"PREPARATION OF SOLID DISPERSION OF POORLY WATER SOLUBLE DRUG FORMULATION AND CONSIDERATION"

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ABSTRACT

This article investigates enhancement of the dissolution profile of furosemide using solid dispersion (SD) with eudragit(RLPO & RSPO) & also control it's by using solvent evaporation technique. 1: 0.5(w/w) 1:1(w/w) ,1:1.5 solid dispersions were prepared by solvent evaporation technique using solvent water and methanol in 1:1 ratio. Dissolution studies using the USP paddle method were performed for solid dispersions of furosemide at 37 ± 0.5 C and 55 rpm in simulated gastric fluid (SGF) of pH 1.2. Fourier transformer infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and x-ray diffractometry (XRD) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Tablets were formulated containing solid dispersion products and compared with pure drug . IR spectroscopy, XRD, and DSC showed change in the crystal structure towards amorphous one of furosemide (FRMD). Dissolution of furosemide improved and release is controlled significantly in solid dispersion with the ratio 1:1.5 of eudragit RLPO & RSPO . Tablets containing solid dispersion exhibited better dissolution profile than pure drug. Thus, the solid dispersion technique can be successfully used for improvement of dissolution of furosemide as well as control it's release.

KEY WORDS Solid dispersion, furosemide, eudragit, dissolution enhancement, control release tablet.

INTRODUCTION :

40% of new chemical entities have poor water solubility. Hence many pharmaceutical industries are busy to enhance solubility of such drugs. Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be rate determining step for appearance of medicinal effect, therefore efforts to increase dissolution of drug with limited water solubility is often needed. Many methods are available to improve these characteristics, including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion is one of these methods , and involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method[1,2,3,4] Among the carriers used in the formulation of SDs, polyethylene glycol and polyvinylpyrrolidone are the most commonly used. Both polymers show excellent water solubility . Others carriers are also used to prepare the solid dispersions like Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, Poly (2-hydroxyethylmethacrylate) etc .Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs.[5,6,7]

Furosemide (FRMD) is 5-(aminosulphonyl)-4-chloro-2-[(2-fuanyl-methyl) amino] benzoic acid, a potent high ceiling (loop) diuretic, mainly used in the treatment of hypertension.[2] The drug has been classified as class IV drug as per the biopharmaceutical classification system (BCS) and having low solubility and oral bioavailability, one of the major cause of the low oral bioavailability of FRMD is its solubility.[8,9] Furosemide, a loop diuretic, inhibits water reabsorption in the nephron by blocking the sodium-potassium-chloride cotransporter (NKCC2) in the thick ascending limb of the loop of Henle. This is achieved through competitive inhibition at the chloride binding site on the cotransporter, thus preventing the transport of sodium from the lumen of the loop of Henle into the basolateral interstitium. Consequently, the lumen becomes more hypertonic while the interstitium becomes less hypertonic, which in turn diminishes the osmotic gradient for water reabsorption throughout the nephron. Because the thick ascending limb is responsible for 25% of sodium reabsorption in the nephron, furosemide is a very potent diuretic. The objective of the present study was to improve the solubility of FRDM by using eudragit polymer in three different ratio. The formulations were characterized by in vitro dissolution study to compare the effects of polymers on the preparation of solid dispersion and dissolution enhance.[10]

MATERIALS AND METHODS:

Materials

All reagents and solvents used were of analytical grade.

Methods

Preparation of Furosemide-Eudragit Solid Dispersion

Physical mixture of FRMD and eudragit RLPO & RSPO (1:0.5,1:1;1:1.5 w/w) were dissolve in methanol by stirring then it kept in dessicator for 24 hrs. Solvent get evaporated and leaving behind thin film of polymers containing drug .Resulting film is pulverized in glass mortar.

Tablet Preparation and Characterization

Tablets containing equivalent of 20 mg of Furosemide (SD product) were compressed on a 16- station single rotary tabletting press (Type CMD3 16. Cadmach Machinery Pvt.Ltd.,Ahamadabad) using an 8-mm standard flat punch by direct compression technique. Prepared tablets were evaluated for hardness (Monsanto hardness tester), friability (Roche Friabilator), weight variation, and drug content. In vitro dissolution study was carried out for different formulation containing SD using USP apparatus type II in simulated gastric fluid (P^H 1.2) as dissolution media.

Determination of drug content[11]

SD equals to single dose of drug (20 mg) was dissolved in 0.1 N NAOH then it is filtered and diluted 2-10 ug/ml and scan at 271 nm and then % drug content is calculated.

Preparation of standard curve

10mg FRMD was accurately weighted and dissolved in 100 ml of Methanol to produce a solution 0.1 mg/ml. 20ml of the solution was transferred in a volumetric flask and volume was made up to 100ml with distilled water. 2,4,6,8 ml of this solution was taken in 10ml volumetric flasks and distilled water was added to adjust the volume up to the mark to prepare standard solutions. These serial dilutions were carried out to get different FRMD concentrations. Standard solutions were then analyzed by UV spectrophotometer (UV-mini-1240, Shimadzu Corp., Kyoto, Japan) at 271nm and absorbance was noted. Then the absorbance values were plotted against drug concentration and standard curve of FRDM was produced .

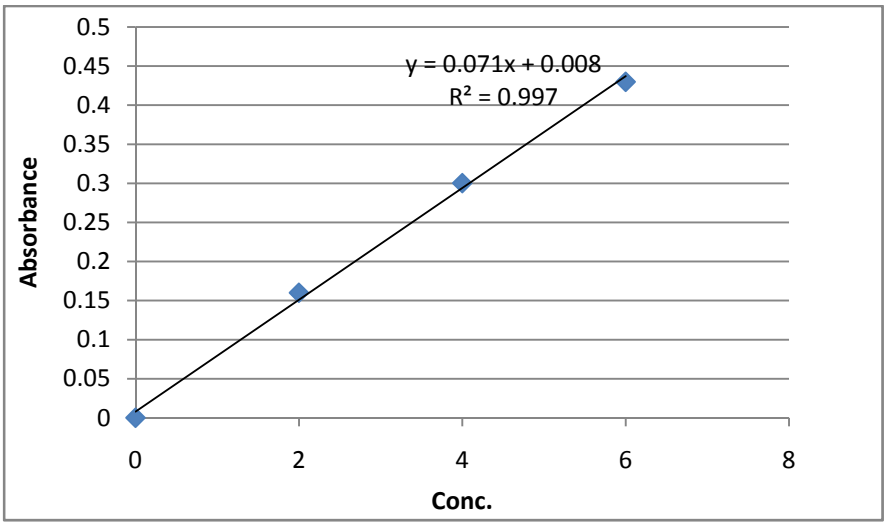

Figure 1. Calibration curve of Furosemide

Solid state studies

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Shimadzu Corporation, (Koyto, Japan) Model - 8400S. Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm -1.

X-ray Diffractometry

X-ray powder diffraction patterns were recorded on Xray powder diffraction system, PANalytical spectris Pvt.Ltd., Singapore using copper target, a voltage of 40 Kv and a current of 30 mA. The scanning was done over 2θ range of 5º to 60º.

Dissolution Rate Studies

The dissolution was studied using USP apparatus II taking 900 ml of dissolution medium, SGF (pH 1.2) for 12 hrs. The rotational speed of the paddle was set at 50 rpm at 37 ± 0.5º C. The 5 mL of aliquots was withdrawn at predetermined time interval for every 30 min for 2 hrs then after every 1 hr. for upto 12 hrs by maintaining sink condition. The samples were analyzed for drug content using double beam UV spectrophotometer (Model No. UV 2401 PC Shimadzu Corporation, Koyto, Japan) at 271 nm.

RESULTS AND DISCUSSION:

Fourier Transform Infrared (FTIR) Spectroscopy

IR spectra of FRMD and its binary systems with Eudragit are presented in Figure 2. & Figure 3 Pure furosemide spectra showed sharp characteristic peaks at same wave number like mixture of drug & polymer ,indicating no modification or interaction between the drug and carrier.

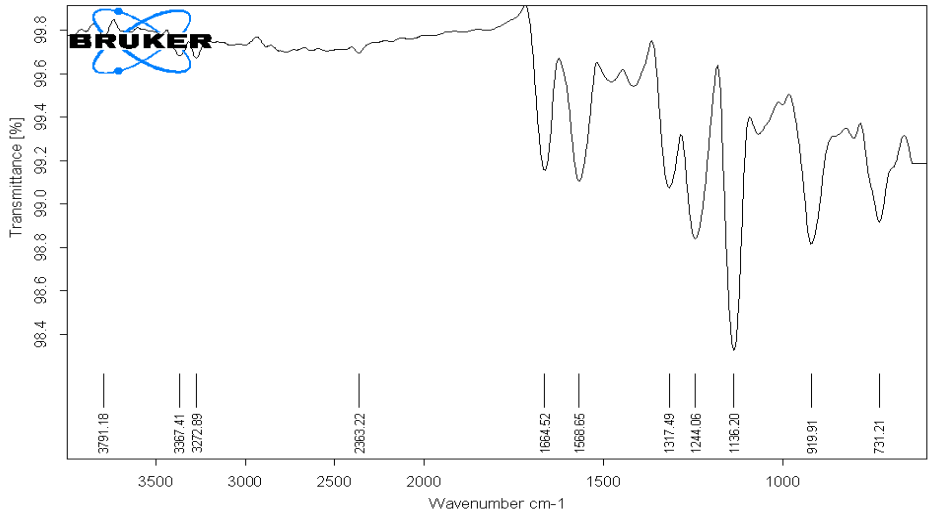

Figure 2. IR Spectrum Of Pure Furosemide

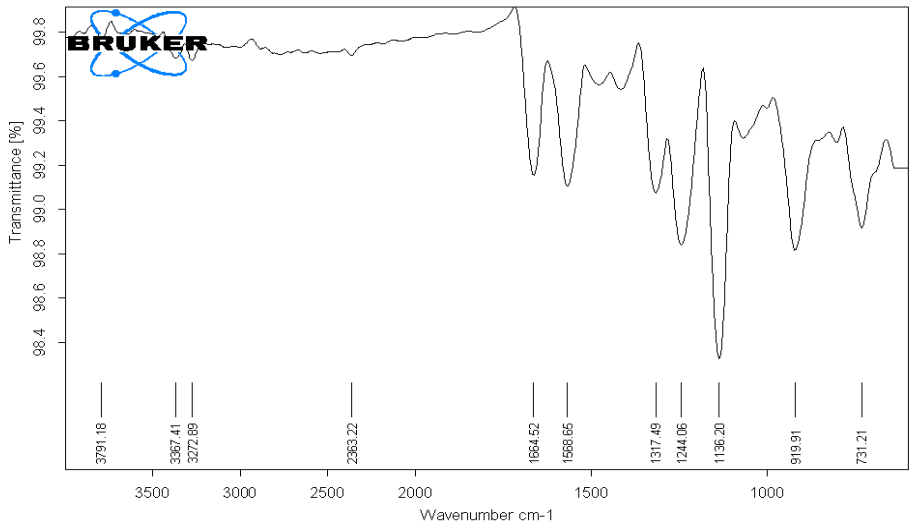

Figure 3. IR Spectrum Of Furosemide + Polymer

X-ray Diffractometry

X-ray powder diffraction patterns were recorded on Xray powder diffraction system.It is shown in figure 4 & figure 5. It shows that there is no significant interaction between drug & polymer.

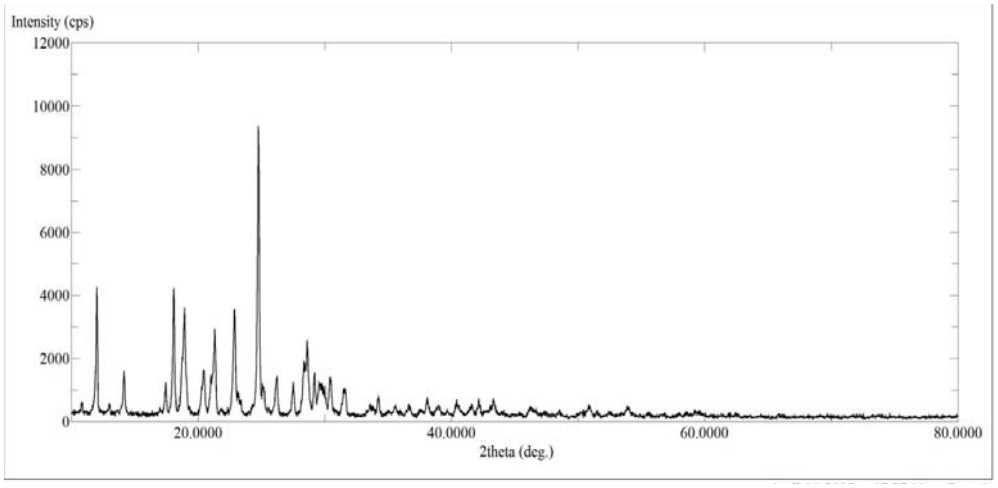

Figure 4 XRD pattern of Furosemide

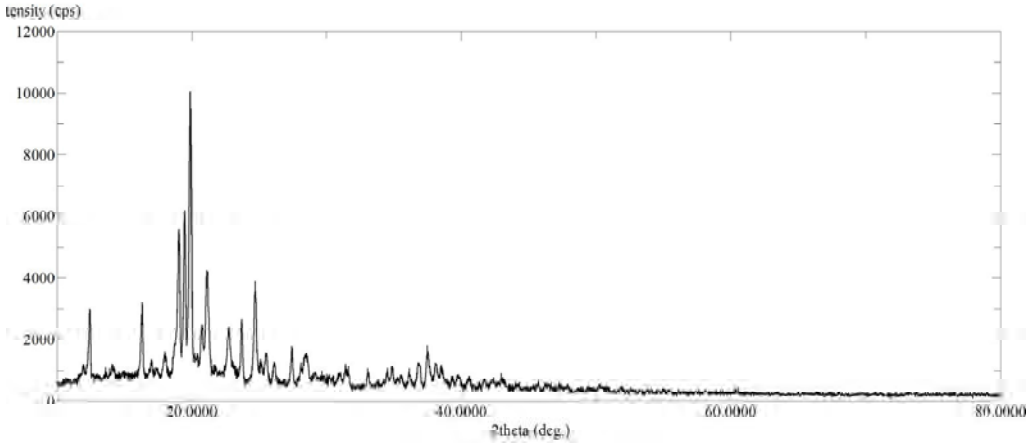

Figure 5 XRD pattern of Furosemide + Polymer

Dissolution Rate Studies

Dissolution profiles of original drug crystals and drug carrier binary systems are presented in Figure 6.. It is evident that the solid dispersion (SD) technique has improved the dissolution rate of FRMD to a great extent. Table 1 summarizes % drug dissolved in 12 hrs . Table 1 shows that in F_3 & F_6 formulation shows cumulative % release to 98.56, 97.216 respectively within 600 min.F_3 & F_6 formulation shows better dissolution than that of other formulation & that of pure drug .

Table no. 1 Cumulative % release of drug in various formulations

Batch	RL 1:0.5 F1	RL 1:1 F2	RL 1:1.5 F3	RS 1:0.5 F4	RS 1:1 F5	RS 1:1.5 F6	Pure drug
% release							
30(min)	6.0736	5.482	14.898	3.597	4.633	2.342	2.33
60	17.684	13.310	21.129	8.601	9.070	14.552	6.25
90	23.582	32.457	25.363	21.269	11.707	21.082	9.55
120	27.520	35.474	37.010	23.861	36.189	25.306	11.23
180	30.943	38.210	49.143	25.005	45.005	38.877	12.36
240	35.745	40.825	52.665	28.796	48.836	45.463	15.69
300	38.80	45.113	60.290	36.533	50.343	55.241	17.69
360	40.894	48.954	68.837	38.00	52.131	58.114	18.14
420	42.406	52.331	84.005	40.624	56.131	63.656	21.44
480	44.90	55.052	90.044	42.509	60.02	69.665	25.124
540	45.565	62.794	93.590	45.132	63.607	79.025	29.55
600	46.747	67.89	98.56	49.054	72.747	97.216	

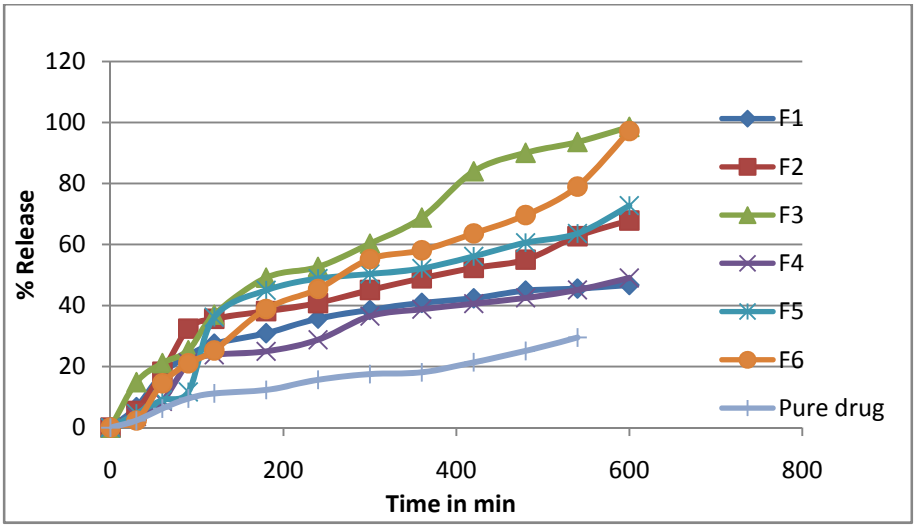

Figure 6. Comparative dissolution study of formulations with pure drug

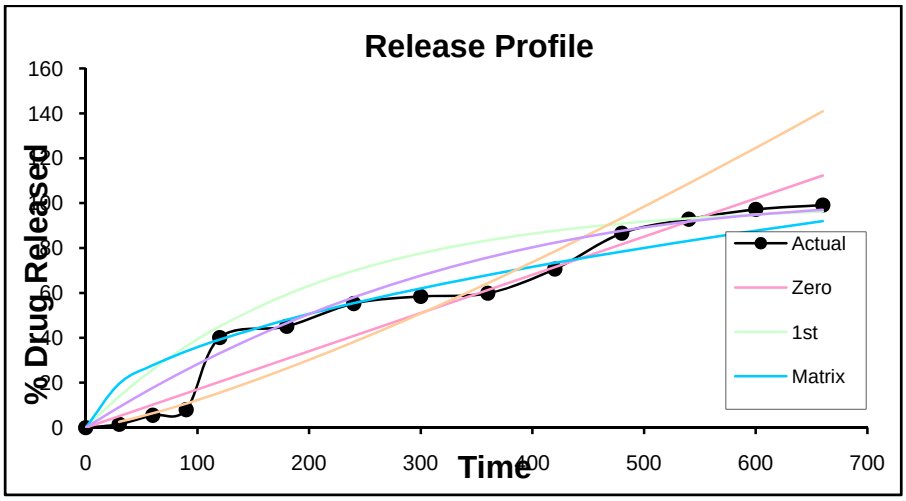

Figure 7. In vitro drug release kinetics of F3 formulation

Table no.2. In vitro drug release kinetics of F3 formulation

	R	k
Zero order	0.9752	0.1521
1st order	0.7632	-0.0037
Matrix	0.9380	3.0386
Peppas	0.9811	0.6427
Hix.Crow.	0.8856	-0.0008

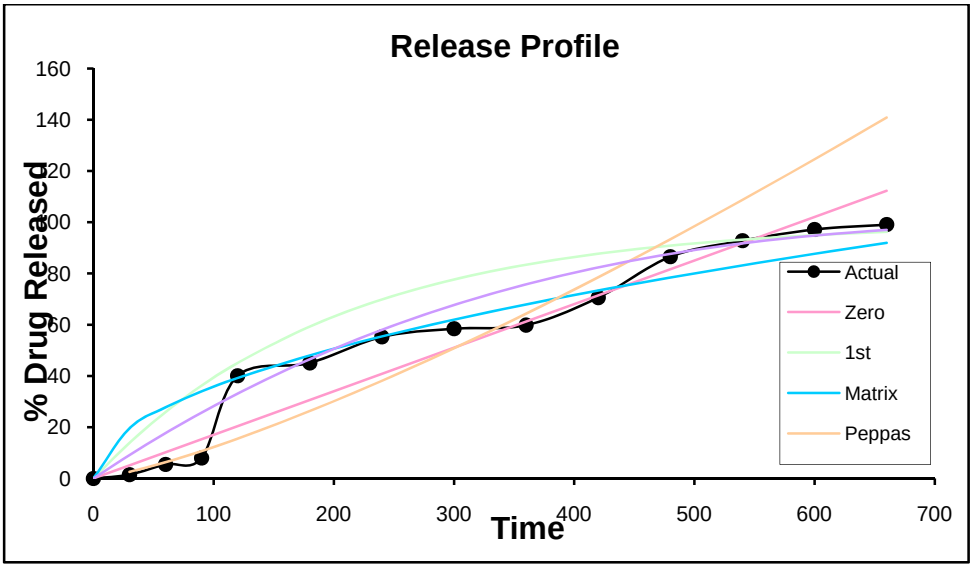

Figure no. 8. In vitro release kinetics of F6 formulation

Table no.3. In vitro drug release kinetics of F6 formulation

	R	k
Zero order	0.9666	0.1986
1st order	0.9176	-0.0050
Matrix	0.9755	3.8133
Peppas	0.9937	1.4330
Hix.Crow.	0.9735	-0.0011

Table no.4. organoleptic properties

Organoleptic properties	Observation
color	White or off white
odour	odourless
Description	Amorphous powder
Melting pt.	206 ° c

Table no.5. Precompression parameters

Batch	**Angle of repose**	**Bulk density**	**Tapped density**	**Carr's index %**	**Hausner's ratio**
F1	31.23±0.065	0.4452±0.005	0.523±0.005	8.85±0.036	0.975±0.001
F2	32.00±0.067	0.4635±0.005	0.5412±0.005	9.80±0.037	1.114±0.0011
F3	34.±0.065	0.4821±0.005	0.5542±0.006	11.21±0.039	1.27±0.0012
F4	32±0.062	0.512±0.006	0.5632±0.005	10.31±0.032	1.84±0.0020
F5	33±0.064	0.542±0.005	0.6012±0.006	12.80±0.035	1.066±0.0011
F6	34.12±0.067	0.5612±0.005	0.501±0.005	9.447±0.036	1.94±0.0015

Table no.6.Post compression parameters

Bath no.	Thickness cm	Hardness Kg/cm^2	Friability %	Weight variation	Drug content %
F1	0.55±0.0059	4.5±0.057	0.145±0.00057	295±15.25	95.30±0.086
F2	0.55±0.0059	4.5±0.058	0.148±0.00056	298±15.25	94.66±0.086
F3	0.55±0.0057	5±0.057	0.146±0.00056	293±15.25	95.36±0.085
F4	0.54±0.0058	4.5±0.057	0.168±0.00057	295±15.52	94.56±0.086
F5	0.55±0.0059	5±0.058	0.136±0.00056	291±15.25	98.78±0.87
F6	0.54±0.0057	4.5±0.058	0.189±0.00057	296±15.25	96.56±0.087

CONCLUSION

This study shows that solubility & dissolution rate of Furosemide can be enhance considerably by formulating in it as solid dispersion in eudragit polymer by using solvent evaporation method. Formulation containing eudragit RL(1:1.5) & RS(1:1.5) shows improve dissolution rate than that of pure drug. Incorparation of eudragit in formulation enhance dissolution as well as control the release of drug. It also shows that as concentration of polymer increases dissolution rate get increases.

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