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RESEARCH ARTICLE

FORMULATION AND EVALUTION OF CONTROLLED RELEASE FRUSEMIDE TABLETS BY BILAYER TECHNOLOGY

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ABSTRACT

The present research was focused to enhance bioavailability and reduce short half-life Problem. Frusemide is a loop diuretic used in the treatment of congestive heart failure edema and hypertension .It has low bioavailability problem and short half-life 1to 1.7 hours and profound diuresis. To overcome this drawback frusemide bilayer tablets were prepared. It consists of loading layer and controlled release layer. Crospovidone and sodium dodecyl sulphate were used for loading dose. Eudragit RL100 was used for controlled release layer. Tablets were evaluated for physicochemical properties such as hardness, friability, thickness, weight variation and drug content uniformity. FT-IR studies revealed that there was no interaction between drug and polymers used in the study. In-vitro dissolution studies were carried out in USP type II paddle type apparatus. F5 formulation showed no significant changes on stability studies when storing at 4ºc, 40°c/75%RH, 60°c/80%RH for 3 months. The drug release from F5 formulation was found to zero order kinetics. It was also found linear in Higuchi's plot which confirms that diffusion is one of the mechanisms of drug release. In this investigation optimized formulation releases the drug up to 24 hours and it also fulfilled requirements such as easy to fabricate, inexpensive and high patient compliance.

Keywords: Frusemide, eudragit RL100, bilayer , sodium dodecyl sulphate controlled release layer.

INTRODUCTION:

Diuretics are generally divided into four major classes which are distinguished by the site at which they impair sodium reabsorption [(1)]. Frusemide is a loop diuretic inhibit water reabsorption in the nephron by blocking the sodium potassium chloride in thick ascending limb of loop of Henle[(2)]. It is labeled in class IV Bio pharmaceutics classification system because of its low water solubility and low permeability [(3)]. Frusemide (4-chloro-2-furfuryl amino 5-sulphonyl benzoic acid) is a potent diuretic to profound diuresis with electrolytic in excess amount can lead water depletion. Frusemide is preferentially adsorbed in the stomach and upper intestine sites it has lowest solubility because of its weekly acidic in nature [(4)]. It is used in the treatment of edema of pulmonary, cardiac or hepatic origin as well as in the treatment of hypertension [(5)]. It has short half-life 1 to 1.7 hours. Hence the present study was aimed to prepare and evaluate bilayer frusemide in order to overcome bioavailability related problems, dose dependent side effects,frequency of administration and

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delayed onset of action. The physiochemical properties, such as its low half-life, molecular weight (330 mg/mol) and its profound diuresis is accelerated to make the bilayer. Eudragit RL is one of controlled release polymer which gives the release up to 24 hours. Metha acrylate co polymers in the trimethyl ammonium ethyl methacrylate as a functional group in Eudragit. Eudragit RL 100 is insoluble, high permeability, PH independent, swelling. It provides time controlled release [6]. The dose related adverse effects have been observed and the treatment with conventional tablets produce short period of maximum diuresis which is inconvenient to the patient. But this bilayer tablet produces same diuretic effect as produced by conventional and eliminate intense diuresis which is well tolerated to patients [7].

MATERIALS

Frusemide is obtained as a gift sample from Arbro pharmaceuticals, Newdelhi. Sodium dodecyl Sulphate was procured from Himedia, Eudragit RL 100 was obtained from Matrix pharmaceuticals, Mumbai. Talc, Magnesium stearate was obtained from Sun pharma, Chennai. Starch was furnished from swastika pharmaceuticals; Crospovidone was furnished from tablets India, Chennai.

PREFORMULATION STUDIES

The parameters like identification of pure drug frusemide by IR spectra (fig1), drug excipients compatablity studies, angle of repose , bulk density, tapped density, Hausner ratio, carr´s index [8,9], and loss on drying were evaluated.

COMPATIBILITY STUDY

Frusemide granules with various excipients in glass vials were taken and kept at various accelerated condition (30ºc/65ºc RH, 40ºc/75ºc RH, 60ºc/80ºc RH) in stability chamber, (osworld stability chamber, India) for three months in open and closed condition. The sample were withdrawn on 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 14th, 21st and 30th days and physical characterstics like colour change if any was recorded. Finally the mixtures with no colour changes were selected for formulations [10].

PREPARATION AND CHARACTERIZATION OF BILAYER TABLETS

The bilayer of frusemide was prepared by direct compression method. The drug and polymers for both fast release and controlled layers were passed through a 180µm sieve before their use in the formulation.

FORMULATION OF FAST RELEASE LAYER [11]

16mg of drug for fast release layer and 34mg drug for controlled release were calculated as per modified release tablets limit given in U.S.P [12]. The fast release granules were prepared by blending drug with crospovidone and sodium dodecoyl sulphate given in table I. The granules were mixed with talc and magnesium stearate.

FORMULATION OF THE CONTROLLED RELEASE LAYER [13]

Controlled release granules were also formulated by direct compression technique by mixing frusemide uniformly with Eudragit RL100 and lactose. It was given in table 2. The controlling granules were also, subjected to similar processing steps on the fast releasing granules.

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CHARACTERIZATION OF GRANULES

Prior to compression, granules were evaluated for their characterestic parameter such as tapped density, Carr´s index and angle of repose. Compressibility index was calculated from the bulk and tapped density using a digital tap density apparatus (Electrolab India).

COMPRESSION OF BILAYER TABLET [14]

The quantity of granules for the controlled release layer was compressed lightly using a single punch machine (Cadmach machinery Co., Pvt., Ltd) equipped with 8mm round flat and plain punches. Over this compressed layer the required quantity of the fast release layer was placed and compressed to obtain hardness in the range of 6-7 kg/cm^2 to form a bilayer matrix.

PHYSICAL TEST FOR BILAYER TABLETS

Standard physical test for the bilayer matrix tablets were performed and average values were tablets calculated. Mass variation was determined by weighing 20 tablets individually. Hardness was determined by taking 6 tablets from each formulation using a Monsanto hardness tester (Royal scientific Pvt., Ltd, and Chennai). The values were given in table 3.

DRUG CONTENT UNIFORMITY

Ten tablets were finely powdered and an amount equivalent to 100mg weighed and transferred to 100ml volumetric flask and sufficient 0.1M sodium hydroxide was added. The flask was shaked for 10 min. Finally the volume was made up to mark with sodium hydroxide. Then it was analyzed in UV spectrophotometer. (Elico Ind, Ltd.,India) at 271nm [15].

DISSOLUTION TEST

Invitro drug release was performed using dissolution apparatus USP type II paddle method (TDT-08L, Elector lab, India.) with a stirring speed of 50 rev/min at 37ºc±0.5 in Hydrochloric acid for 2 hours and 900ml of 7.5phosphate buffer for 24 hours. The samples were taken at pre-selected time intervals with replacement of equal volume of dissolution media the collected samples were diluted and the absorbance was measured spectrophotometerically at 271nm. (UV- visible spectrophotometer 1601, Shimadzu Corporation, Japan) (USP, 2006) [16].

STABLITY STUDIES

The tablets were packed and kept for 3 months at 4ºc in refrigerator, 40ºc/75% RH in a stability chamber (Oswald, Mumbai) 60ºc/80% in incubator. At the interval of 15 days tablets were withdrawn and evaluated for physical properties like thickness, hardness, diameter, friability, weight variation and content uniformity, *Invitro* drug release and assay were also carried out [17].

MECHANISM OF DRUG RELEASE

Korsemeyer desired a simple relationship which described drug release from a polymeric system equation to find out the mechanism of drug release, The drug release data was fitted in korsemeyer –peppas model.

$$Mty/M\alpha = Kt$$

Mt/Mα is the fraction of drug released at time‘t’, K is the rate constant and n is the release exponent [18]

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RESULT AND DISCUSSION

The prepared bilayer tablets were evaluated for various physical properties .The bulk density for the granules of various formulation ranged between 0.8±0.15 and 2.42±0.42gm/ L as determined by the tap method. This value of bulk density indicates of good packing character. The compressibility index of all formulation was found to be below 15% indicates desirable flow property. The flow properties of granules were further analysed by determining angle of repose for all granules. It ranged between 22.5±0.3 to 25.03±0.2. The value indicates good flow property of granules with Eudragit RL100. Average weight 200±0.3, hardness 7.0kg/cm^2 ±0.5. The percentage friability of all formulation was 0.7±0.2%. It indicates good handling properties of bilayer tablets.The drug content uniformity in bilayer was 98.5%±0.14.

FT-IR spectrum of frusemide bilayer controlled release tablets revealed there is no major interaction between drug and polymers.The release of frusemide from fast release layer was analysed by plotting the cumulative percentage drug release Vs time .It shows an initial burst effect 30% of frusemide is released within 2 hours of dissolution study was showed (fig.3).

Eudragit RL100 has been used as the release retardant polymer in controlled release dosage forms. Eudragit reduced the drug release due to reduction in the penetration of solvent molecule into the system. The rate of release is controlled by the permeability of matrix structure. Formulation of bilayer tablet containing drug: polymer ratio 1%, 2%, 3%,4% showed that it could not control the release beyond 15 hours.

5% showed the desire release profile over the test period for 24 hours.In this selected formulation the calculated regression coefficient for Higuchi, peppa's models were 0.992, 0.965 respectively. Therefore the release seems to fit the higuchi model was showed in (fig.4). Higuchi's, peppa's plot (fig4, fig.5) states that release followed the diffusion controlled mechanism.

TABLE1
COMPOSISTION OF FAST RELEASE LAYER.

Composition	**Fast release layer**
Frusemide	12mg
Crospovidone	4mg
Sodium dodecyl sulphate	4mg
Starch	78mg
Talc	1mg
Magnesium stearate	1mg

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TABLE II
COMPOSITION OF CONTROLLED RELEASE LAYER.

Composition	DRUG: EUDRAGIT RL 100 RATIO				
	(F1) 1%	(F2) 2%	(F3) 3%	(F4) 4%	(F5) 5%
Frusemide	38 mg	38mg	38mg	38mg	38mg
Eudragit RL 100	4mg	8mg	12mg	16mg	20mg
Lactose	56 mg	52mg	48mg	44mg	40mg
Talc	1mg	1mg	1mg	1mg	1mg
Magnesium stearate	1mg	1mg	1mg	1mg	1mg

TABLE III
PHYSICO-CHEMICAL PARAMETERS OF OPTIMIZED FRUSEMIDE TABLETS

Optimized formulation	Thickness (mm)±S.D	Weight variation (mg)±S.D	Friability (%)±S.D	Hardness (kg/cm^2)±S.D	Drug content (%)±S.D
F5	8.0±0.02	200±0.3	0.7±0.2	7±0.5	98.5±0.14

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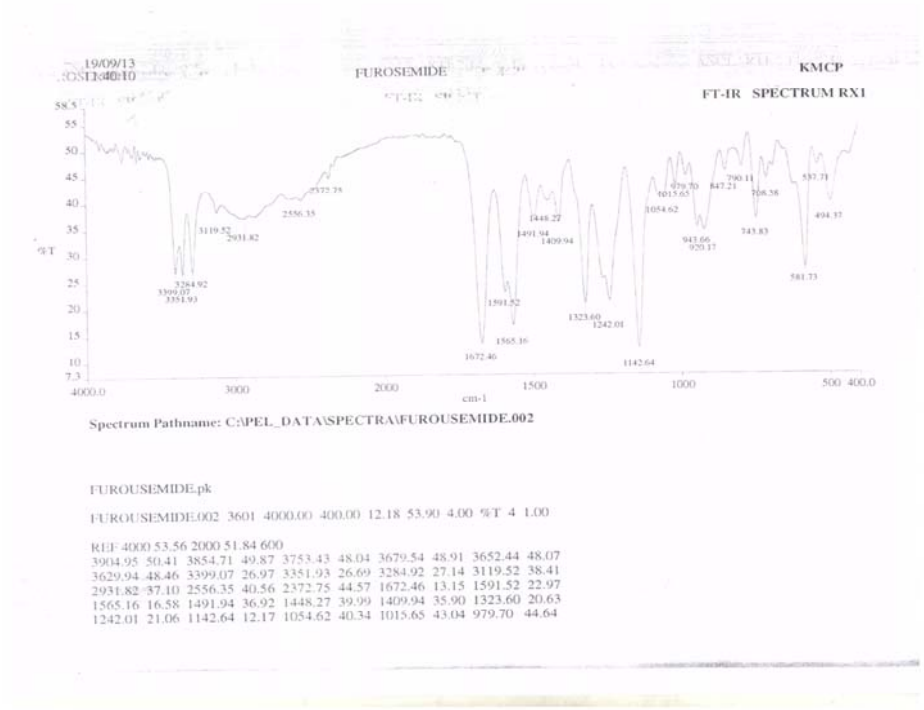
Figure.1



Controlled Release IR

Figure.2

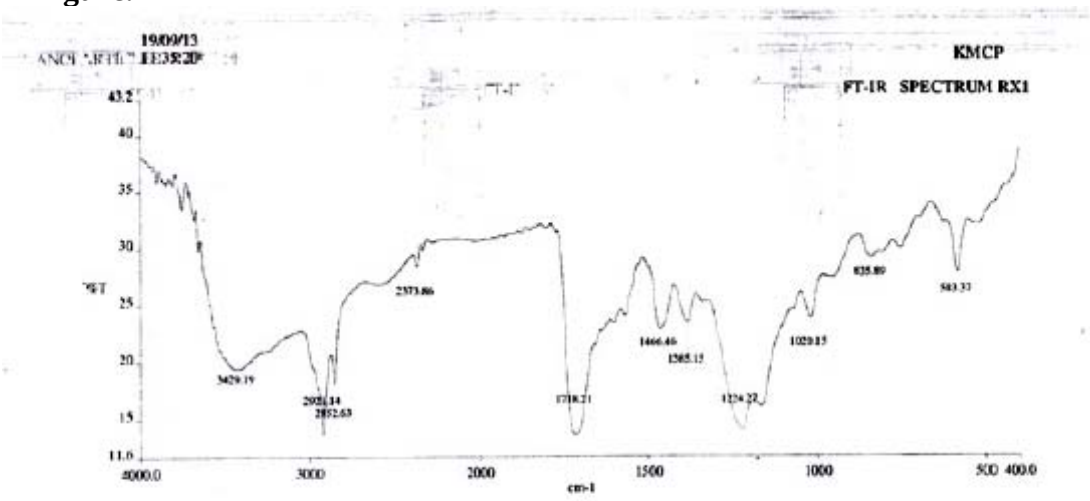


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Figure.3

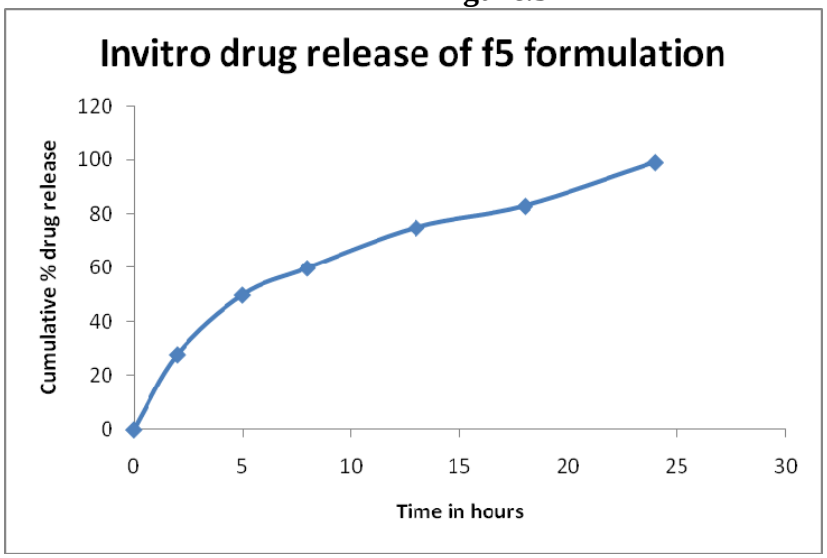


Figure.4

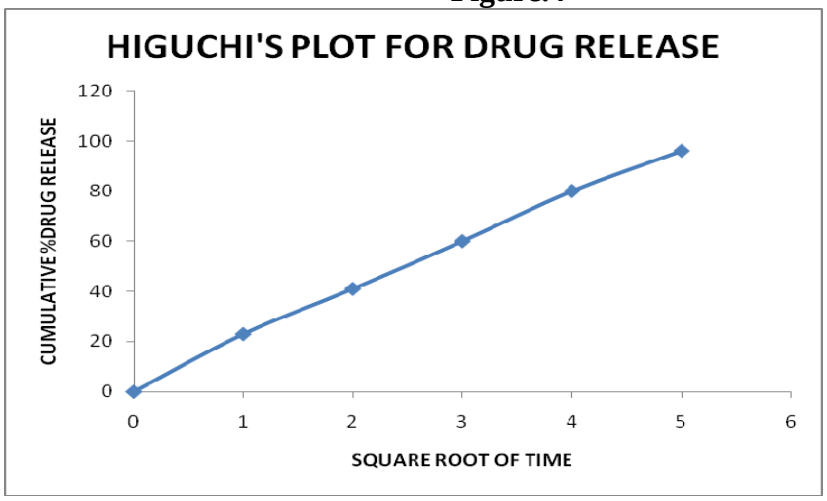
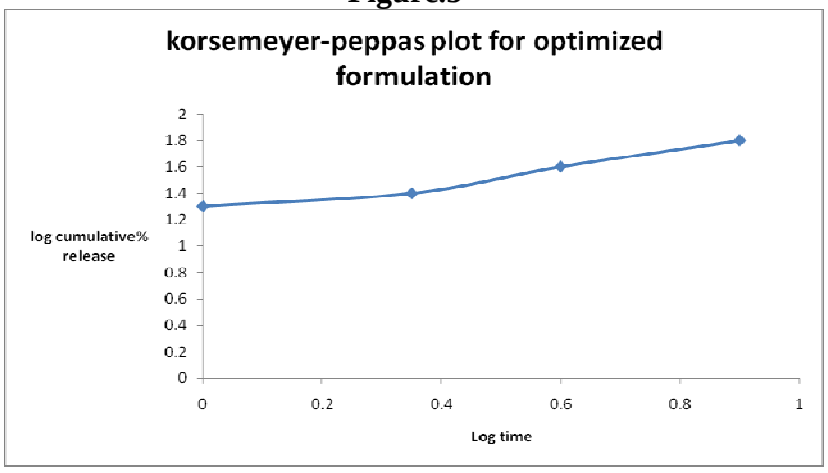


Figure.5



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CONCLUSION

In this research frusemide bilayer tablets were prepared with modified release by direct compression method. So this method is given maximum benefit for manufactures. All evaluation tests values for optimized formulation also have been claimed the standard limits. By implementing bilayer concept frusemide´s short half-life, profound dieresis, bioavailability problems and frequency of dosage have been rectified. So loading layer and controlled release layer have provided quick onset of action and prolonged action. This present research will be benefitted for patients and it will be concentrated for further bioequivalence studies in future.

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