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FORMULATION AND EVALUATION OF OSMOTICALLY CONTROLLED BILAYER TABLETOF FUROSEMIDE

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ABSTRACT
The current research work study deals with the development of Osmotically Controlled Bilayer Tablet of Furosemide. The aim & objective of research work was to improve the bioavailability & half-life of Furosemide drug by using push pull method using various polymers such as Carbopol 934P & PVP k30. To study the effect of varying concentration of control release agent (polymer)in both Drug layer and Push layer. The venlafaxine Hcl is an Anti-diuretic and anti-hypertensive gives short eliminations half-life of 1-3 hr. Furosemide is absorbed from the gastrointestinal tract. It displays variable bioavailability form oral dosage from ranging from 10-90%. Metabolism of furosemide occurs mainly in the kidneys and the liver to a smaller extent. The kidneys are responsible for 85 % of total Furosemide clearance the elimination half-life up to 100min. Furosemide osmatic tablets given orally administrated gets a good first pass effect. The bioavailability is 10-90 %. The preparation of osmotic tablets was characterized for % yield, % drug content, %, bulk density, tapped density, Housner's ratio, carr's index, Angle of repose, in-vitro drug release (%CDR) for anti – diuretic activity. The FTIR shows the detect the functional group in Furosemide active drug. The UV analysis of Furosemide shows absorbance at 269 nm. In that release kinetics the korsemeyer peppas model is best fir model for prepared osmotic tablets. The results give prepared osmotic tablet enhanced drug content, bulk density, tapped density, Housner's ratio, carr's index, Angle of repose. In the optimized F4 (Carbopol 934P +drug) trial which release Furosemide 16.9±1.2 % in 1st hr. & remaining drug released upto12 hrs. which is 96.2 ±2.45%. The Osmotic Tablets were found to be stable under stability condition, which that the better drug delivery system (ODDS) & Novel drug delivery system for improved therapeutic effect of anti-diuretic as well as anti-hypertensive drug Furosemide.

KEYWORDS: Controlled Release, Furosemide, Polymers, anti-diuretic, Osmotic tablets, anti-hypertensive, In-Vitro drug release.

INTRODUCTION
The oral route for drug delivery is the most popular, desirable, and most preferred method for administrating agents therapeutically for systemic effects because it is natural, convenient, and cost-effective to the manufacturing process. The oral route is the most commonly used route for drug administration. Although the different way of administration was used for the delivery of drugs, the oral route remains the preferred mode. Even for sustained release systems, the oral route of administration has been investigated the most because of the flexibility in designing dosage forms. Present controlled release drug delivery systems are for a maximum of 12 hours' clinical effectiveness. Such systems are primarily used for drugs with short elimination half-life.

The delivery of drugs has achieved acute diseases or chronic illnesses to the patients for many years. These drug delivery systems include tablets, injectable, suspensions, creams, ointments, liquids, and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques used to get the therapeutic agents inside the human body. Conventional drug therapy require periodic doses of therapeutic agents. These agents were formulated to produce maximum stability, activity and bioavailability.

Osmotic devices are the most promising strategy based system for controlled drug delivery. They are among the most reliable controlled drug delivery system and employed as oral drug delivery systems or implantable devices. Osmosis is an aristocratic phenomenon; Osmosis exploited to develop delivery systems with every desirable property of an ideal controlled drug delivery system. The osmotic system utilizes the principles of osmotic pressure for the delivery of the

drug.

Osmosis refers to the process of movement of solvent from a lower concentration of solute towards a higher concentration of solute across a semi permeable membrane. Abbe Nollet first reported the osmotic effect in 1748, but Preffer (1877) had been a pioneer of quantitative measurement of osmotic effect. He measured the impact in 1877 by utilizing a membrane, which is selectively permeable to water but impermeable to sugar. The membrane separated the sugar solution from pure water. Pfeiffer observed water flow into the sugar solution halted when a pressure P was applied to the sugar solution. Pfeiffer postulated that the sugar solution's osmotic pressure is directly proportional to the solution concentration and absolute temperature. Van't Hoff established the analogy between the Pfeiffer results and theideal gas laws by the expression.

DRUG PROFILE

- Furosemide is an Anti-hypertensive and Anti-diuretic class.
- This drug show in Anti-hypertensive properties.
- It is a chemically 4-chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid
- Furosemide is a BCS IV gives Low solubility & Low permeability.
- It is a white powder.
- It is a practically insoluble in water, soluble in Methanol, ethanol.
- The drug is officially available in British Pharmacopoeia.

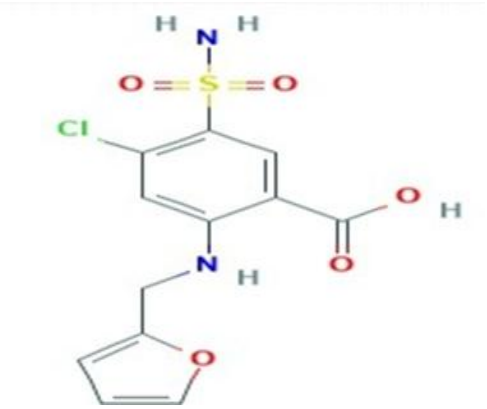

Figure 1: Chemical structure of Furosemide.

Furosemide is a potent Loop diuretic widely used for the treatment of hypertension and edema. Its short biological half-life 2-3 Hrs. and thus frequent administration (Twice or Thrice daily) makes it suitable candidate for controlled release and/or sustained release (CR/SR) preparations. Furosemide is low soluble drug (BCS class IV), so complete drug release obtains very slow.

Conventional drug delivery systems have insignificant control over the drug release and so effective concentration at the target site cannot be achieved. However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract, but drug release from osmotic drug delivery system is independent of gastric physiological factor as the release of drug from this type of system is guided by osmosis, which itself is independent of pH of environment.

Furosemide is absorbed from the gastrointestinal tract. It displays variable bioavailability form oral dosage from ranging from 10-90%. Metabolism of furosemide occurs mainly in the kidneys and the liver to a smaller extent. The kidneys are responsible for 85 % of total Furosemide clearance the elimination half-life up to 100min. M.P. of furosemide is 220℃.

Push-Pull osmotic pump is a modified multi chamber Elementary osmotic pump, which can deliver both poor water- soluble and highly water- soluble drugs at a concentrate. Side effects are muscle spasm, diarrhea, constipation, headache, dizziness.

Contraindications to furosemide use include patients with documented allergy to furosemide and patients with anuria.

Mechanism of Action

Furosemide promotes diuresis by blocking tubular reabsorption of sodium and chloride in the proximal and distal tubules as well as in the thick ascending loop of Henley. This diuretic effects achieved through the competitive inhibition of sodium-potassium-chloride transporters expressed along these tubules in the nephron, preventing the transport of Na ion from the luminal side into the baso-lateral side for reabsorption.

Furosemide exerts direct vasodilator effects which results in the therapeutic effectivenessin the treatment of acute pulmonary edema. Vasodilation leads to reduce responsiveness to vasoconstrictors, such as Angiotensin-2 and nor-adrenaline, and decreased production of endogenous natriuretic hormones with vasoconstriction properties.

Polymers used in osmotic tablet

Sr. No.	Properties	Carbopol 934P	PVP k30
1)	**Synonyms**	carboxyvinyl polymer	Povidone
2)	**Chemical name**	Carboxy polymethylene	Poly (1-vinyl-2-pyrrolidinone)
3)	**Description**	A white, fluffy, acidic, hygroscopic powder with a slight characteristic odour. Carbopol is soluble in water, alcohol, and glycerin. Agents that can neutralize carbopol include sodium hydroxide, potassium hydroxide, sodium bicarbonate, borax, amino acids, polar organic amines.	PVP is soluble in water and many organic solvents and it forms hard, transparent, glossy film. It is compatible with most inorganic salts and many resins. PVPstabilizes emulsions, dispersions and suspensions.
4)	**Applications**	Carbopols are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. In tablet formulations, Carbopols are used as dry or wet binders and as a rate controlling excipient. In wet granulation processes, water or an alcohol-water blend is used as the granulating fluid.	PVP K-30 can be used as film forming agent, viscosity-enhancement agent, lubricator and adhesive. Povidone K 30 is a new and excellent pharmaceutical excipient. It is mainly used as binder for tablet, dissolving assistant for injection, flow assistant for capsule. PVP-K30 also used as assistant in the realm of paint and coating, pigments, plastics and resin, glass fiber, inks, adhesives, detergents, films, TV tube, tabulating,rubberized, disinfector, paper, textile dying and printing

MATERIALS AND METHODS

Furosemide, Carbapol s934P, PVP, Kcl, MCC, and magnesium stearate, Talc, Distilled water

Experimental methods

Preparation of furosemide push-pull osmotic tablets

Bilayer osmotic tablets were prepared according to formulation given in Table 01. The drug layer was comprised of Furosemide (40mg), Carbopol 934 P, Kcl, MCC, and magnesium stearate. All the ingredients weighed accurately and shifted through 60# then mixed properly. The push layer comprises of Carbopol934P, MCC, Kcl, Magnesium stearate, Talc. All the ingredients weighed accurately and shifted through 60# then mixed properly. Bilayer standard tablets having 10 mm diameter and 6-7 kg/cm^2 hardness were prepared. Prepared tablets were evaluated for various parameters.

Preparation of Furosemide push- pull osmotic tablets

Bilayer osmotic tablets were prepared according to formulation given in Table The drug layer was comprised of Furosemide (40mg), Carbopol-934p, kcl, PVP and magnesium stearate. All the ingredients weighed accurately and shifted through 60# then mixed properly. Then mix powder was blended and granulated with IPA in a mortal pastle. The wet mass was forced through 16 # and the granules so obtained were dried at room temperature for 2 hr. Dried granules were passed through 20 # and the fines were separated using 40 # to obtain 20-40 # granules. These granules were lubricated with mixture of talc and magnesium stearate. The push layer comprise of carbopol, MCC, kcl, Magnesium stearate. All the ingredients weighed accurately and shifted through 16 # then mixed properly. Bilayer standard tablets having 10 mm diameter and 6-7 kg/cm^2 hardness were prepared. Prepared tablets were evaluated for various parameters.

Coating of tablets

A 5% w/v solution of Ethyl Cellulose was used as a semipermeable membrane provider. Dibutyl phthalate was used as a plasticizer. All weighed tablets put in Beaker. Dip the tablets in that beaker containing coating solution and emove carefully. After coating tablets were drilled and in vitro release study of tablets was tested for 12 hours by using 7.4 phosphate buffe.

Table 1: Preparation of Furosemide push pull osmotically controlled release tablets *Drug Layer(400mg).*

Ingredient	F1	F2	F3	F4
Drug	10%	10%	10%	10%
PVP-K-30	10%	15%	20%	25%
Carbopol 934p	30%	25%	20%	15%
MCC	45%	45%	45%	45%
Magnesiumstearate	3%	3%	3%	3%
Talc	2%	2%	2%	2%
Methanol	q.s	q.s	q.s	q.s

Push layer(250mg)

Ingredients	F1	F2	F3	F4
PVP-K-30	10%	15%	20%	25%
Kcl	25%	25%	25%	25%
Carbapol934p	30%	25%	20%	15%
Ferric oxide	0.2%	0.2%	0.2%	0.2%
MCC	28.8%	28.8%	28.8%	28.8%
Magnesiumstearate	3%	3%	3%	3%
Talc	3%	3%	3%	3%
Methanol	q.s	q.s	q.s	q.s

Table 2: Coating composition.

Sr.No.	Ingredients	Quantity
1)	Ethyl cellulose : DibutylPhthalate	(9:1w\w)(polymer:Plasticizer)
2)	Methanol : Purified water	(9:1w\w)(polymer:Plasticizer)

EVALUTION STUDIES

Solubility study

It was important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in drugs.

Analytical methods

Determination of λ max

The absorption maximum of the standard solution was scanned between 200- 400 nm regions on Jasco V-630 UV-Visible spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

To identify the λmax of furosemide 10 mg of the pure drug was accurately weighed and dissolved in 10ml methanol and the volume was made up to 10 ml with methanol to give a standard stock solution of 1000 µg/ml. Further 1000ppm withdrawn 2.5ml of Aliquote diluted to 25 ml of volumetric flask and prepare 100 ppm and Suitable dilutions were made with distilled water to get standard solutions of concentration: 5,10,15,20,25 µg/ml.

Identification by FTIR spectroscopy

Furosemide discs were prepared by pressing the Furosemide with potassium bromide and the spectra between 4000^{-1} to 500^{-1} cm was obtained under the operational conditions. The absorption spectra obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

Identification by melting point

Melting point of the drug was obtained by the melting the drug in melting point apparatus.

Determination of bulk density and tapped density

An accurately weighed quantity of the powder was carefully poured into the graduated cylinder and the volume was measured then the graduated cylinder was closed with lid, set into the density determination apparatus (Bulk density apparatus, Electro lab, Mumbai). The density apparatus was set for 500 taps and after that, the volume was measured and continued operations till the two consecutive readings were equal. The bulk density and tapped density were calculated using the following formulas.

$$\text{Bulk density} = \frac{\text{Mass of microspheres}}{\text{Initial volume of microspheres}}$$

Determination of tapped density

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Final volume of microspheres after tapping}}$$

Compressibility index (Carr's Index) & Hausner Ratio

The Compressibility index and Hausner's ratio are measures for the property of a powder to be compressed.In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, they are frequently greater inter particular interaction. A greater difference between the bulk and tapped densities will be observed. These differences are directly related to the compressibility index and the Hausner Ratio. The compressibility index and Hausner ratio may be calculated using measured values for bulk density and tapped density as follows.

$$\text{Compressibility Index} = \frac{Vt - Vb}{Vt} \times 100$$

$$\text{Hausner's ratio} = \frac{Vt}{Vb}$$

Table 3: acceptance criteria of flow properties.

Sr. No.	Flow Properties	Angle of Repose (θ)	Comp. Index(%)	Hausner ratio
1.	Excellent	25-30	<10	1.00-1.11
2.	Good	31-35	11-15	1.12-1.18
3.	Fair	36-40	16-20	1.19-1.25
4.	Passable	41-45	21-25	1.26-1.34
5.	Poor	46-55	26-31	1.35-1.45

Angle of repose

The flow properties of the drug are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces of the drug are determined by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder andthe horizontal plane.

$\tan \theta = h/r$

$\theta = \tan^{-1} h/r$

Where,

H = height of pile

R = radius of the base pile

θ = angle of repose

Percentage yield.

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula.

$$\text{Percentage yield} = \frac{\textit{Practical yield of microspheres}}{\textit{Theratical yield of microspheres}} \times 100$$

Drug content estimation

The Furosemide tablets were tested for their drug content. Five tablets were finely powdered; quantities of the powder equivalent to 10 mg of Furosemide were accurately weighed and transferred to a 100-ml of volumetric flask. The flask was filled with Phosphate buffer (pH 7.4) solution and mixed thoroughly. The solution was made up to volume and filtered. Dilute 10 ml of the resulting solution to 200 ml with Phosphate buffer (pH 7.4) and measure the absorbance of the resulting solution at the maximum at 276 nm using a JASCO UV/Vis double beam spectrophotometer. The linearity equation obtained from calibration curve as described previously was use for estimation of Furosemide in the tablet formulations values are shown.

In-vitro drug release study

In vitro drug release studies of the prepared matrix tablets were conducted for a period of12 hours using an eight station USP XXII type 2 apparatus (ELECTROLAB, India) at 37±0.5^{0}C the paddle speed was 100 ± 1 rpm. The dissolution medium used in each flask was 900 ml of buffer media pH – 7.4 at different intervals, 10 ml of samples were withdrawn and filter through a whatman filter paper. The equivalent volume of the medium was added to the dissolution vessel. After filtration and appropriate dilution, the sample solutions were analyzed at 276 nm by using double beam U.V-visible spectrophotometer (SHIMADZU-1700) and dissolution medium as blank. Experiments were performed in triplicates. The amount of drug present in the samples was calculated with the help of calibration curve constructed from reference standard. Dissolution data of prepared tablets are reported in fallowing table.

Mechanism of drug release.

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained and was plotted as

- To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained w Cumulative percentage drug released Vs Time (*In-vitro* drug release plots).
- Cumulative percentage drug released Vs Square root of time (Higuchi's plots).
- Log cumulative percentage drug remaining Vs Time (First order plots).
- Log percentage drug released Vs Log time (Peppas plots).

First order model

This model has also been used to describe absorption and/or elimination of some drugs, the release of the drug which followed first order kinetics can be expressed by the equation.

$\log C = \log C_0 - Kt / 2.303$

Where, C_0 is the initial concentration of drug,

The data obtained are plotted as log cumulative percentage of drug remaining *vs.* time which would yield a straight line with a slope of -K/2.303.

Higuchi release model

To Study Higuchi release kinetics, the release rate data was fitted to the following equation.

$F = KH.t1/2$

Where, F = Amt. of drug release

KH = release rate constant,

T = Time release

When the data is plotted as a cumulative percentage drug release vs. square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

Korsmeyer and Peppas release model

The release rate data was obtained by the following equation,

$Mt/M\infty = KM.t^n$

Where, $Mt/M\infty$= the fraction of drug release,

KM = release constant,

t= release time

n = diffusional exponent for the drug release that dependent on the shape of the matrix dosage form. When the data is plotted as log percentage release vs. log time, yields as straight line with a slop equal to 'n' and 'K' can be obtained form Y – intercept. For Non- Fickian release the 'n' values falls between 0.5 and 1.5 while for Fickian (case I) diffusion n= 0.5 and Zero order release (case II) n=1.0

Zero order release rate kinetics.

To studies the zero-order release kinetics the release rate is fitted to the following equation.

F= K0t

Where, F = Fraction of drug release

K0 = release rate constant

t = release time

When the data is plotted as cumulative percentage drug release vs. time., if the plot is linear then the rateobeys Zero-order release kinetics, with a slope equal to K0.

Stability Study

Stability tests are much simpler and needed less frequently for coarse dispersion, where particle sizes and phase changes must be followed. To overcome the problem of metastable formation which are not thermodynamically stable and takes long time to separate, thermodynamic stability test is recommended. Stability was carried out as per ICH guidelines.

Table 4: stability conditions.

Study Condition Specification	Time periods
$40^0C \pm 2^0C/75\% \pm 5\%$ RH	30 Days
$40^0C \pm 2^0C/75\% \pm 5\%$ RH	60 Days
$40^0C \pm 2^0C/75\% \pm 5\%$ RH	90 Days

Types of stability studies

1. The results provide an estimate of the kinetic parameters for the rate of reactions.
2. The results can be used to characterize the relationship between degradation and storage condition.
3. The results supply critical information in the design and analysis of long-term stability studies under ambient conditions at the planning stage.
4. Long–term studies, which include both pre-approval and post-approval stability studies, are usually conducted under ambient condition.
5. A pre-approval stability study is also known as NDA stability study, the purpose of it is to determine (estimate) a drug expiration dating applicable to all future batches.
6. A post approval stability study is usually referred to as a marketing stability study; the purpose of itis to make sure that the drug product currently on market can meet the USP/NF specifications up to the end of expiration dating period.

The procedure was divided into two parts,

Part I

Achieving of 60% RH

26.66 gm of sodium hydroxide was weighed and dissolved in 100 ml of distilled water to get 26.66% sodium hydroxide solution. The solution was placed in the desiccator over which a wire mesh was placed, over which the dosage form was placed and the desiccator was sealed. The desiccator was placed in the oven maintained at 25^0C to create the Relative Humidity OF 60%.

Achieving of 75% RH

Saturated solution of sodium chloride was prepared and placed in the desiccators over which a wire mesh was placed, over which the dosage form was placed and the desiccator was sealed. The desiccator was kept in oven maintained at 40^0C to create the relative humidity of 75%.

Part II

The sealed formulation was placed in amber colored bottles, tightly plugged with cotton and capped. They were then stored at 25^0C /60% RH and 40^0C / 75% RH for two months and evaluated for their physical appearance and drug content

RESULT AND DISCUSSION

Analysis of Drug

1. **Description:** white powder.
2. **Solubility of drug:** poorly soluble in water and highly soluble in methanol
3. **Melting Point:** melting point of furosemide was determined by capillary tube method and it was found to be218℃.

Determination of λ max in Methanol

The absorption maximum for Venlafaxine Hydrochloride in 0. Methanol was found to be 269 mand absorption maximum was shown in Figure 2.

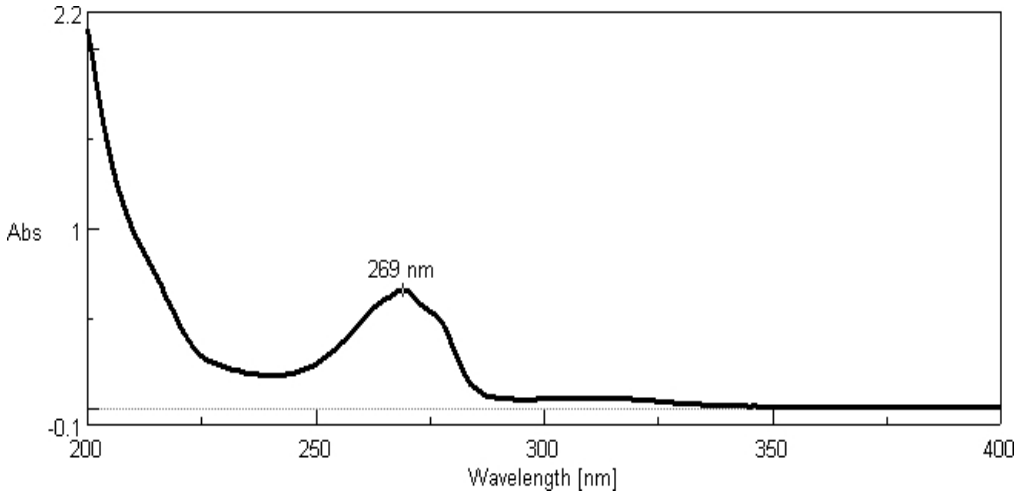

Figure 2: calibration curve of Furosemide in Methanol.

Preparation of standard graph of Venlafaxine Hydrochloride in 0.1N NaOH

Absorbance was obtained in various concentrations of Furosemide in methanol were given in Table 4 and shown in Figure 3. The graph of absorbance vs. concentration for Furosemide was found to be linear in the concentration range of 2-10 µg /ml. The calibration curve parameters shown in Table 5. So the drug obeys Beer- Lambert's law in the range of 2-10 µg/ml.

Table 4: Spectrophotometric Data of concentration and absorbance for Furosemide in methanol

S. No	Concentration(µg/ml)	Absorbance
1	0	0.000
2	2	0.1892
3	4	0.3023
4	6	0.4293
5	8	0.5730
6	10	0.7266

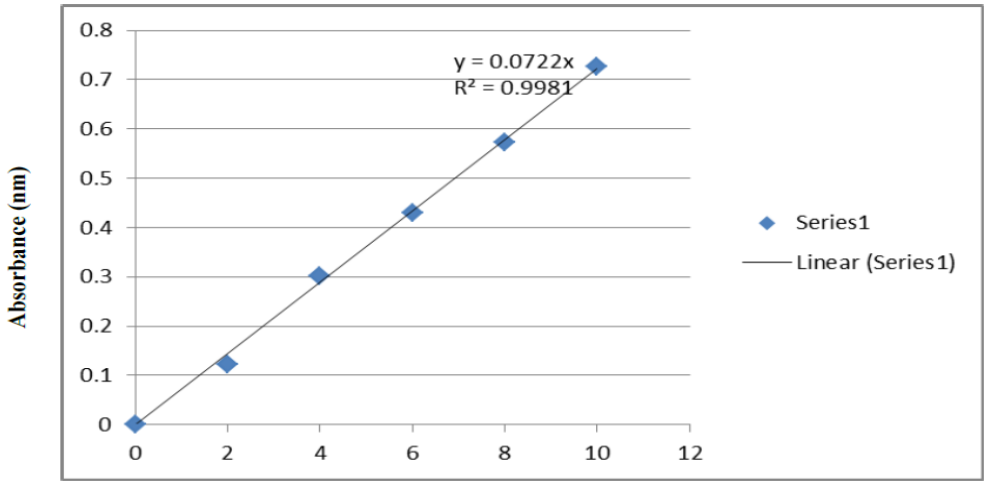

Figure 3: Standard graph of Furosemide in methanol.

Table 5: Data for calibration curve Parameters for Furosemide in methanol

S. No	Parameters	Values
1	Absorbance maximum(ƛmax) nm	269 nm
2	Correlation coefficient (r)	0.9981
3	Slope (m)	0.0722
4	Intercept (c)	0.1104
5	Regression equation	y = 0.0722x+0.110

Identification by FTIR spectroscopy

The FTIR spectrum of Furosemide was showed in Figure 4.

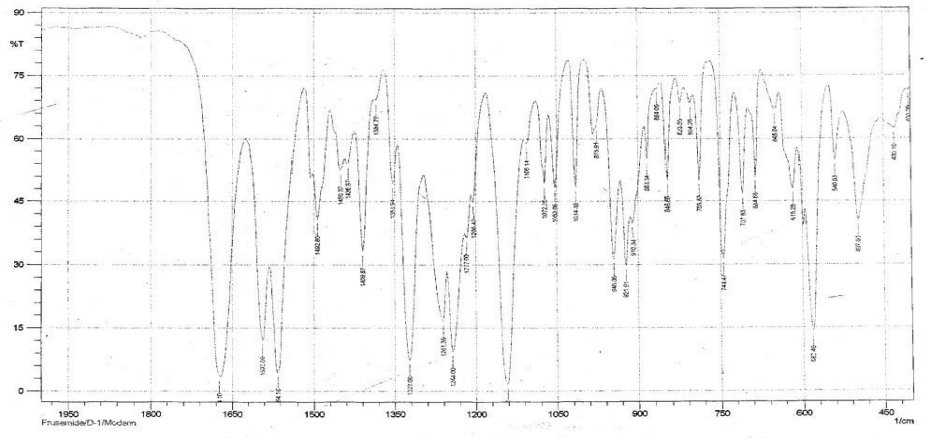

Fig. 4: FTIR spectrum of Furosemide.

Melting point

Melting point values of Furosemide sample was found to be range 206 ºC. The reported melting point for Venlafaxine Hydrochloride was 206 ºC. Hence, experimental values were in good agreement with official values.

Table 06: Values of pre- compressive parameters of push layer.

Sr. No.	Formulationn code	Bulk Density	Tapped Density	Carr' Index	Hausner ratio	Angle of repose
1	F1	0.35±0.01	0.40±0.02	6.23	1.16	27º92'±0.31
2	F2	0.32±0.05	0.42±0.02	15.65	1.34	27º67'±0.62
3	F3	0.38±0.019	0.43±0.05	12.06	1.07	31º03'±0.37
4	F4	0.37±0.015	0.43±0.02	15.42	1.05	30º51'±0.52

Evaluation of Tablets

The tablet formulations were subject to various post-compressive evaluation tests, such as drug content, hardness, friability and weight variation. The results for all the formulations were shown in table.

Weight variation test

It was carried out as per official method and the average percentage deviation of all the formulation was found to be withinthe limit (as per Pharmacopoeial standard).

Content uniformity

was also carried out as per official method and it was found that all batches show good content uniformity. The values for all the formulations were in the ranges from 93.22 to 98.44%.

Hardness test states that all the formulations were found in the range 7 to 8 kg/cm^2**.**

Friability test: Another measure of tablet hardness was the friability. Compressed tablets that lose less than **1 %** of their weight are generally considered acceptable.

Table 07: Physical characteristics of prepared push pull tablets (n=3)

Formulationcode	Hardness(Kg/cm^2)	Weight variation	Friability(%)	Drug content(%)
F1	7.4	648± 2.149	0.55	97.68
F2	7.3	649 ±1.176	0.69	93.96
F3	7.3	648 ±2.149	0.53	96.98
F4	7.3	647± 3.521	0.61	98.44

In-vitro Dissolution Studies

In-vitro drug released profiles of Furosemide osmotic tablets were performed in each formulation using phosphate buffer (pH 7.4) up to 12 hours. It was represented in Table 8 and showed in Figure 6.

Table 08: *In-vitro* drug released profiles of Furosemide osmotic tablets

Time (hr.)	F1	F2	F3	F4
1	19.36±1.06	20.54±1.2	7.051±1.45	26.21±1.2
2	28.6±1.45	36.02±1.1	16.34±1.3	35.68±1.13
3	35.37±1.41	45.41±1.3	21.68±1.5	39.40±1.9
4	41.57±1.23	53.54±1.2	25.65±1.87	44.12±1.0
5	47.20±1.1	59.45±1.06	32.30±1.4	46.93±1.6
6	53.40±1.4	63.30±1.5	48.21±1.8	63.05±1.0
7	56.64±1.5	68.5±1.1	53.22±0.67	72.12±1.0
8	63.52±1.1	73.2±1.4	61.44±1.43	79.03±0.7
9	68.23±1.7	79.52±1.2	68.14±1.6	84.12±1.1
10	76.30±1.8	75.13±1.1	77.1±1.7	90.04±1.6
11	82.20±0.95	83.60±1.43	86.77±1.14	93.06±1.3
12	86.34±1.94	88.37±2.03	91.26±1.4	95.28±2.45

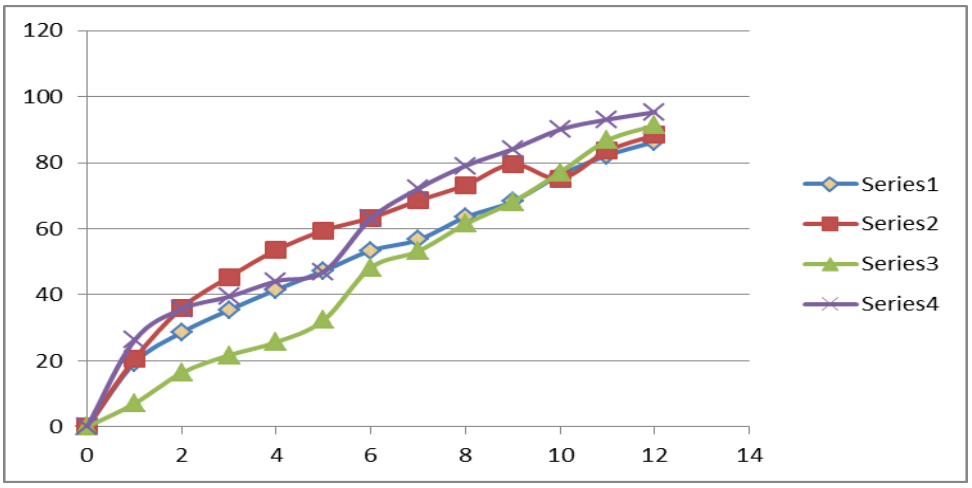

Fig. 6: Std. graph of in-vitro drug release of formulations (F1-F4).

Release Kinetics of In-vitro Drug Release

The kinetics of *in-vitro* drug released was determined by applying the drug release data to various kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas. The results obtained were represented in Table 9. and shown in Figures 7 to 11.

Table 9: Release kinetics of *in-vitro* drug release.

Formulationcode	Zeroorder R^2	First order R^2	Higuchi R^2	Peppas		Best model
				R^2	n	
F1	0.9621	0.9501	0.9723	0.9908	0.432	Peppas
F2	0.9650	0.9705	0.9663	0.9909	0.456	Peppas
F3	0.9503	0.8439	0.9782	0.9908	0.485	Peppas
F4	0.9900	0.9471	0.9530	0.9985	0.402	Peppas

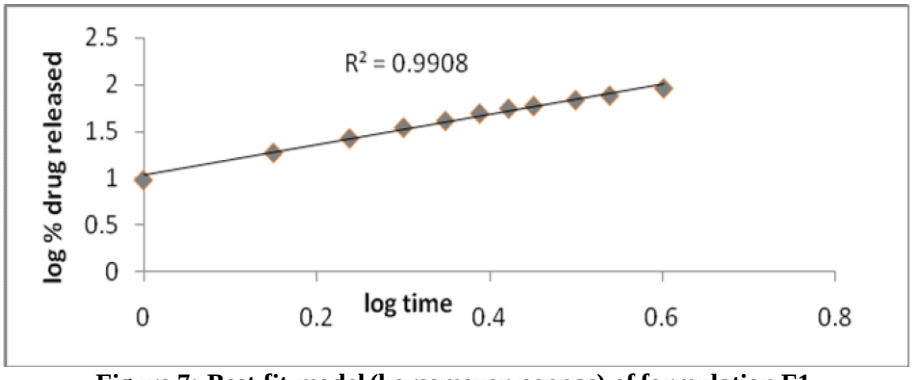

Figure 7: Best fit model (korsemeyer peppas) of formulation F1.

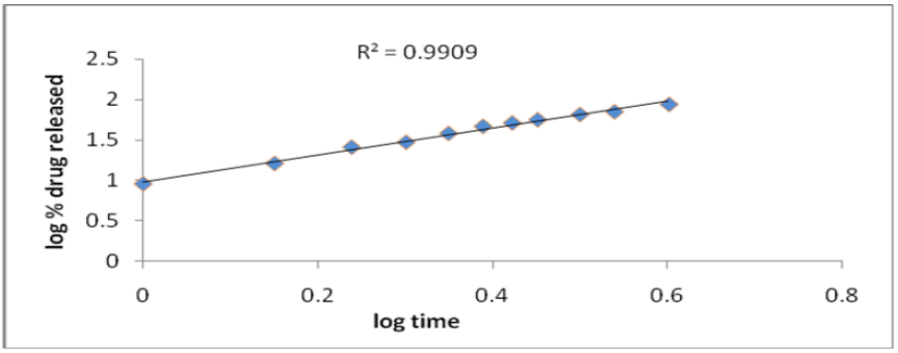

Figure 8: Best fit model (korsemeyer peppas) of formulation F2.

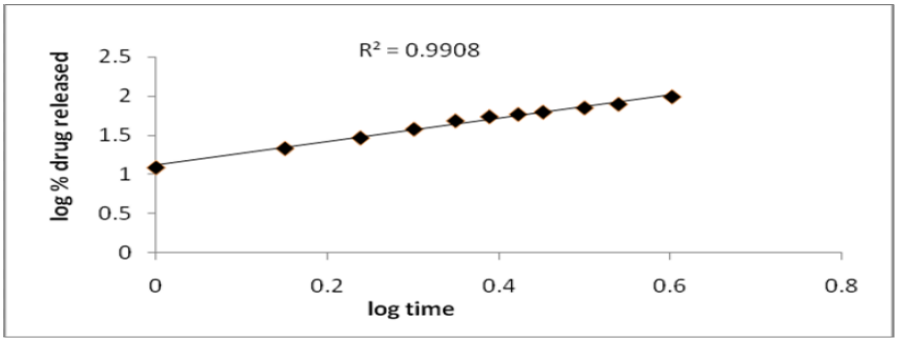

Figure 9: Best fit model (korsemeyer peppas) of formulation F3.

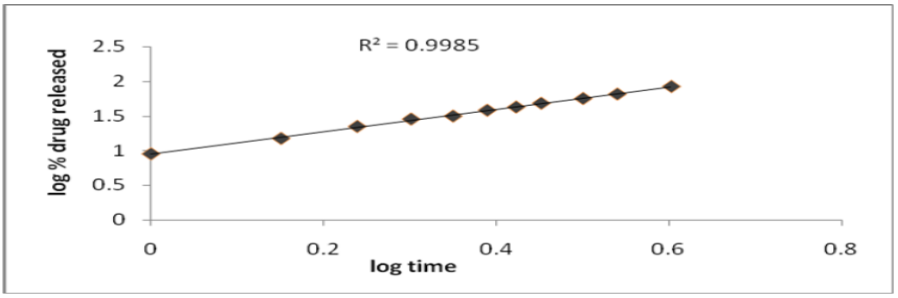

Figure 10: Best fit model (korsemeyer peppas) of formulation F4.

DISCUSSION

Physical characteristics of prepared bilayer push pull tablets.

Prepared bilayer push pulls tablets of Furosemide of all the formulations (F1 to F4) were circular in shape. All the formulations were evaluated for hardness, friability, weight variation and drug content. As summarized in Table, the drug content for all formulations ranged from 93.22 to 98.44% that is within the IP limit. For all formulations, % friability was less than1% and sufficient hardness ranging from.7.0 to 8.0 Kg/cm^2. The values of Compressibility indices were between 5.35 to 10.90% indicate excellent flow property. Tablets were evaluated for weight variation, thickness and diameter and the values were found to be within BP limits.

CONCLUSION

- Extended release formulations of Furosemide were developed based on push-pullosmotic technology.
- Furosemide sustained release osmotic bilayer tablet were formulated by using various polymer such as carbapol and PVPK-3
- The manufacturing procedure was standardized
- Sustain release osmotic bilayer tablet of furosemide was successfully prepared by wetgranulation method and conformed that it was a best method for preparing granules for osmotic bilayer tablet.
- The identification of drug was carried out by FTIR spectroscopy and melting point. The physicochemical parameter such as appearance solubility study were performed by suitable method. The analytical profile of drug was evaluated for determination of absorption maximum, developed standard graph.
- *In-vitro* drug dissolutions study was performed on type II dissolution apparatus and due to drug release was found to be 86-95 %.

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