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ENHANCED DISSOLUTION RATE OF EPALRESTAT SOLID DISPERSION - FORMULATION AND EVALUATION

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Abstract:

Epalrestat was selected as a model drug, because it's having poor aqueous solubility and low dissolution rate, while high permeability through the membranes (BCS class II drugs). So, the present work reveals the increasing the dissolution of Epalrestat without micronising it by solid dispersion technique. Solid dispersions were prepared using poloxamer-407, gelucire-50/13, PVPk-30, PEG 4000, PEG 6000 as carriers by physical mixing, solvent evaporation method techniques. The carrier concentration was taken in the ratios of 1:10, 1:20, and 1:30 with respect to the drug in the investigation. Effect of poloxamer-407, gelucire-50/13, PVPk-30, PEG 4000, PEG 6000 on solubility studies of Epalrestat was conducted in 0.1N HCl, distilled water, pH 6.8. the blend was subjected to precompression and post compression parameters. The In vitro drug release from the formulation follows the first order kinetics than zero order kinetics because of regression coefficient.

Keywords: *Epalrestat, Solid dispersion, Physical mixing, Solvent evaporation method, carriers, In vitro drug release*

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INTRODUCTION:

Several pharmaceutical techniques are being developed for the enhancement of solubility and dissolution rate of poorly water-soluble drugs [1]. Solid dispersion is one of the novel techniques among micronization, nanosuspension, supercritical fluid process, solid dispersion, solid solution, sonocrystallization, co-solvency and hydrotrophy in enhancing the solubility of poorly soluble drugs [2,3]. Solid dispersion is one of the pharmaceutical techniques for increasing the dissolution, absorption and therapeutic efficacy of drug. Here, one or more active ingredients dispersed in an inert carrier matrix at solid state to prepare a fusion at melting state [4]. In the solid dispersion, the drug is molecularly dispersed in amorphous state and result in the enhancement of solubility and dissolution rate as compared to the crystalline substance. There are several carriers available for enhancement of the solubility and dissolution rate such as polymers, superdisintegrants, cyclodextrins, carbohydrates, surfactants, hydrotropes, polyglycolized glycerides, acids and dendrimers [5]. Even though various carriers are available for the improvement of dissolution rate of the drug, there is need of development of new carriers.

Epalrestat was selected as a model drug, because it's having poor aqueous solubility and low dissolution rate, while high permeability through the membranes (BCS class II drugs). Generally solid dispersion is simple method to enhance the dissolution characteristic of class II drugs, only few products using SD few marketed, because of stability problems [6,]. Normally micronized form of API shows high dissolution behavior than the un micronized API. So, the present work reveals the increasing the dissolution of Epalrestat without micronising it by solid dispersion method [8].

MATERIALS AND METHODS:

Materials

Epalrestat obtained from Micro labs. PEG-4000, PEG-6000 obtained from Qualigens fine chemicals. Poloxamer-407, PVP k-30 obtained from Hymedia.

Methods

PRE-FORMULATION STUDIES

Determination of melting point

Melting point of epalrestat was determined by capillary method [9].

Solubility

The solubility of epalrestat was determined by adding excess amount (10mg) of drug in 25ml volumetric flask containg 0.1N Hcl kept in rotary shaker for 24hrs at room temperature (37±2). The samples were filtered through Whatmann filter paper, pore size 0.45µm and analyzed by the spectroscopy [10].

Preparation of Epalrestat solid dispersions

Solid dispersions were prepared using poloxamer-407, gelucire-50/13, PVPk-30, PEG 4000, PEG 6000 as carriers by physical mixing, solvent evaporation method techniques [11,12]. The carrier concentration was taken in the ratios of 1:10, 1:20, and 1:30 with respect to the drug in the investigation. They methods employed for the preparation of solid dispersions are: Physical mixing. Solvent evaporation method.

Physical mixture (PM)

The drug (epalrestat) and carrier, each in a known quantity, were weighed individually and put through sieve no. 80. Drug and polymer were triturated together for 5 minutes before being screened through sieve no. 80 once again. The materials that passed through sieve no. 80 were collected and put into a clean, dry glass mortar [13]. The mixture is collected and sealed hermetically in a wide-mouthed amber-colored glass container after passing through sieve no. 80.

Table 1: formulation of physical mixers

Contents	f1	f2	f3	f4	f5	f6	f7	f8	f9	f10	f11	f12	f13	f14	f15
% API	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
%PEG 4000	10	20	30	-	-	-	-	-	-	-	-	-	-	-	-
%PEG 6000	-	-	-	10	20	30	-	-	-	-	-	-	-	-	-
%PVP k-30	-	-	-	-	-	-	10	20	30	-	-	-	-	-	-
%Poloxamer-407	-	-	-	-	-	-	-	-	-	10	20	30	-	-	-
%Gelucire50/13	-	-	-	-	-	-	-	-	-	-	-	-	10	20	30

Solvent Evaporation Method (SD)

This process starts with the preparation of a solution having a physical mixture of the drug and carrier dissolved in ethanol, followed by the removal of the solvent and the creation of a solid dispersion. To create a solid, first ethanol is used to dissolve the medicine and the carrier [14]. The solvent is then evaporated under vacuum. In the highly water-soluble carrier, they were able to develop a solid form of the highly lipophilic medication as a result. The typical temperature range for solvent evaporation is 23–65 °C. Inferring from the foregoing technique that the 1:30 formulation provides the best dissolving profile and good outcomes in comparison to other formulations.

Table 2: formulation of solid dispersions

Contents	f1	f2	f3	f4	f5	f6	f7	f8	f9	f10	f11	f12	f13	f14	f15
% API	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
%PEG 4000	10	20	30	-	-	-	-	-	-	-	-	-	-	-	-
%PEG 6000	-	-	-	10	20	30	-	-	-	-	-	-	-	-	-
%PVP k-30	-	-	-	-	-	-	10	20	30	-	-	-	-	-	-
%Poloxamer-407	-	-	-	-	-	-	-	-	-	10	20	30	-	-	-
%Gelucire50/13	-	-	-	-	-	-	-	-	-	-	-	-	10	20	30

EVALUATION OF PODER BLEND

PRECOMPRESSION PARAMETERS OF THE POWDER BLEND

Angle of repose

100 grammes of the mixture were precisely weighed and then slowly poured down the funnel, which had its tip fixed 2.5 cm above the graph paper that was positioned on a flat surface. The mixture was poured until the conical pile's peak just touched the funnel's tip [15]. Angle of repose is computed using the formula below

$$\theta = \text{Tan}^{-1}(h/r)$$

Where,

ɵ = angle of repose,

r=radius of the pile,

h=height of the pile,

Bulk density

Bulk density is defined as a mass of a powder divided by the bulk volume. Pouring the mixture into a graduated cylinder allowed for the calculation of apparent bulk density (*b). The powder's bulk volume (V*) and weight (M) were calculated. The formula was used to get the bulk density [16].

$$*b = M/V*$$

Tapped density

For a predetermined amount of time (about 250), the measuring cylinder containing a known mass of mix was tapped. Measurements were made of the blend's weight (M) and the lowest volume (Vt) that the cylinder could hold. Using the formula, the tapped density (*t) was determined [17].

$$*t = M/V_t$$

Compressibility index

The simplest method for measuring the free flow of powder is compressibility; the compressibility index (C.I), which is computed using the formula, provides information on how easily a material may be made to flow,

$$C.I\ (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio

The Hausner ratio is a proximate indicator of powder flow simplicity. It was determined using the formula,

$$\text{Hausner ratio} = *t/*d$$

Where,

*t=tapped density.

*d=bulk density

CHARACTERIZATION

Solubility studies:

The excess of drug was added to screw-capped vials containing carrier solution (2%, 4%, 6%, 8%, 10% w/v concentration range), prepared in phosphate buffer p^H 6.8 and 0.1N HCl vials were shaken mechanically at 35 ± 2^0c for 24hr. After 2days, aliquots were withdrawn, filtered through whatmann filter paper and UV spectrophotometrically (shimadzu) assayed for drug content at 401 nm [18,19].

Drug content analysis

Accurately weighed quantities of solid dispersion equivalent to 10mg of epalrestat were taken in to a10ml volumetric flack and add small volume of

ethanol for solubilizes the drug and make with 0.1N HCl [20]. The stock solutions were filtered, suitably diluted with 0.1N HCl and assayed for drug content using a double beam UV spectrophotometer at 401nm.

***In-vitro* Drug release study:**

The dissolving medium employed was 900 ml of 0.1N HCl. In a hard gelatin capsule, solid dispersions amounting to 50mg of epalrestat were administered. It was set to 50 rpm on the USP Dissolution Apparatus II (basket type, electro lab) stirrer. A constant 37.2°C was maintained. At various time intervals, 0.5 ml of an aliquot of the dissolving medium was removed, and the removed volume was replaced with new dissolution media [21]. After the appropriate dilution, the samples were examined for epalrestat using a shimadzu UV-Visible spectrophotometer to measure absorbance at 401 nm. The amount of epalrestat that was dissolved at various points in time was determined and shown versus time

RESULTS AND DISCUSSION:

Table 3: Solubility profile of Epalrestat in different media

Solvent	Amount soluble (mg/ml)
Phosphate buffer (p^H 6.8)	2.261
0.1N HCl	0.412
Water	0.009

Solubility studies of Epalrestat was conducted and it was found that drug had highest solubility in 6.8 pH Phosphate buffer.

SOLUBILITY STUDIES

Table 4: Effect of PEG4000 on solubility of Epalrestat in 0.1N HCl

Concentration of (%w/v)	% solubility of Epalrestat
0	7.13
2	10.26
4	14.12
6	15.64
8	20.98
10	25.06

Solubility studies of Epalrestat was conducted in 0.1N HCl, in that solubility was increased with increase in carrier concentration, because of polar groups of PEG 4000.

Table 5: Effect of PEG6000 on solubility of Epalrestat in 0.1N HCl

Concentration of (%w/v)	% solubility of Epalrestat
0	7.46
2	10.82
4	14.56
6	19.24
8	24.93
10	29.54

Solubility studies of Epalrestat was conducted in 0.1N HCl, in that solubility was increased with increase in carrier concentration, because of polar groups of PEG 6000.But when compared to PEG 4000, high solubility was observed

Table 6: Effect of PVP k-30 on solubility of Epalrestat in 0.1N HCl

Concentration of (%w/v)	% solubility of Epalrestat
0	7.45
2	8.89
4	11.32
6	13.98
8	16.23
10	18.59

Solubility studies of Epalrestat was conducted in 0.1N HCl, in that solubility was increased with increase in carrier concentration, because of polar groups of PVP K30.

Table 7: Effect of poloxamer-407 on solubility of Epalrestat in 0.1N HCl

Concentration of (%w/v)	% solubility of Epalrestat
0	7.46
2	15.98
4	24.16
6	36.29
8	45.24
10	56.46

Solubility studies of Epalrestat was conducted in 0.1N HCl, in that solubility was increased with increase in carrier concentration, because of polar groups of Polaxamer. Highest solubility was observed when compared to all other polymers.

Table 7: Effect of gelucire-50/13 on solubility of Epalrestat in 0.1N HCl

Concentration of (%w/v)	% solubility of Epalrestat
0	7.46
2	12.64
4	18.85
6	23.24
8	29.87
10	35.17

Solubility studies of Epalrestat was conducted in 0.1N HCl, in that solubility was increased with increase in carrier concentration, because of polar groups of Gelucire 50/13. In this, high solubility was observed when compared to other polymer but low solubility then polaxamer.

Table 8: Effect of PEG4000 on solubility of Epalrestat in Dis. water

Concentration of (%w/v)	% solubility of Epalrestat
0	2.54
2	3.74
4	4.91
6	6.12
8	8.03
10	10.11

Solubility studies of Epalrestat was conducted in water, in that solubility was increased with increase in carrier concentration, because of polar groups of PEG 4000.

Table 9: Effect of PEG6000 on solubility of Epalrestat in Dis. water

Concentration of (%w/v)	% solubility of Epalrestat
0	2.54
2	4.72
4	7.34
6	9.98
8	13.62
10	16.87

Solubility studies of Epalrestat was conducted in Water, in that solubility was increased with increase in carrier concentration, because of polar groups of PEG 6000.But when compared to PEG 4000, high solubility was observed

Table 10: Effect of PVP k-30 on solubility of Epalrestat in Dis. water

Concentration of (%w/v)	% solubility of Epalrestat
0	2.51
2	4.22
4	5.62
6	8.04
8	9.55
10	11.54

Solubility studies of Epalrestat was conducted in Water, in that solubility was increased with increase in carrier concentration, because of polar groups of PVP K30.

Table 11: Effect of poloxamer-407 on solubility of Epalrestat in Dis. water

Concentration of (%w/v)	% solubility of Epalrestat
0	2.51
2	9.24
4	17.89
6	25.22
8	33.14
10	40.34

Solubility studies of Epalrestat was conducted in Water, in that solubility was increased with increase in carrier concentration, because of polar groups of Polaxamer. Highest solubility was observed when compared to all other polymers.

Table 12: Effect of gelucire-50/13 on solubility of Epalrestat in Dis. water

Concentration of (%w/v)	% solubility of Epalrestat
0	2.53
2	7.65
4	11.32
6	15.54
8	20.12
10	25.71

Solubility studies of Epalrestat was conducted in Water, in that solubility was increased with increase in carrier concentration, because of polar groups of Gelucire 50/13.In this, high solubility was observed when compared to other polymer but low solubility then polaxamer.

Table 13: Effect of PEG4000 on solubility of Epalrestat in phosphate buffer p^H6.8

Concentration of (%w/v)	% solubility of Epalrestat
0	38.03
2	42.65
4	45.15
6	51.56
8	56.32
10	61.45

Solubility studies of Epalrestat was conducted in phosphate buffer p^H6.8, in that solubility was increased with increase in carrier concentration, because of polar groups of PEG 4000.

Table 14: Effect of PEG6000 on solubility of Epalrestat in phosphate buffer p^H6.8

Concentration of (%w/v)	% solubility of Epalrestat
0	40.31
2	45.54
4	52.63
6	56.98
8	63.87
10	70.75

Solubility studies of Epalrestat was conducted in phosphate buffer p^H6.8, in that solubility was increased with increase in carrier concentration, because of polar groups of PEG 6000.But when compared to PEG 4000, high solubility was observed

Table 15: Effect of PVP k-30 on solubility of Epalrestat in phosphate buffer p^H6.8

Concentration of (%w/v)	% solubility of Epalrestat
0	40.21
2	44.14
4	52.42
6	56.86
8	59.83
10	65.19

Solubility studies of Epalrestat was conducted in phosphate buffer p^H6.8, in that solubility was increased with increase in carrier concentration, because of polar groups of PVP K30.

Table 16: Effect of Poloxamer-407 on solubility of Epalrestat in phosphate buffer p^H6.8

Concentration of (%w/v)	% solubility of Epalrestat
0	40.15
2	46.31
4	54.45
6	59.87
8	65.52
10	72.60

Solubility studies of Epalrestat were conducted in phosphate buffer p^H6.8, in that solubility was increased with increase in carrier concentration, because of polar groups of Polaxamer. Highest solubility was observed when compared to all other polymers.

Table 17: Effect of Gelucire-50/13 on solubility of Epalrestat in phosphate buffer p^H6.8

Concentration of (%w/v)	% solubility of epalrestat
0	40.45
2	46.26
4	49.52
6	53.12
8	57.45
10	62.24

Solubility studies of Epalrestat was conducted in phosphate buffer p^H6.8, in that solubility was increased with increase in carrier concentration, because of polar groups of Gelucire 50/13. In this, high solubility was observed when compared to other polymer but low solubility then polaxamer.

Dissolution data

Table 18: *in-vitro* drug release profile of PEG4000

Time (min)	pure drug	F1	F2	F3
0	0	0	0	0
5	1.06±0.09	6.86±0.59	8.51±1.o5	16,50±1.50
10	3.83±0.29	15.17±0.60	18.93±1.04	32.31±1.52
15	5.39±0.19	20.47±0.60	28.85±1.05	53.49±1.53
20	6.74±0.09	22.73±0.61	35.82±1.04	67.05±1.55
30	7.60±0.29	25.02±0.61	45.03±1.05	75.53±1.56
45	7.89±0.19	27.32±0.62	51.82±1.04	78.88±1.58
60	8.31±0.09	28.62±0.63	54.15±1.05	83.12±1.41
90	8.45±0.10	28.89±0.63	54.67±1.06	84.78±.075

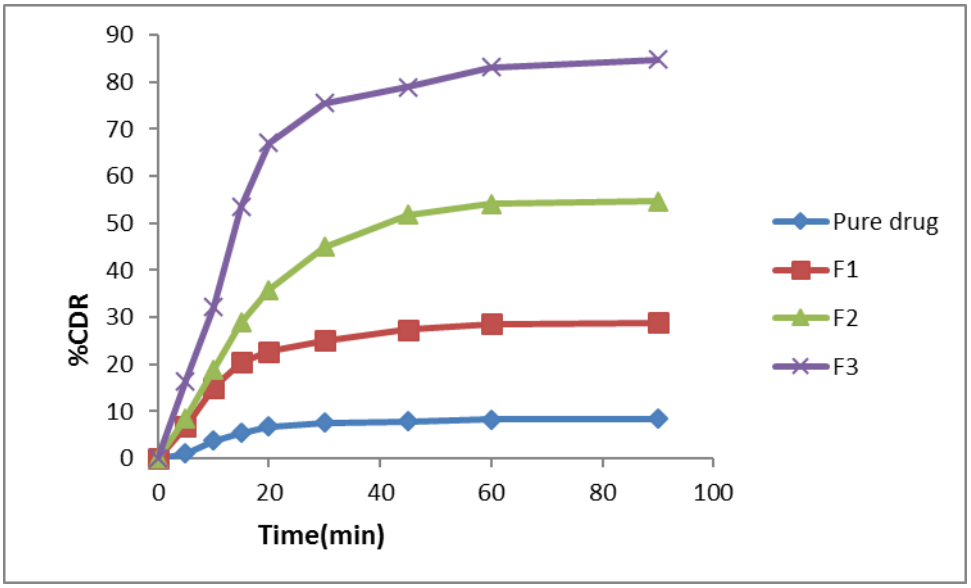

Fig 1: Drug release profile of PEG4000

Drug release studies of PEG4000 were conducted, in that high drug release was occur in f3 formulation when compared other f1&f2. Because of increasing carrier concentration and also increasing polar groups.

Table 19: *in-vitro* drug release profile of PEG6000

Time (min)	pure drug	F4	F5	F6
0	0	0	0	0
5	1.06±0.09	7.12±0.61	9.47±1.17	28.84±1.72
10	3.83±0.29	12.54±0.62	19.72±1.18	41.07±1.74
15	5.39±0.19	23.35±0.62	32.09±1,19	47.45±1.75
20	6.74±0.09	26.79±0.63	38.5±1.20	68.81±1.77
30	7.60±0.29	30.26±0.64	49.03±1.21	78.44±1.79
45	7.89±0.19	31.63±0.64	57.63±1.23	85.35±1.96
60	8.31±0.09	34.07±0.65	59.92±1.78	88.98±1.82
90	8.45±0.10	34.40±0.66	60.81±1.25	89.84±1.84

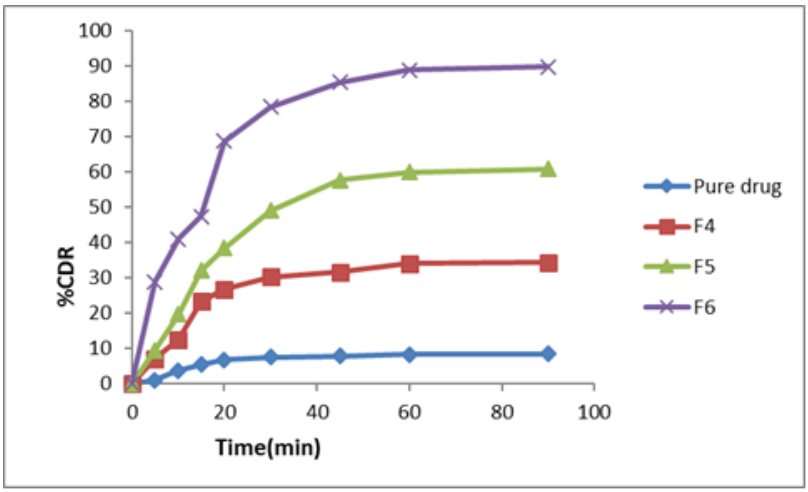

Fig 2: Drug release profile of PEG6000

Drug release studies of PEG6000 were conducted, in that high drug release was occur in f6 formulation when compared other f4&f5. Because of increasing carrier concentration and also increasing polar groups.

Table 20: *in-vitro* drug release profile of PVP k30

Time (min)	Pure drug	F7	F8	F9
0	0	0	0	0
5	1.06±0.09	2.53±0.54	4.08±1	37.42±1.47
10	3.83±0.29	6.36±0.55	7.61±1.01	47.15±2.96
15	5.39±0.19	10.23±0.56	18.18±1.02	57.82±1.42
20	6.74±0.09	14.77±0.53	25.36±1.03	72±1.50
30	7.60±0.29	19.04±0.56	36.10±1.04	77.81±1.51
45	7.89±0.19	20.17±0.56	49.28±0.95	88.78±1.53
60	8.31±0.09	22.27±0.57	52.07±0.04	91.86±1.26
90	8.45±0.10	23.76±0.027	53.77±0.96	93.07±1.56

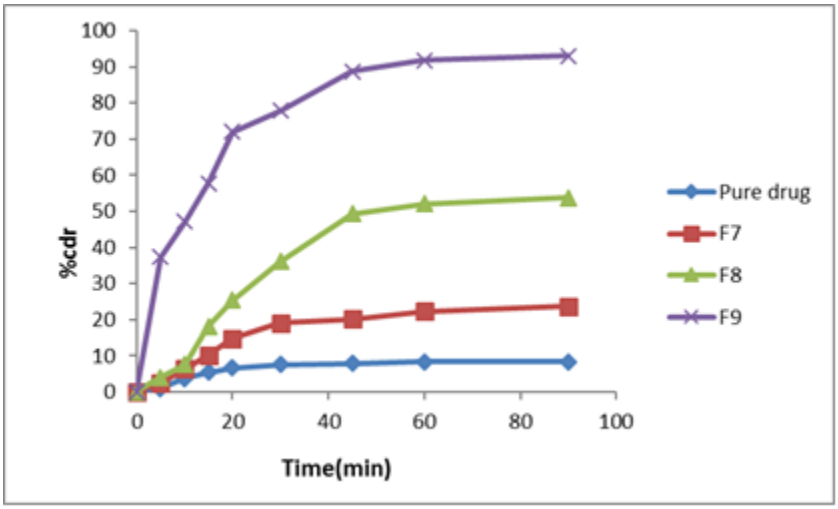

Fig 3: Drug release profile of pvp k30

Drug release studies of pvp k30 were conducted, in that high drug release was occur in f6 formulation when compared other f4&f5. Because of increasing carrier concentration and also increasing polar groups.

Table 21: *in-vitro* drug release profile of poloxamer 407

Time (min)	Pure drug	F10	F11	F12
0	0	0	0	0
5	1.06±0.09	10.04	7.7	26.1417
10	3.83±0.29	28.67	26.68	37.4615
15	5.39±0.19	35.52	49.36	50.9118
20	6.74±0.09	48.62	63.1612	81.5818
30	7.60±0.29	51.42	77.7912	92.4401
45	7.89±0.19	62.73	81.3512	96.3601
60	8.31±0.09	65.66	87.7525	97.2901
90	8.45±0.10	66.29	88.5925	98.2301

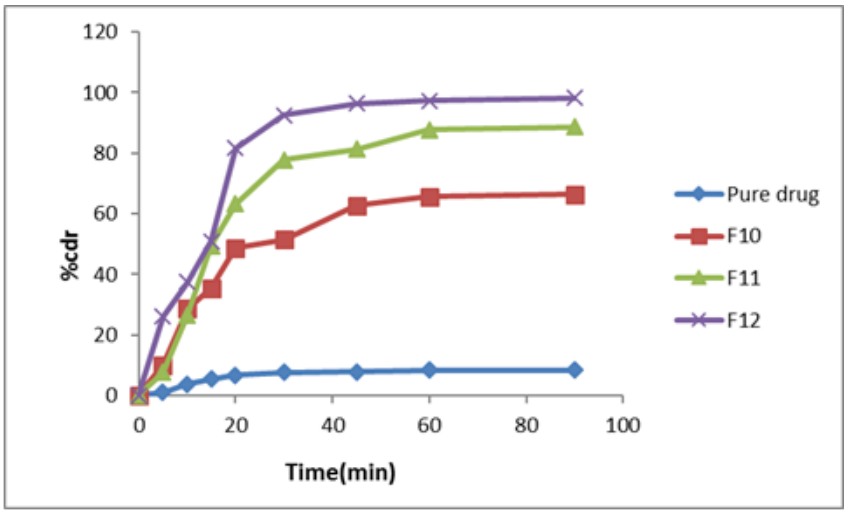

Fig 4: Drug release profile of poloxamer

Drug release studies of poloxamer were conducted, in that high drug release was occur in f12 formulation when compared other f10&f11.Because of increasing carrier concentration and also increasing polar groups.

Table 22: *in-vitro* drug release profile of gelucire 50/13

Time (min)	Pure drug	F13	F14	F15
0	0	0	0	0
5	1.06±0.09	3.130.54	14.898	5.5637
10	3.83±0.29	5.980.54	26.4118	35.0414
15	5.39±0.19	9.790.55	33.532	59.2514
20	6.74±0.09	18.6602	54.4	71.7714
30	7.60±0.29	29.8011	66.9509	89.97
45	7.89±0.19	36.0505	73.3111	92.4514
60	8.31±0.09	39.2205	79.1712	95.741
90	8.45±0.10	39.6006	80.5	97.4505

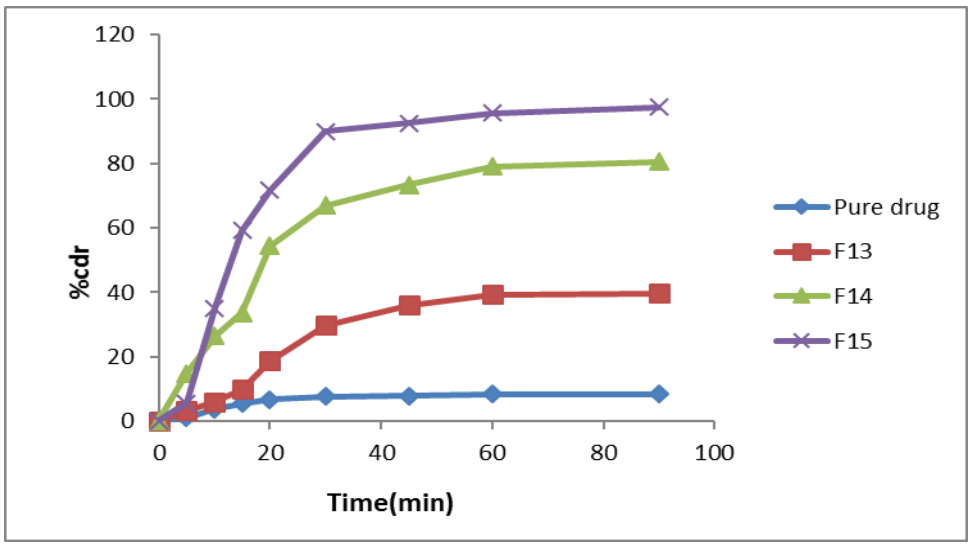

Fig 5: Drug release profile of gelucire

Drug release studies of gelucire 50/13 were conducted, in that high drug release was occur in f15 formulation when compared other f14&f13.Because of increasing carrier concentration and also increasing polar groups.

Physical mixture

Table 23: *in-vitro* drug release profile of PEG4000

Time (min)	Pure drug	F1	F2	F3
0	0	0	0	0
5	1.06±0.09	1.54	2.36	9.61
10	3.83±0.29	2.49	4.16	17.58
15	5.39±0.19	4.37	15.44	30.87
20	6.74±0.09	8.13	20.91	36.42
30	7.60±0.29	11	22.9	39.4
45	7.89±0.19	12.97	24.9	40.66
60	8.31±0.09	14.95	26.91	40.18
90	8.45±0.10	15.1	27.76	41.44

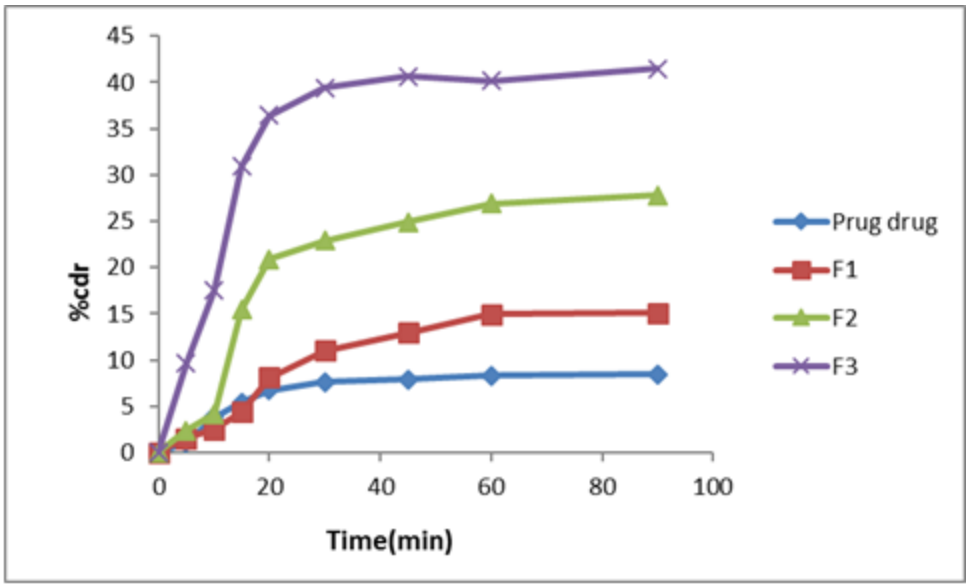

Fig 6: Drug release profile of PEG4000

Drug release studies of PEG4000 were conducted, in that high drug release was occur in f3 formulation when compared other f1&f2. Because of increasing carrier concentration and also increasing polar groups.

Table 24: *in-vitro* drug release profile of PEG6000

Time (min)	Pure drug	F4	F5	F6
0	0	0	0	0
5	1.06±0.09	1.23	4.14	3.49
10	3.83±0.29	3.1	7.73	8.77
15	5.39±0.19	8.09	17.27	22.85
20	6.74±0.09	10.96	22.76	33.57
30	7.60±0.29	13.55	26.53	39.15
45	7.89±0.19	14.92	28.57	42.15
60	8.31±0.09	15.99	30.47	45.19
90	8.45±0.10	16.15	30.92	46.5

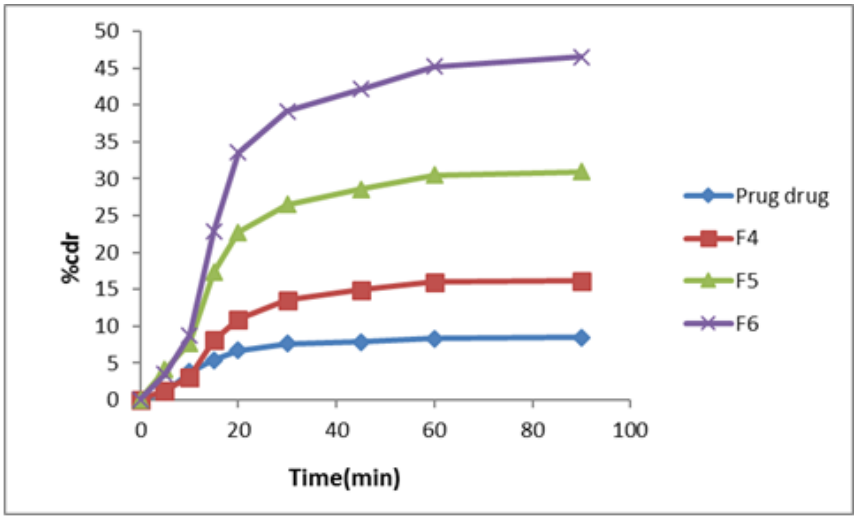

Fig 7: Drug release profile of PEG6000

Drug release studies of PEG6000 were conducted, in that high drug release was occur in f6 formulation when compared other f4&f5. Because, of increasing carrier concentration and also increasing polar groups.

Table 25: *in-vitro* drug release profile of PVPk30

Time (min)	Pure drug	F7	F8	F9
0	0	0	0	0
5	1.06±0.09	1.23	4.14	6.99
10	3.83±0.29	3.1	8.32	14.93
15	5.39±0.19	8.09	15.5	22.95
20	6.74±0.09	10.03	22.75	28.42
30	7.60±0.29	11.06	26.52	33.94
45	7.89±0.19	12.1	28.56	34.28
60	8.31±0.09	13.76	30.61	37.23
90	8.45±0.10	14.51	30.9	37.59

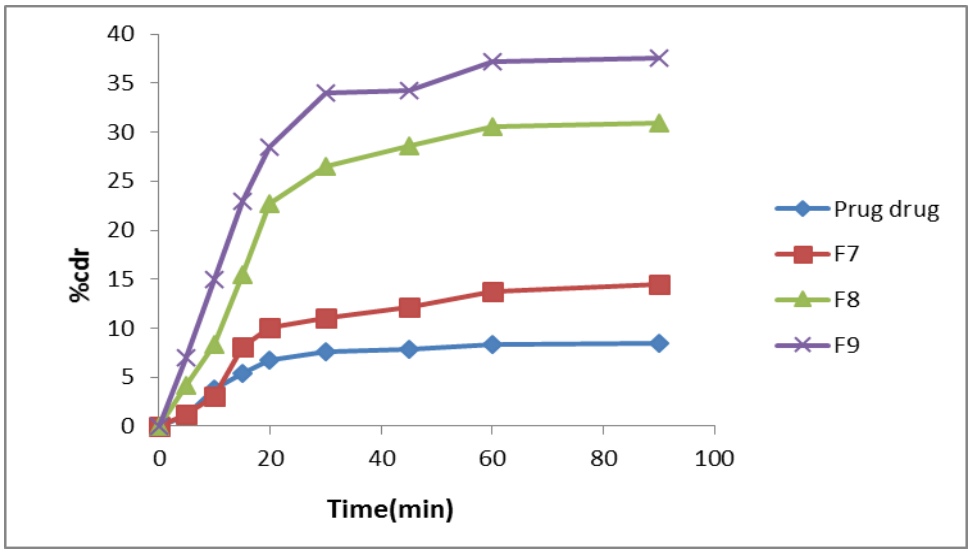

Fig 8: Drug release profile of pvp k30

Drug release studies of pvp k30 were conducted, in that high drug release was occur in f6 formulation when compared other f4&f5. Because of increasing carrier concentration and also increasing polar groups.

Table 26: *in-vitro* drug release profile of polamer 407

Time (min)	Pure drug	F10	F11	F12
0	0	0	0	0
5	1.06±0.09	1.5403	4.7312	9.611
10	3.83±0.29	4.35	10.1103	22.8215
15	5.39±0.19	8.7318	18.48	32.6735
20	6.74±0.09	10.6719	20.44	36.4917
30	7.60±0.29	14.806	26.55	41.223
45	7.89±0.19	17.7406	30.36	44.2433
60	8.31±0.09	19.4611	32.43	45.5515
90	8.45±0.10	19.9659	32.74	45.9816

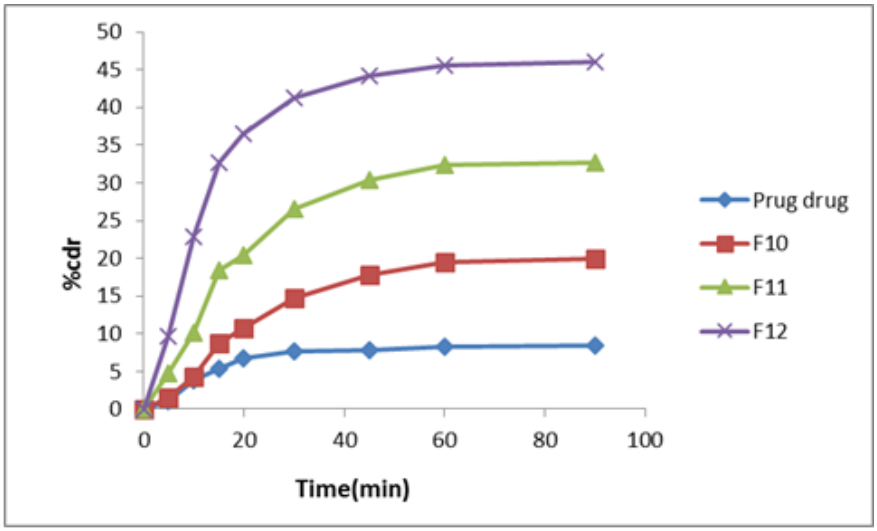

Fig 9: Drug release profile of Poloxamer 407

Drug release studies of poloxamer were conducted, in that high drug release was occur in f12 formulation when compared other f10&f11.Because of increasing carrier concentration and also increasing polar groups.

Table 27: *in-vitro* drug release profile of gelucire 50/13

Time (min)	Pure drug	F13	F14	F15
0	0	0	0	0
5	1.06±0.09	1.5403	4.7302	3.49151
10	3.83±0.29	4.3504	10.1013	8.77152
15	5.39±0.19	6.2504	16.1102	16.7315
20	6.74±0.09	10.6502	18.64	28.2615
30	7.60±0.29	13.8504	25.3301	33.7915
45	7.89±0.19	15.8406	30.9001	36.7415
60	8.31±0.09	17.5519	32.381	37.1011
90	8.45±0.10	18.0306	33.29	38.33

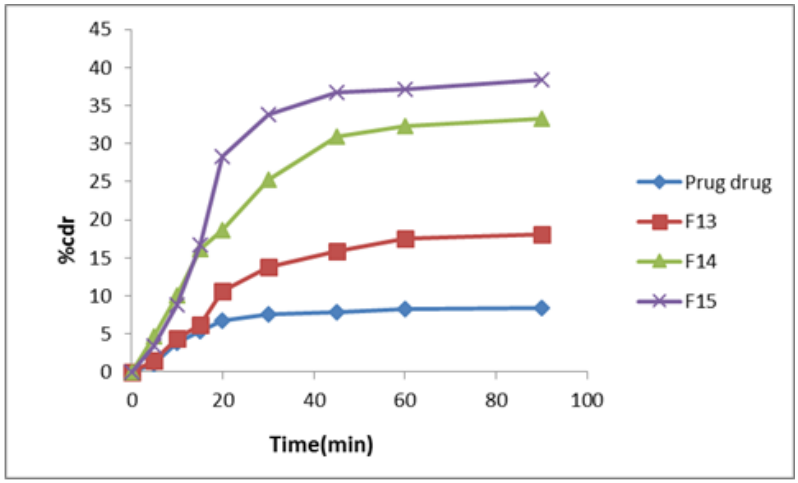

Fig 10: Drug release profile of gelucire

Drug release studies of gelucire 50/13 were conducted, in that high drug release was occur in f15 formulation when compared other f14&f13.Because of increasing carrier concentration and also increasing polar groups.

Solid dispersions:

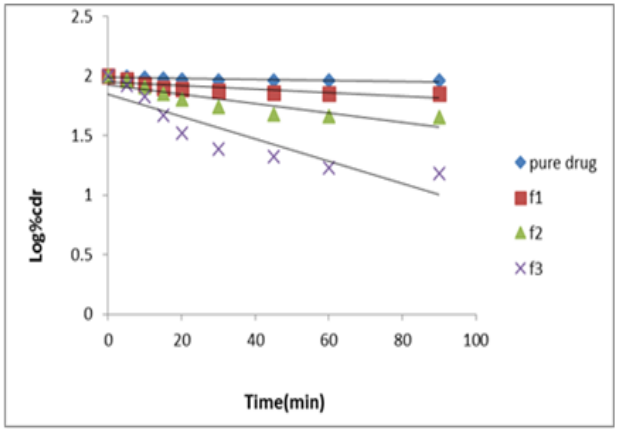

Fig 11: Zero-order plot of PEG4000

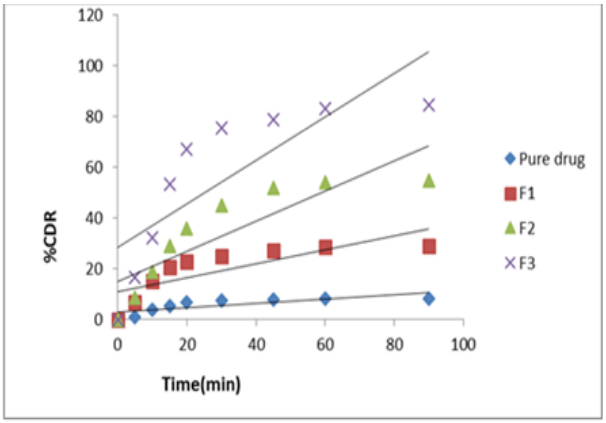

Fig 12: first-order plot of PEG4000

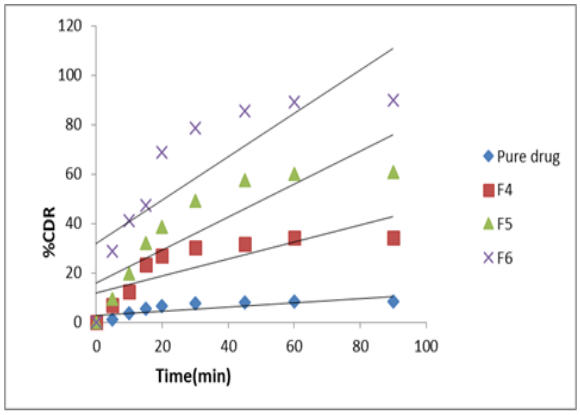

Fig 13: Zero-order plot of PEG6000

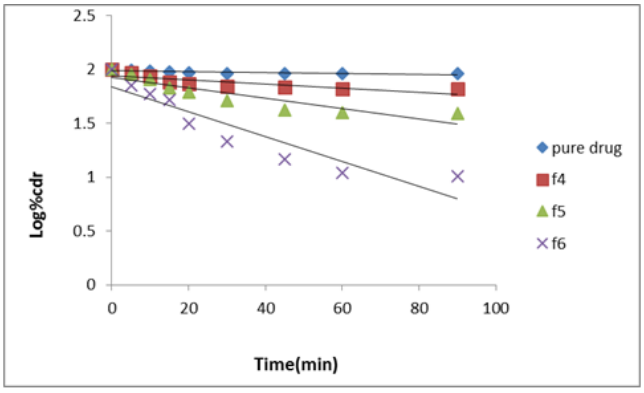

Fig 14: first-order plot of PEG6000

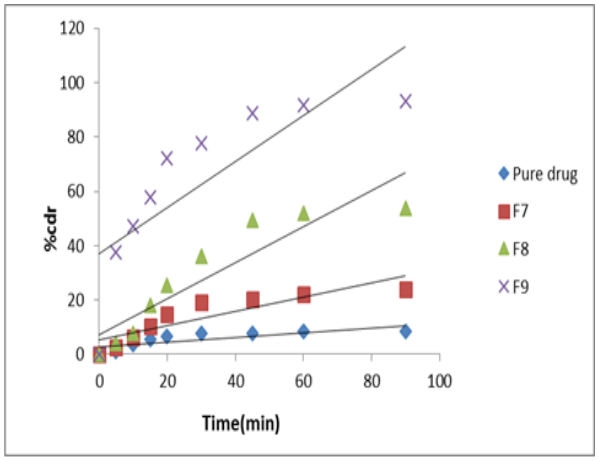

Fig 15: Zero-order plot of pvpk30

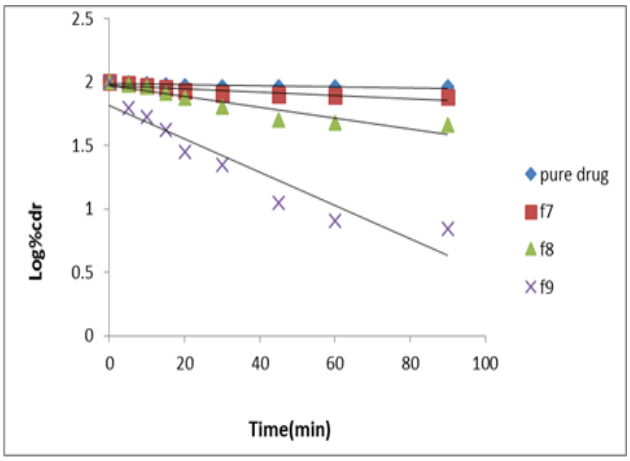

Fig 16: first-order plot of pvpk30

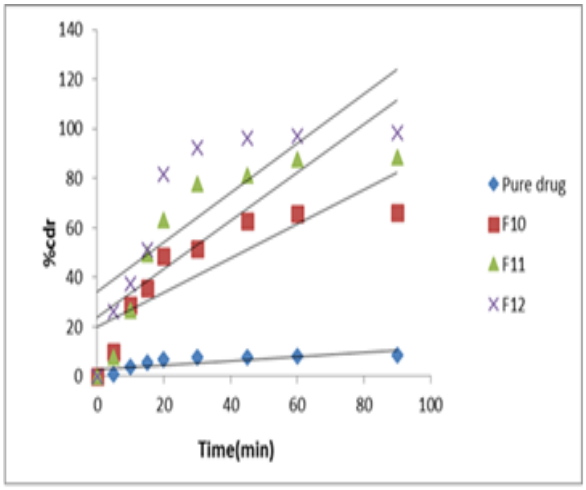

Fig 17: Zero-order plot of poloxamer

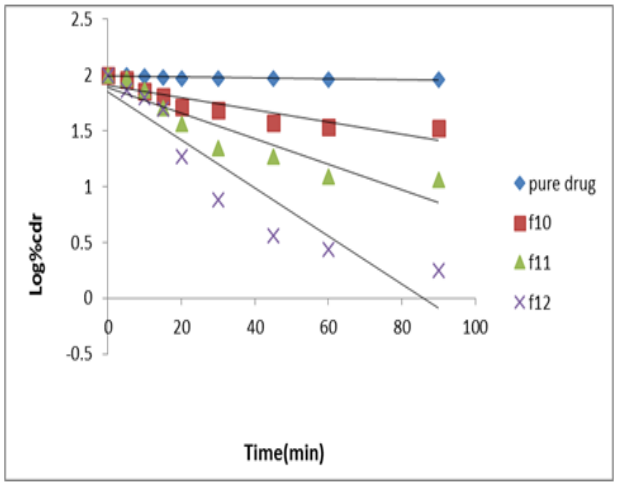

Fig 18: first-order plot of ploxame

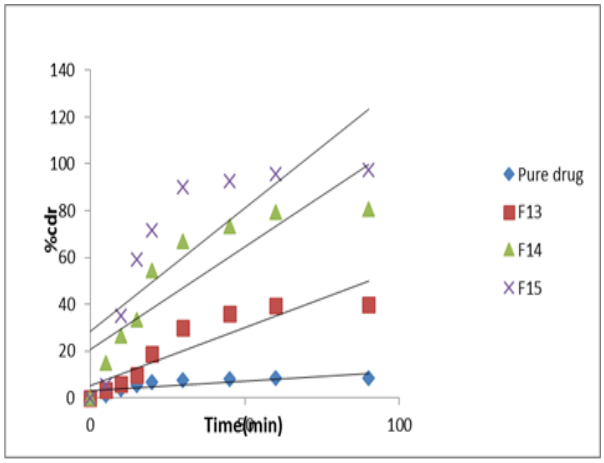

Fig 19: Zero-order plot of gelucire

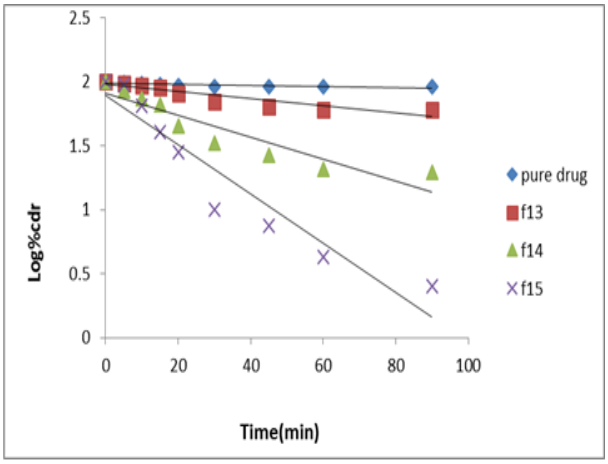

Fig 20: first-order plot of gelucire

Physical mixture:

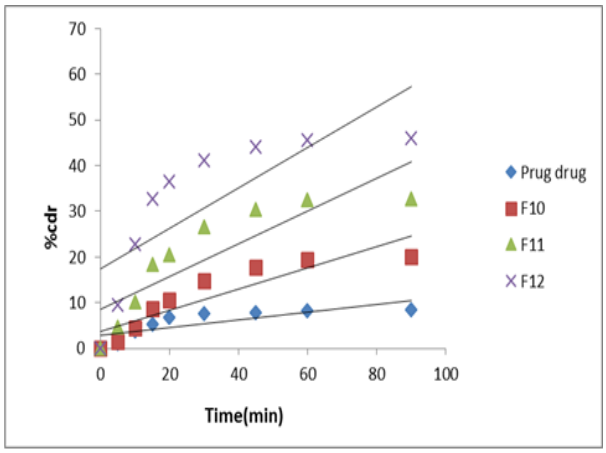

Fig 21: Zero-order plot of poloxamer

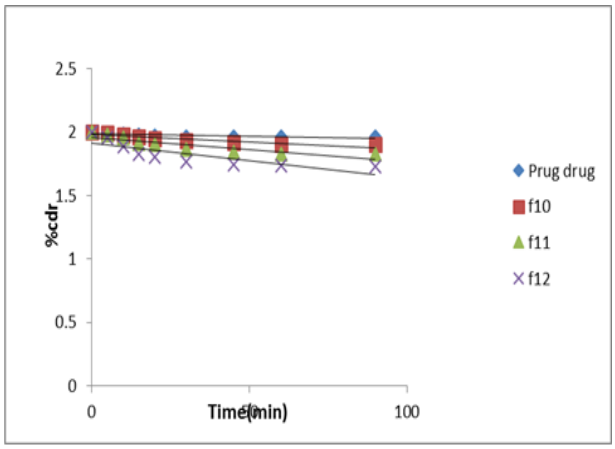

Fig 22: First-order plot of poloxamer

Table 28: Comparative drug dissolution profile (0.1N HCl)

Time (min)	Test 1	Test 2	Innovator
0	0	0	0
5	26.14221364	5.567007686	13.64189189
10	38.46927284	35.04828982	14.24470721
15	50.91698842	59.25682038	14.78963964
20	81.58381596	71.7746348	15.7222973
30	92.44288932	89.97874994	17.00427928
45	96.36422136	92.45209192	17.76587838
60	97.29930824	95.73662646	18.11227477
90	98.23439511	97.45444597	18.28468468

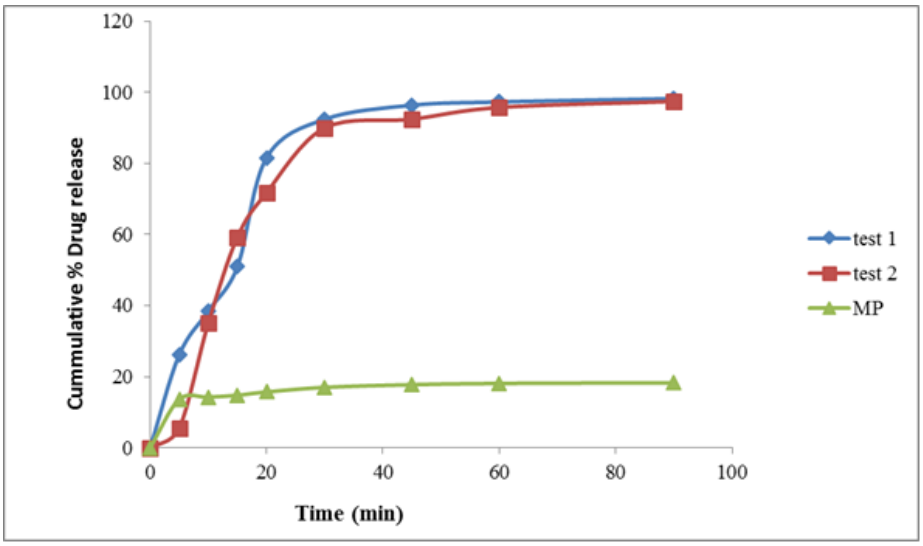

Fig 23: Comparative drug dissolution profile

***IN-VITRO* release study**

The dissolution profile of the sample containing 50mg of Epalrestat in all formulations was conducted. According to *in-vitro* dissolution data of all the above formulations polo-407, Gelucire 1:30 showed better results. By compare the all above formulations polo-407 gave better results and also improve the wettability and solubility than other. Above 1:30 formulation showed the better results because of the conversion of crystalline form to amorphous, also increase the surface area, wettability, porosity and flow property of the formulation

Table 29: Compilation of the results from the mathematical model

Solid dispersions	Ratios	Zero order	First order
Pure drug		0.630	0.637
PEG4000	**1:10**	0.681	0.683
	1:20	0.735	0.819
	1:30	0.649	0.860
PEG6000	**1:10**	0.646	0.652
	1:20	0.748	0.796
	1:30	0.679	0.809
PVP k-30	**1:10**	0.778	0.800
	1:20	0.741	0.859
	1:30	0.654	0.870
Poloxamer-407	**1:10**	0.714	0.809
	1:20	0.743	0.860
	1:30	0.768	0.911
Gelucire-50/13	**1:10**	0.752	0.844
	1:20	0.738	0.866
	1:30	0.649	0.878

CONCLUSION:

Compounds with poor water solubility are extremely challenging to be developed as a BCS class I drugs. Solid dispersion is the one of the pharmaceutical strategies to improve the oral bio availability. Solid dispersion method can able to improve their dissolution by increasing drug-polymer solubility, amorphous fraction, practical wettability and practical porosity. Epalrestat was selected as a model drug, because it's having poor aqueous solubility and low dissolution rate, while high permeability through the membranes (BCS class II drugs). Generally solid dispersion is simple method to enhance the dissolution characteristic of class II drugs, only few products using SD few marketed, because of stability problems. Normally micronized form of API shows high dissolution behavior than the un micronized API. So, the present work reveals the increasing the dissolution of Epalrestat without micronising it by solid dispersion method. The In *vitro* drug release from the formulation follows the first order kinetics than zero order kinetics because of regression coefficient.

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