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Research Article

Formulation And Characterization Of Floating Bilayer Tablet Of Furosemide Using Natural Polymers

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ABSTRACT

Introduction: Floating bilayer tablets, designed to improve the bioavailability of drugs with narrow absorption windows or solubility issues, offer a promising solution for sustained drug delivery in the upper gastrointestinal tract. This study focuses on formulating and characterizing floating bilayer tablets of furosemide, a diuretic with a short half-life and erratic absorption, using natural polymers to enhance its therapeutic performance.

Materials and Methods: The instant release layer of furosemide was prepared by direct compression using different super disintegrants. The gastroretentive control layer was also prepared by direct compression using various polymers. Pre-compression parameters such as bulk density, Carr's index, and Hausner's ratio were evaluated, followed by post-compression assessments including hardness, friability, weight variation, drug content, and in vitro dissolution studies.

Results: Pre-compression evaluations showed satisfactory flow properties and compressibility. Post-compression assessments confirmed adequate tablet strength, uniformity, and low friability, ensuring product integrity. The optimized bilayer tablet formulation demonstrated controlled and sustained drug release over 12 hours, indicating improved therapeutic efficacy and prolonged gastric retention.

Conclusion: The study successfully formulated and characterized floating bilayer tablets of furosemide, showing potential for enhanced drug absorption and therapeutic outcomes. These tablets could reduce dosing frequency and improve patient compliance. Further pharmacokinetic and pharmacodynamic studies are recommended to validate their clinical effectiveness.

Keywords: Floating bilayer tablets, Furosemide, Natural polymers, Sustained release, Drug delivery.

Introduction

Floating drug delivery systems have garnered significant interest in the pharmaceutical industry due to their potential to improve the bioavailability and therapeutic efficacy of drugs, particularly those with narrow absorption windows or solubility issues (Pawar et al., 2011). Among these systems, floating bilayer tablets offer a promising approach for delivering drugs to the upper gastrointestinal tract, where prolonged gastric residence time can enhance drug absorption (Gaur et al., 2011). Furosemide, a potent loop diuretic commonly used in the management of conditions such as congestive heart failure and edema, presents challenges related to its short half-life and erratic absorption (Vazir and Martin, 2013). Developing a floating bilayer tablet of furosemide using natural polymers presents an opportunity to overcome these challenges and optimize its therapeutic performance.

Natural polymers, such as hydroxypropyl methylcellulose (HPMC), sodium alginate, and chitosan, have gained popularity in pharmaceutical formulations due to their biocompatibility, biodegradability, and safety profiles. These polymers offer unique properties that can be leveraged to formulate floating bilayer tablets with desirable drug release profiles and floating behavior (Saripilli et al., 2017).

In this study, we aimed to formulate and characterize floating bilayer tablets of furosemide using a combination of natural polymers. The bilayer design allows for the incorporation of immediate-release and sustained-release

layers, providing flexibility in drug release kinetics. By formulating furosemide into a floating bilayer tablet, we aimed to achieve prolonged gastric retention, sustained drug release, and enhanced therapeutic outcomes. The use of natural polymers in the formulation offers several advantages, including improved drug stability, reduced gastric irritation, and enhanced patient compliance. Furthermore, the floating behavior of the tablet ensures prolonged residence time in the stomach, leading to increased drug absorption and therapeutic efficacy.

This study provides valuable insights into the formulation and characterization of floating bilayer tablets of furosemide using natural polymers. The optimized formulation has the potential to address the limitations associated with conventional dosage forms of furosemide and improve patient outcomes in the management of various medical conditions.

Material and Methods

Preparation of instant layer of Furosemide (Phase-1)

Fast dissolving (Instant Layer) tablets of Furosemide were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations (Kumar *et al.,* 2007). The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60.

Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included angle of repose, bulk density, tap density, Carr's index and Hausner's ratio.

The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Nine different formulations of Furosemide were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablets weighing 100mg, were obtained. Composition of tablets is mentioned in Table 1.

Table 1: Composition of Furosemide fast dissolving (Instant release) tablets

Ingredients(mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Furosemide	10	10	10	10	10	10	10	10	10
Sodium Starch glycolate	10	15	20	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	15	20	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20
Microcrystalline cellulose	65	60	55	65	60	55	65	60	55
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight	100	100	100	100	100	100	100	100	100

Preparation of Furosemide gastroretentive tablets

Direct compression was followed to manufacture the floating tablets of Furosemide. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table 2 and all the formulation were used for further evaluations parameters (Girish *et al.,* 2007).

Optimization of gastro retentive tablets of Furosemide

Table 2: Various formulations of Furosemide gastro retentive tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Furosemide	30	30	30	30	30	30	30	30
Xanthan gum	90	120	-	-	-	-	30	40
Guar gum	-	-	90	120	-	-	30	40
Sodium alginate	-	-	-	-	90	120	30	40
PVP K30	15	15	15	15	15	15	15	15
Sodium bicarbonate	10	10	10	10	10	10	10	10

Citric acid	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	85	55	85	55	85	55	85	55
Total Weight	250	250	250	250	250	250	250	250

Evaluation of precompression parameter

1. **Bulk Density:**To determine the bulk density, a precisely weighed powder blend from each formula was gently shaken to disperse any agglomerates, and it was then placed into a measuring cylinder. The volume occupied by the powder was measured, providing the bulk volume. The bulk density of the powder blends was calculated using the following formula:[9,12]

ρbulk = m/Vo

2. **Tapped Density:**To establish the tapped density, an accurately weighed powder blend from each formula was lightly shaken to disrupt any agglomerates, and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was observed, yielding the tapped volume.

The tapped densities (TD) of the powder blends were determined using the following formula:[12]

$\rho t = m/V_t$

3. **Angle of Repose**: The angle of repose is a measure used to assess the flow properties of solids. It is a characteristic linked to the friction or resistance between particles. The angle of repose (θ) for the powder was determined by pouring the powder through a funnel. The tip of the funnel's orifice was fixed at a height of 1 cm above a horizontal surface, and the powder was allowed to flow solely due to gravity. The angle of repose, θ, was calculated using the following relationship.[16,17]

θ = tan −1(h/r)

The angle of repose (θ) is calculated using the formula: tan θ = h/r, where 'h' represents the height of the pile of powder (h=1) and 'r' is the radius of the base of the cone.

4. **Hausner Ratio**: Hausner's ratio is determined using the equation: Hausner's Ratio = Tapped bulk density / Loose bulk density. A Hausner ratio less than 1.12 indicates good flow, while a ratio greater than 1.35 suggests poor flow.[9,16]

Hausner's Ratio = ρt / ρbulk

5. **Compressibility Index**:The compressibility index is a straightforward measure that can be determined with small quantities of powder. In theory, materials that are less compressible tend to flow more easily. The compressibility index of the powder blends is determined using the following formula: [8]

CI = ρt – ρbulk / ρt × 100

Evaluation of post compression parameter

1. **Shape and colour of tablets:**

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

2. **Thickness test**

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan) (Kumar *et al.,* 2003).

3. **Weight variation test**

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

4. **Hardness test**

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2.

5. **Friability test**

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

% Friability=(Weight before friability−Weight after friabilityWeight before friability)×100**% Friability**=(Weight before friabilityWeight before friability−Weight after friability)×100

6. Uniformity of drug content
The test is mandatory for tablets with 10mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCl (Simulated gastric fluid of pH 1.2 without enzymes) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 272nm for Furosemide.

7. Dissolution rate studies of gastroretentive tablet
In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50°c and rpm of 75. One Furosemide tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37°C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCl and take the absorbance at 272nm using spectroscopy (Higuchi, 1963; Korsmeyer *et al.,* 1986).

8. Formulation development of bilayer tablet
Optimized formulation IF-7 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet.

9. Evaluation of bilayer tablets
All the tablets were evaluated for following different parameters which includes;

10. General Appearance
Five tablets from different batches were randomly selected and organoleptic properties suchas color, odor, taste, shape, were evaluated. Appearance was judged visually.

11. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

12. Thickness and diameter
Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

13. Hardness
For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach) (Munira *et al.,* 2015).

14. Friability
The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

15.Uniformity of weight
Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

16. Drug content
Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of Furosemide was transferred to 10ml standard flask. The powder was dissolved in 10 ml of 0.1 N HCl and made up to volume with 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.2 ml to 10 ml suitably 10 ppm solutions of and determines the Conc. of drug at 272nm.

17.Dissolution rate studies
In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5°C temperature over a 12 hrs period for Furosemide bilayer tablets using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested. The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5°C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the concentration of dissolved drug was determined using U.V. (Labindia 3000 plus) spectrophotometer (Higuchi, 1963; Korsmeyer *et al.,* 1986).

Results and Discussion

The pre-compressional parameters of the furosemide instant layer tablets, shown in Table 3, provide insights into the powder's flow properties and compressibility. Generally, the formulations exhibited acceptable loose bulk densities, tapped bulk densities, Carr's index, and Hausner's ratio, indicating satisfactory flowability and compressibility. However, some formulations showed slightly higher Carr's index and Hausner's ratio, suggesting potential compression challenges. These parameters are crucial for tablet uniformity, strength, and disintegration.Post-compression properties, detailed in Table 4, reveal key quality and performance metrics. Hardness test results indicate adequate tablet strength, while low friability values demonstrate resistance to breakage. Uniformity in weight, thickness, and drug content meets pharmacopeial standards, ensuring consistent dosing. Table 5 details the pre-compression properties of the furosemide control layer tablets, essential for uniformity and consistency in manufacturing. Satisfactory compressibility and flowability are indicated by the compressibility index and Hausner ratio.

Post-compression properties of the control layer tablets, presented in Table 6, confirm that the tablets meet quality standards in hardness, friability, weight variation, thickness, and drug content, ensuring strength, integrity, and consistent drug distribution.

In-vitro drug release study data in Table 7 show the cumulative percentage of drug release over time for different formulations, critical for evaluating dissolution behavior and release kinetics.

Table 8 summarizes the post-compression parameters of the optimized bilayer tablet formulation, confirming quality and therapeutic suitability. Table 9 presents dissolution rate studies, demonstrating sustained release characteristics and controlled drug delivery**.**

FTIR of Furosemide Pure drug

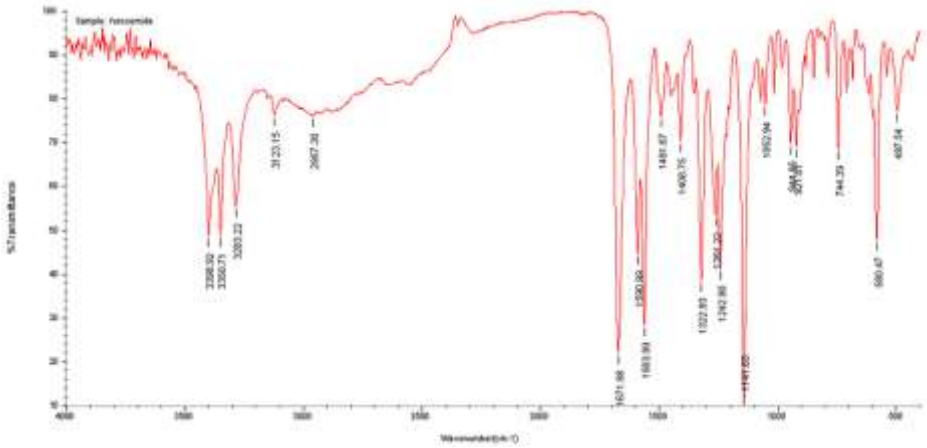

Figure:1 FTIR of Furosemide pure drug

Table 3: Results of pre-compressional parameters of furosemide instant layer tablets

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.365	0.452	19.248	1.238
IF2	0.358	0.465	23.011	1.299
IF3	0.362	0.472	23.305	1.304
IF4	0.374	0.482	22.407	1.289
IF5	0.369	0.476	22.479	1.290
IF6	0.347	0.456	23.904	1.314
IF7	0.356	0.462	22.944	1.298
IF8	0.374	0.485	22.887	1.297
IF9	0.352	0.465	24.301	1.321

Table 4: Results of post-compression furosemide instant layer tablets

F. Code	Hardness test (kg/cm²)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)	Disintegration time (sec.)
IF1	3.3±0.2	0.685±0.012	102±2	2.1±0.2	98.78±0.15	102±2
IF2	3.2±0.3	0.654±0.025	98±1	2.2±0.3	97.85±0.32	95±4
IF3	3.4±0.1	0.632±0.023	100±3	2.1±0.2	96.65±0.14	85±3

IF4	3.6±0.1	0.558±0.041	101±1	2.2±0.2	98.12±0.32	120±2
IF5	3.5±0.2	0.712±0.056	103±2	2.3±0.1	98.65±0.18	105±4
IF6	3.5±0.3	0.695±0.074	99±4	2.1±0.1	99.45±0.32	69±5
IF7	3.4±0.2	0.693±0.065	101±5	2.2±0.2	98.74±0.16	110±4
IF8	3.6±0.3	0.674±0.035	103±2	2.3±0.3	97.65±0.14	105±3
IF9	3.5±0.2	0.685±0.025	102±03	2.2±0.2	97.65±0.14	95±2

Table 5: Result of pre-compression properties of Furosemide control layer tablets

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.415	0.523	20.65	1.260
F2	0.423	0.547	22.67	1.293
F3	0.415	0.536	22.57	1.292
F4	0.478	0.587	18.57	1.228
F5	0.465	0.572	18.71	1.230
F6	0.432	0.547	21.02	1.266
F7	0.442	0.553	20.07	1.251
F8	0.436	0.532	18.05	1.220

Table 6: Results of post compression properties of Furosemide Control release tablets

F. code	Thickness (mm)	Hardness (kg/cm²)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.5±0.2	5.2±0.2	498±5	0.858±0.023	98.89±0.15
F2	3.4±0.1	5.3±0.1	495±6	0.658±0.032	99.85±0.25
F3	3.5±0.3	5.1±0.3	498±4	0.489±0.15	98.89±0.32
F4	3.6±0.2	5.4±0.2	502±8	0.558±0.015	99.56±0.18
F5	5.5±0.3	5.3±0.1	505±5	0.658±0.032	99.28±0.32
F6	3.4±0.2	5.4±0.3	504±7	0.856±0.025	99.56±0.25
F7	3.4±0.3	5.2±0.1	503±6	0.658±0.032	99.23±0.36
F8	3.4±0.2	5.1±0.2	502±5	0.758±0.012	99.12±0.28

Table 7: *In-vitro* drug release study of tablets

Time	% Cumulative Drug Release							
(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	48.85	43.32	40.32	39.98	35.65	33.32	22.32	18.85
1	63.32	58.85	53.32	56.65	46.65	48.85	36.65	26.65
1.5	79.98	66.65	63.32	69.98	68.98	68.85	48.85	45.58
2	88.85	89.98	78.85	76.65	73.32	74.45	56.65	55.69
3	98.78	96.65	88.85	88.85	86.65	81.32	68.98	68.78
4	-	98.85	96.65	98.85	94.45	89.98	72.32	73.32
6	-	-	99.45	-	98.11	94.65	86.65	82.23
8	-	-	-	-	-	99.45	92.32	89.95
12	-	-	-	-	-	-	99.12	93.32

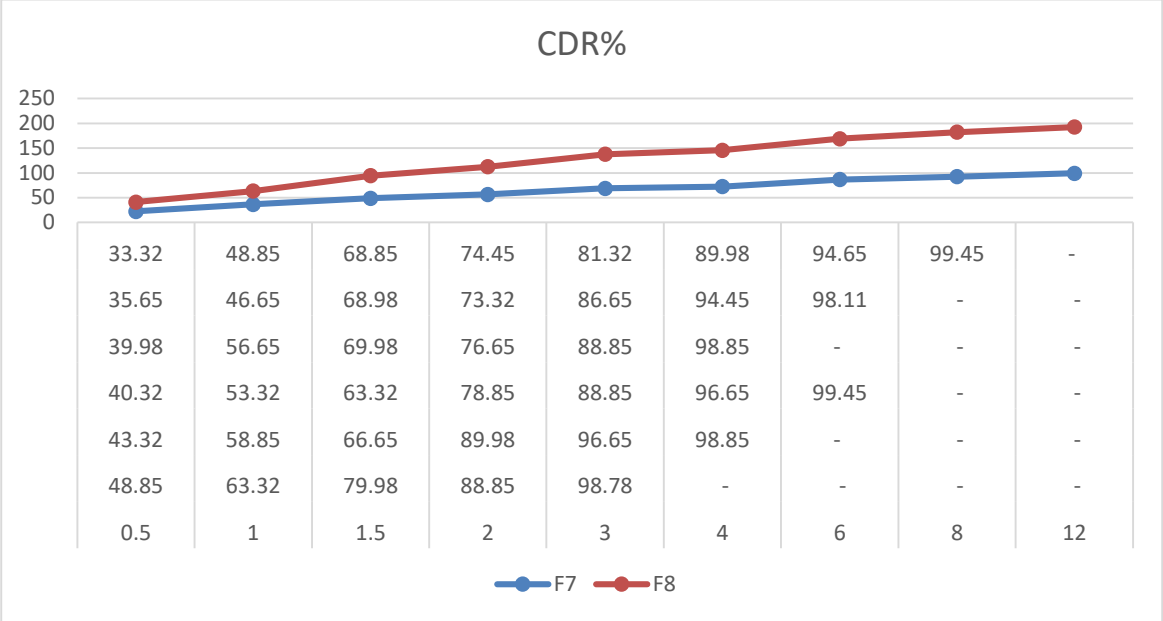

Figure:2 *In-vitro* drug release study of tablets

Table 8: Post-compression parameters of optimized formulation of bilayer tablets

Formulation	Hardness (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)	(% Label Claim)
Optimized Formulation	6.8	0.685	Passes	5.12	99.45

Table 9: Results of Dissolution rate studies of bilayer tablets

Time (Hour)	% Drug Release
0.5	25.32
1	36.45
1.5	39.98
2	46.65
4	53.32
6	68.78
8	73.32
10	88.85
12	98.78

Conclusion

In conclusion, the formulation and characterization of floating bilayer tablets of furosemide using natural polymers have been successfully conducted, as evidenced by the comprehensive analysis of pre-compressional and post-compression parameters, as well as in vitro drug release studies. The pre-compressional parameters indicated satisfactory flow properties and compressibility of the powder blends, while the post-compression properties confirmed the tablets' quality, uniformity, and drug content. The in vitro drug release studies revealed sustained release characteristics, highlighting the potential of the developed formulations for controlled drug delivery. Overall, the findings suggest that the floating bilayer tablets of furosemide hold promise as a novel dosage form with enhanced therapeutic efficacy, improved patient compliance, and reduced dosing frequency. Further studies, including pharmacokinetic and pharmacodynamic evaluations, are warranted to validate their clinical utility and ensure their suitability for therapeutic applications.

References

1. Pawar, V.K., Kansal, S., Garg, G., Awasthi, R., Singodia, D. & Kulkarni, G.T. (2011) Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. *Drug Delivery*, 18, 97–110 [DOI: 10.3109/10717544.2010.520354] [PubMed: 20958237].
2. Gaur, P.K., Mishra, S., Prabhakaran, P., Bhardwaj, S., Puri, D., Kumar, S.S., Dubey, J., Verma, A. & Verma, N. (2015) Prospectives and potentials of bilayer technology: A novel approach. *Journal of Pharmaceutical Sciences and Pharmacology*, 2, 148–161 [DOI: 10.1166/jpsp.2015.1053].

3. Vazir, A. & Cowie, M.R. (2013) The use of diuretics in acute heart failure: Evidence based therapy?. *World Journal of Cardiovascular Diseases*, 03, 25–34 [DOI: 10.4236/wjcd.2013.32A004].
4. Rajeswari, S. (2017) Natural polymers: A recent review. *World Journal of Pharmacy and Pharmaceutical Sciences*, 6, 472–494 [DOI: 10.20959/wjpps20178-9762].
5. Kumar, C.N. (2007) AB, Pandit HK, Singh SP, Design and evaluation sustained release bilayer tablets of propranolol hydrochloride. *Acta Pharmaceutica*, 57, 479–489.
6. Kumar, A., Agarwal, S.P. & Khanna, R. (2003) Modified released bi-layered tablet of melatonin using betacyclodextrin. *Pharmazie*, 58, 642–644 [PubMed: 14531461].
7. Girish, S.S., Devendra, K.J. & Dhananjay, M.M. (2007) Preparation and in vitro evaluation of bilayer and floating-bioadhesive tablets of rosiglitazone maleate. *Asian Journal of Pharmaceutical Sciences*, 2, 161–169.
8. Marshall, K., Lachman, N. & Liberman, H.A. (1987). *The Theory and Practice of Industrial Pharmacy*, 3rd edn. Varghese Publishing House: Mumbai, pp. 66–69.
9. Reddy, S., Panakanti, P.K., Kandaghatla, R. et al (2010) Formulation and release characteristic of a bilayer matrix tablet containing glimepiride immediate release component and metformin hydrochloride as sustained release component. *International Journal of Pharmaceutical Sciences*Nanotechnol, 3, 851–859.
10. Kumar, A., Agarwal, S.P. & Khanna, R. (2003) Modified release bi-layered tablet of melatonin using betacyclodextrin. *Pharmazie*, 58, 642–644 [PubMed: 14531461].
11. Kumar, V.B., Prasad, G., Ganesh, B. et al. (2010) Development and evaluation of guaifenesin bilayer tablet. *Int. J. PharmSci. Nanotechnol.*, 3, 1122–1127.
12. Logidhasan, L., Suresh, S. & Mathivanan, M. Formulation and in vitro evaluation of bilayer floating tablets of aceclofenac and ranitidine HCl. *International Research Journal of Pharmacy* [App].Sci (2013), Vol. 3, pp. 88–94.
13. Munira, M.M., Kane, S. & Abhang, P. (2015) Formulation and evaluation of bilayer tablet for bimodal release of venlafaxine hydrochloride. *Frontiers in Pharmacology*, 6, 1–10.
14. Higuchi, T. (1963) Mechanism of rate of sustained action medication. *Journal of Pharmaceutical Sciences*, 52, 1145–1149. 24 [DOI: 10.1002/jps.2600521210] [PubMed: 14088963].
15. Korsmeyer, R.W., Von Meerwall, E. & Peppas, N.A. (1986) Solute and penetrant diffusion in swellable polymers. II. Verification of theoretical models. *Journal of Polymer Science Part B*, 24, 409–434 [DOI: 10.1002/polb.1986.090240215].