.48	0.51	5.88	1.06	28.1
C5	0.46	0.49	6.52	1.06	29.3

The values of bulk density and tapped density of various formulations were found to be in the range of 0.48 to 0.58 (gm/mL) and 0.49 to 0.62 (gm/mL) respectively. Carr's index of the prepared blend falls in the range of 5.16 to 6.52. The Hausner's ratio falls in the range of 1.03 to 1.08. The values of angle of repose were found in the range of 28.1° – 29.5°. From these results, it was concluded that the coating powder blends have good flow properties and can be used for tablet coating.

Post-compression parameters

The results of physical parameters of the core tablets and coated tablets were within the limits and acceptable range, shown in Table 8 & 9.

Table 8: Post compression Properties of Core tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)
F1	272	6.0±0.03	5.1±0.23	0.15	99
F2	271	6.0±0.15	4.9±0.11	0.14	98.5
F3	272	6.1±0.06	5.1±0.40	0.14	97.25
F4	272	6.0±0.01	5.0±0.11	0.18	99.5
F5	273	6.1±0.02	5.2±0.32	0.12	98.5

The thickness of the core tablet ranged between 6.0 – 6.1 mm with SDs of 0.1 to 0.25 all the batches showed uniform thickness. The friability was in the range of 4.1 – 5.2 %. The hardness of the tablets was in the range of 4.9 – 5.2 kg/cm². The drug content estimation showed values in the range of 97.25 to 99. This reflects good uniformity in the drug content among different core tablets.

Table 9: Post compression Properties Coated tablet

Formulation code	Weight variation	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug content(%)
C1	542	7.1±0.16	6.2±0.28	0.14	97.5
C2	542	7.2±0.08	6.1±0.17	0.15	98.5
C3	548	7.1±0.11	6.0±0.13	0.14	99.5
C4	546	7.2±0.05	6.1±0.26	0.18	99
C5	549	7.0±0.09	6.0±0.15	0.10	97.25

The thickness of the coated tablet ranged between 7.0 – 7.1 mm. All the batches, coated showed uniform thickness. The friability was in the range of 0.10 – 0.18 %. The hardness of the tablets was in the range of 6.0 – 6.2 kg/cm². The drug content estimation showed values in the range of 97.25 to 99.5. This reflects the good uniformity in the drug content among different coated tablets.

Floating lag time and total floating time of core and coated tablets

All formulations were remain floating up to 12 hrs except F5. The F4 formulation started floating after 11 sec. When compared to other formulations it has shown least lag time in all 12 hrs floating formulations as in Table 10&11.

Table 10: Floating lag time and total floating time of various formulations of core tablets

Formulation code	Floating lag time (sec.)	Total floating time (hrs)
F1	17 sec	>12
F2	15 sec	>12
F3	13 sec	>12
F4	11 sec	>12
F5	09 sec	>10

Table 11: Floating lag time and total floating time of various formulations of coated tablets

Formulation code	Floating lag time (sec.)	Total floating time (hrs)
C1	28 sec	>12
C2	26 sec	>12
C3	23 sec	>12
C4	21 sec	>12
C5	20 sec	>12

All formulations were remain float up to 12 hrs, and a lag time below 30 sec.

***In-vitro* drug release studies of core tablets& coated tablets**

In-vitro drug release studies of phospholipid dispersions floating tablets core and coated tablets were carried out in 1.2 pH and percentage drug release at previous time intervals was calculated. The values obtained are shown in the Table 12& 13. The graph was plotted by taking the time on X-axis and corresponding percentage drug dissolved on Y-axis as shown in the Figure4&5. It was observed from the study that the ratio of carrier increases, the drug dissolution rate was also increased. It was found F4 formulation is best among the other formulations, as it has showed 96.36% of drug release within 12 hrs.

Table 12: *In-vitro* drug release studies of Furosemide phospholipid dispersed core tablets

Time (hrs)	Cumulative percentage of drug release.				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
0.5	8.43 ± 0.42	9.56 ± 0.86	9.40 ± 0.94	11.30 ± 0.86	14.26 ± 0.40
1	11.39 ± 1.24	14.48 ± 0.83	16.62 ± 0.91	18.24 ± 1.43	23.19 ± 1.09
2	23.74 ± 0.93	27.32 ± 1.07	29.41 ± 1.19	32.12 ± 0.81	39.86 ± 0.44
4	30.55 ± 0.85	37.68 ± 0.86	41.42 ± 0.76	45.74 ± 1.33	53.64 ± 0.89
6	41.16 ± 1.04	47.25 ± 1.64	51.56 ± 0.96	55.21 ± 0.72	67.38 ± 1.04
8	58.17 ± 1.88	61.41 ± 1.58	64.41 ± 1.18	68.15 ± 0.67	83.23 ± 1.22
10	70.34 ± 0.87	76.88 ± 0.83	79.61 ± 0.88	81.41 ± 1.04	99.43 ± 0.65
12	84.11 ± 0.93	86.56 ± 1.22	91.79 ± 1.47	96.36 ± 0.77	---

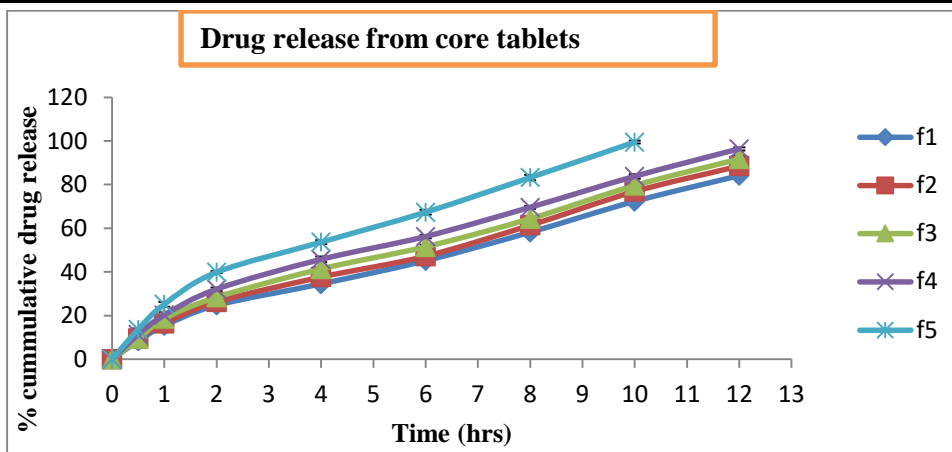


Figure 4: *In-vitro* drug release from core tablet

In-vitro drug release of compression coated tablet

Table 13: *In-vitro* drug release profile of Furosemide from compressed coated tablets

Time (hrs)	Cumulative percentage of drug release.				
	C1	C2	C3	C4	C5
0	0	0	0	0	0
0.5	13.78 ± 0.71	7.85 ± 0.53	7.25 ± 0.25	6.8 ± 0.56	5.08 ± 0.30
1	19.83 ± 0.34	14.71 ± 0.62	13.70 ± 0.38	11.63 ± 0.30	10.15 ± 0.62
2	27.26 ± 0.87	23.54 ± 0.64	20.39 ± 0.55	19.34 ± 0.61	18.29 ± 0.67
4	40.87 ± 0.55	38.66 ± 0.61	36.25 ± 0.96	30.42 ± 0.42	29.75 ± 0.72
6	55.16 ± 0.23	53.42 ± 0.83	49.22 ± 0.45	41.67 ± 0.33	40.31 ± 0.47
8	68.52 ± 0.14	66.08 ± 0.55	64.55 ± 0.44	56.32 ± 0.78	53.90 ± 0.88
10	81.84 ± 0.70	79.30 ± 0.68	77.56 ± 0.48	74.82 ± 0.65	62.34 ± 0.54
12	94.75 ± 0.80	93.80 ± 0.59	93.31 ± 0.40	87.56 ± 0.80	79.73 ± 0.95

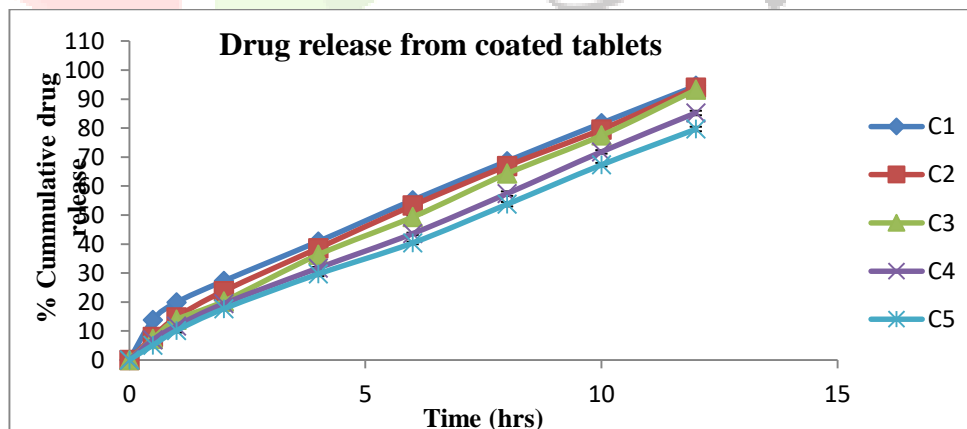


Figure 5: *In-vitro* drug release profile from coat tablet formulation

Dissolution profile Kinetic modeling

Dissolution data of optimized formulations were fitted to various mathematical models (zero order, first order, Higuchi and Korsmeyer –Peppas) to describe the kinetics of drug release. An ideal controlled drug delivery system should be able to release a high percentage of drug constant

release rate (zero order kinetics) during the dissolution. Goodness-of-fit test (R^2) was taken as a criterion for selecting the most appropriate model.

Table 15: Dissolution profile modeling of coated formulations

Formulation	Cumulative % drug release	Time (hrs)	R^2 value			
			Zero-order	First order	Higuchi	Kores Meyer-Peppas
C1	94.75	12	0.9853	0.8978	0.9766	0.9906
C2	93.8	12	0.9895	0.8775	0.9693	0.9933
C3	93.31	12	0.9964	0.8906	0.9563	0.9971
C4	87.56	12	0.9950	0.9155	0.9349	0.9932
C5	79.73	12	0.9941	0.9456	0.9964	0.9456

In the above table, the C3 formulation is considered as optimized coated formulation because it follows zero order drug release rate than other formulations.

CONCLUSION

Furosemide phospholipid dispersed floating tablets were prepared by direct compression method and evaluated successfully. PLD 4 was used for core tablet preparation. The prepared core tablets of furosemide solid dispersion were evaluated for weight variation, thickness, hardness, friability, drug content, in-vitro drug release studies and release kinetics and all the results were within the limits. The F4 core formulation was optimized and was used for compressed coating floating tablets. Among different coated formulations, C3 was optimized and showed 93% release in zero order manner. *In-vivo* bioavailability studies were needed to prove its efficacy.

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