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Improvement in Dissolution Rate of Flutamide by Using Gelucire 50/13 and PVP K 30 by Solid Dispersion Technique

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Keywords: Enhancement of solubility, Gelucire 50/13, Phase solubility studies, phosphate buffer, pH 7.2, *in vitro* evaluation

ABSTRACT

Flutamide, an anticancer drug for prostatic carcinoma has poor aqueous solubility and low oral bioavailability. The purpose of the study was to enhance solubility and dissolution of Flutamide by various solid dispersion techniques by using lipid based carriers. The preformulation study was carried out like Phase solubility and drug and polymer interaction by FTIR. The result shows that there was no interaction between drug and carriers. Flutamide were formulated by using polymers such as PVP K30 and Gelucire 50/13 in the ratios of 1:1, 1:2 by various solid dispersion techniques such as a fusion, solvent evaporation, co-grinding and co-precipitation methods. The prepared solid dispersion particle was carried out for different characterization like drug content, SEM, *in vitro* drug release and stability. SEM studies shows that, Where Flutamide prepared by fusion method with Gelucire 50/13, the particles having spongier in nature with relatively blunt margins shows a waxy appearance which enhances for obtaining large surface area in which particle size get reduced which could accelerate solubility and dissolution. Finally *in vitro* release was carried out with phosphate buffer PH 7.2 for a period of 6 hours the entire solid dispersion particle compared with physical mixture and pure drug.. The percentage drug release from the fusion method in the ratio of 1:2. Gelucire 50/13 shows the maximum drug release within 6 hours was found to be 91.06 %. The stability test suggests that, the release profile and drug content of the FDT is almost unchanged as stored at 4ºC with 3weeks of storing. Based on these results, it can be concluded that Flutamide can be formulated with fusion method with Gelucire 50/13 shows best release. Enhanced solubility and dissolution in phosphate buffer pH 7.2.

INTRODUCTION

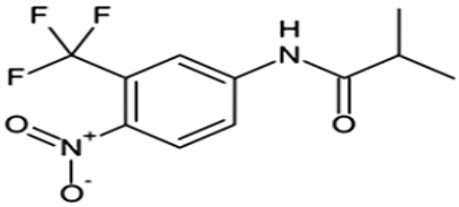
Enhancement of the bioavailability of poorly water soluble drugs has been one of the main targets of drug development during the last decade and will continue in the upcoming years. Several techniques have been developed concerning enhancement of the dissolution rate of these drugs, including particle size reduction, salt formation and preparation of solid dispersions[1]. (SDs) Solid dispersions can be defined as molecular mixtures of poorly water soluble drugs in hydrophobic carriers, which present a drug release profile that is driven by the polymer properties. During the solid dispersion preparation, the aim is to disperse the drug homogeneously within the carrier matrix and to encapsulate the hydrophobic drug to ensure complete wetting, fast carrier dissolution and improved drug stability [2].

The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols and lipids, such as polyglycolized glycerides (Gelucire) [3]. The solvent evaporation, melt adsorption, fusion, spray drying, spray congealing, and supercritical fluid precipitation are the techniques reported for the preparation of solid dispersions.

Recently, many workers reported solid dispersions using Gelucire by fusion and solvent evaporation techniques. Polyglycolized glycosides are available with a range of properties depending on their hydrophilic lipophilic balance (HLB) over the range of 1 to 18 and the melting point between 33°C and 70°C. The carbamazepine solid dispersions with Gelucire 50/13 have shown that crystallinity reduction and wetting with hydrophilic lipid are the main mechanisms responsible for increase in the dissolution rate.

Flutamide, selected in the current studies, is a poorly water soluble drug known to demonstrate dissolution or solubility limited absorption. Based upon its aqueous solubility and various dissolution parameters, the drug bioavailability can ambiguously be regarded as limited solely to dissolution [4].

Flutamide, 2-methyl-N [4-nitro-3(trifluoromethyl) phenyl] propanamide, is a nonsteroidal compound with an androgenic properties which appears to be act by inhibiting the uptake and binding of androgen in target tissues. It is used usually in the palliative treatment of prostatic carcinoma, congenital adrenal hyperplasia, hirsutism, malignant neoplasms [5].



Scheme I. Flutamide (2-methyl-*N*-[4-nitro-3-(tri-fluoromethyl)phe-nyl]propanamide).

It is practically insoluble in water, freely soluble in alcohol and in acetone, soluble in chloroform and in ether. Therefore, improvements in solubility or dissolution rate of poorly water soluble drugs can be achieved through the formation of solid dispersions.

In the present study, solvent evaporation (SE), co-grinding (CG), co-precipitation (CP) and fusion method has been used to prepare solid dispersions[6] with lipid carrier i.e. Gelucire 50/13 and PVP K30. Gelucires are a group of glyceride based excipients, composed of mixtures of mono, di, and triglycerides with polyethylene glycol esters of fatty acid and are classified by two numbers, the first referring to the approximate melting point of the base and the second to the hydrophilic lyophilic balance (HLB) value[7].

The nature and proportion of the components in the Gelucire determine the hydrophobicity and the drug release properties of the corresponding dosage forms [8]. Solid dispersions in the form of dried powder were characterized in comparison with pure Flutamide and corresponding physical mixtures in the same ratios by using Fourier Transform Infrared spectroscopy (FTIR), Differential Scanning Calorimetric Analysis (DSC), Powder X-ray Diffractometry (PXRD) techniques, and *in vitro* drug release.

MATERIALS AND METHODS

MATERIALS

Flutamide was kindly supplied by Panchsheel Organics Pvt Ltd, Gelucire 50/13 and PVP K30 were obtained from Dr. Reddy's Laboratories. All other chemicals and solvents were of analytical reagent grade.

METHODS

Preparation of physical mixture and solid dispersions physical mixtures (PM)

For the sake of comparison physical mixtures of Flutamide were prepared by mixing accurately weighed amounts of Flutamide with Gelucire 50/13, PVP K30 (ratio of drug: carrier was 1:1, 1:2) poured in a mortar by simple trituration. Stored in air tight container for further process.

Solvent evaporation method (SE) [9]

Solid dispersions were prepared by dissolving accurately weighed amounts of Flutamide and Gelucire 50/13 in Ethanol. After complete dissolution of Flutamide and Gelucire 50/13 in ethanol sonicated the solution for 20 minutes, and then the solvent was evaporated under reduced pressure at room temperature in a desiccator. Subsequently the solid mass was grounded and passed through sieve no.100 and then dried mass was packed in an airtight container**.**

Co-grinding method (CG)

Flutamide was triturated with minimum quantity of ethanol in a glass mortar until it is dissolved. The Gelucire 50/13 was gradually added and prepared suspension was triturated rapidly at room temperature until the solvent evaporated. Solid mass was grounded and passed through sieve no 100 and then dried mass was packed in removed airtight container.

Co-precipitation method (CP)

Solid dispersions were prepared by dissolving accurately weighed amounts of Gelucire 50/13 in water and Flutamide in ethanol. After complete dissolution, the aqueous solution of Gelucire 50/13 was then poured into the ethanolic solution of Flutamide. Solvent was evaporated under reduced pressure at room temperature in a desiccator. Subsequently the solid mass was grounded and passed through sieve no.100 and then dried mass was packed in an airtight container**.**

Fusion method (FM)

Solid dispersion was prepared by different ratio (1:1, 1:2) of drug and carrier melting the Gelucire 50/13 in China dish; it was kept into the liquid paraffin bath. The Flutamide was dissolved in a melted Gelucire 50/13. Solidification was reached by cooling to room temperature

under ambient conditions. Afterwards, the mixture was pulverized. Solid dispersion mass was kept into desiccator overnight allowed to solidify. Then solidified mass was milled by using screen size of 100, and then dried mass was packed in an airtight container.

Evaluation and characterization of solid dispersion

All the formulations were evaluated by phase solubility studies and *in vitro* dissolution studies. Selected samples of solid dispersion are characterized by UV, FTIR and SEM.

Phase solubility studies [10]

Solubility measurements were performed in triplicate using the method reported by Higuchi and Connors. An excess amount of Flutamide was added to the aqueous solutions with increasing concentrations of Gelucire 50/13 (i.e.1, 2, 5, 10 % w/v). Then the flasks were maintained at room temperature for 7 days with continuous stirring by using magnetic stirrer. The saturated solution was sonicated for 20 minutes and then centrifuged, the supernant were filtered through a Whatman filter paper No. 1.The filtrate was suitably diluted and analyzed spectrophotometrically at 264 nm on UV visible Spectrophotometer.

Determination of λ max and calibration data of Flutamide[11]

Stock solution of 100 µg/ml was prepared by dissolving 10 mg of pure drug in 100 ml of buffer of pH 1.2, buffer of pH 7.2 and distilled water. Solutions were suitably diluted to produce 10 µg/ml. The solutions were scanned between 200 to 400 nm. The drug exhibited λ_{max} of 264, 209 and 200 nm in buffer of pH 1.2, buffer of pH 7.2 and distilled water respectively and these values were used for further analysis. The stock solutions were suitably diluted with buffer of pH 1.2, buffer of pH 7.2 and distilled water. The absorbance of these solutions was measured at 264 nm and a graph of concentration v/s absorbance was plotted.

Fourier transforms infrared spectroscopy (FTIR)

Compatibility studies of drug with the polymer mixtures (intactness of the drug in the physical admixtures) were determined by IR spectroscopy using Shimadzu FT-IR by KBr method. FT-IR spectra of prepared samples were taken in the wavelength region was 600-3800 cm^{-1} at ambient temperature and the resolution was 4 cm^{-1} and compared the position and relative intensity of absorption band of physical admixtures and pure drugs.

Scanning electron microscopy (SEM)

Scanning electron micrograph of the solid dispersion prepared with Gelucire 50/13 in two ratio are shown 3 at a magnification ratio of x2000. Pure Flutamide was irregular crystalline shape, whereas the solid dispersion prepared by solvent evaporation method were spherical in shape, with small internal diameter (1-10).Therefore it is possible that the reduced particles size, increased surface area, and the close contact between the hydrophilic carriers and Flutamide may be responsible for the enhanced drug solubility and dissolution rate found for the solid dispersion particles.

In vitro Dissolution studies

The dissolution profile of pure Flutamide was compared with the PM and SD, using USP dissolution apparatus DS8000-Type II (Lab India, Chennai). All tests were conducted in 900 ml of distilled water maintained at 37±0.2ºC with a paddle rotation speed at 100 rpm. After every 30 mins time intervals, 10 ml of samples of dissolution medium were withdrawn and replaced by equal amount of fresh medium and then filtered through a membrane filter (0.45 µm) and the percentage of dissolved drug was determined using UV spectrophotometric method at 264 nm.

Stability studies

The stability studies were carried out as per the ICH Guidelines. The solid dispersion particles containing Gelucire 50/13 and PVP K30 ratio of 1:2 only taken for the stability studies, they were kept in small airtight glass containers and stored at different elevated temperature such as 4ºC, room temperature and 45ºC. The Drug content was observed in different time interval of I week, II and III week. At the end of every week drug content was determined.

RESULTS AND DISCUSSION

Phase Solubility Studies

Table 1: Phase solubility data for Flutamide using Gelucire 50/13

Sr. No.	Concentration of Flutamide (Mg/Ml)	Concentration of Gelucire 50/13 (%W/V)
1	1	0.151
2	2	0.313
3	5	0.712
4	10	0.911

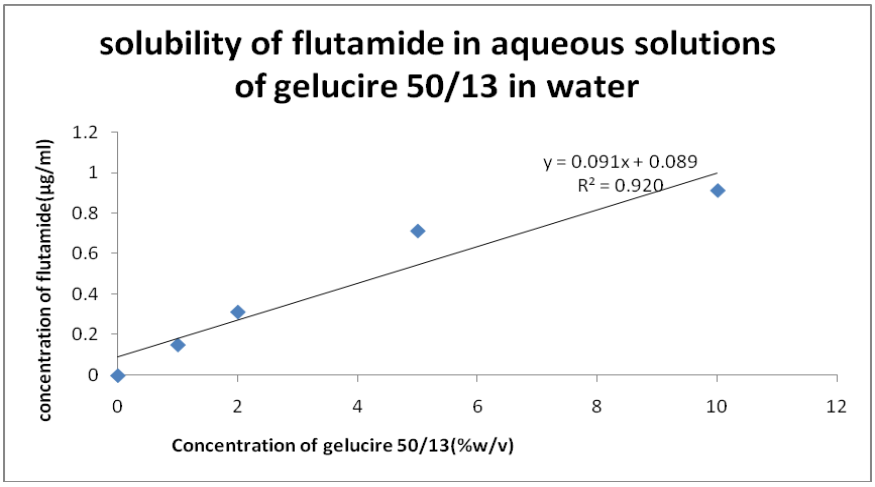


Fig. 1: Phase solubility graph of Flutamide in Gelucire50/13

Ka=slope/intercept (1-slpoe)

The values of apparent stability constant Ks, between each drug-carrier combination were computed from equation the phase solubility profile as described below:

Ks = slope/intercept (1-slope)

= 0.920/.08976 (1-0.920)

Ks = 128.1194

Phase solubility studies, the current study shows that Gelucire 50/13 have a significant solubilizing effect on Flutamide. The Fig.ure 9 shows the phase solubility curve of Flutamide in the presence of Gelucire 50/13.The solubility of Flutamide in water at room temperature is 128.1194 µg/ml. Therefore Flutamide can be considered to be a water insoluble drug. From these curve it can be seen that the apparent solubility of Flutamide increased with increasing carrier concentrations. Gelucire 50/13 shows linear graph with increasing concentration of carriers.

Construction of Calibration Curves

Table 2: Calibration curve data for Flutamide in phosphate buffer 7.2

Sr. No.	Concentration of Flutamide in µg/Ml	Absorbance at 306 nm
1	5	0.053
2	10	0.141
3	15	0.21
4	20	0.25
5	25	0.34
6	30	0.41
7	35	0.473
8	40	0.493

The standard calibration curves for Flutamide was plotted using phosphate buffer (pH 7.2) and it was found are linear (Fig.ure 8). The absorbance data for calibration curves of Flutamide are depicted in Table 4. The calibration curves yields a straight line, which shows that the drug follows Beer's law in the concentration range 5-40 µg/ml with R^2 value of 0.987 for Flutamide phosphate buffer (pH 7.2) at λ_{max} of 306 nm respectively.

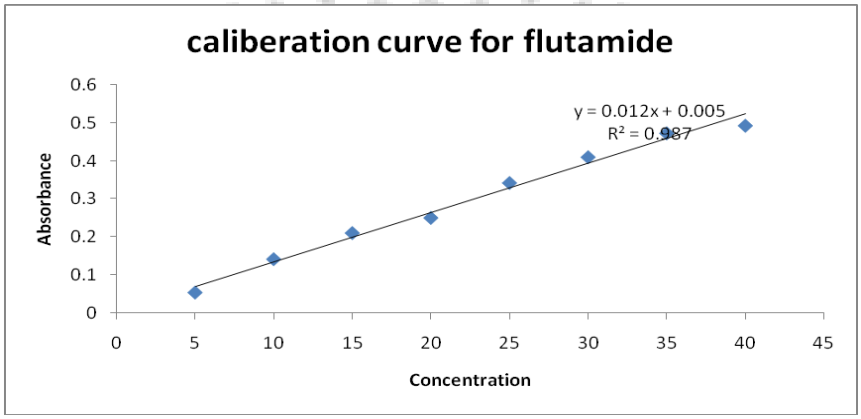


Fig. 2: Calibration curve for Flutamide in phosphate buffer 7.2

Compatibility Studies

From the results, IR spectrum of pure drug was found to be similar to the standard IR spectrum of which indicates that the obtained sample was pure Flutamide The IR spectra of all the pure samples and the Flutamide physical admixtures of suitable proportion of polymers were

subjected to the study and the results were showed in Fig.ure 3 to 7. The interpretation of the spectra with the functional group of the pure drug and the physical admixtures were given below.

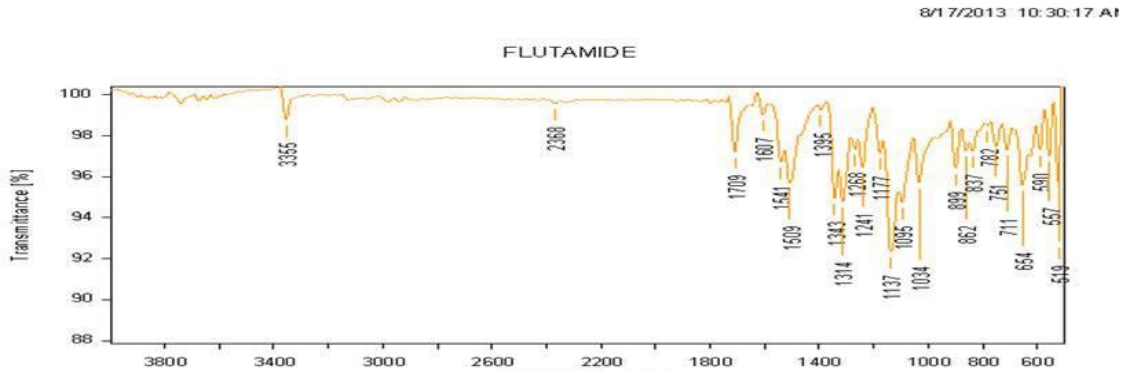


Fig.. 3: IR spectra studies of pure Flutamide

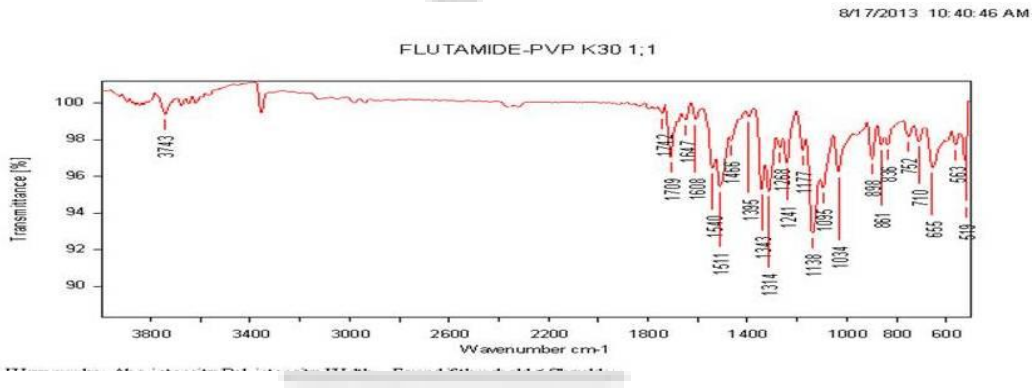


Fig. 4: IR spectra studies of physical mixture of Flutamide and PVP in the ratio 1:1

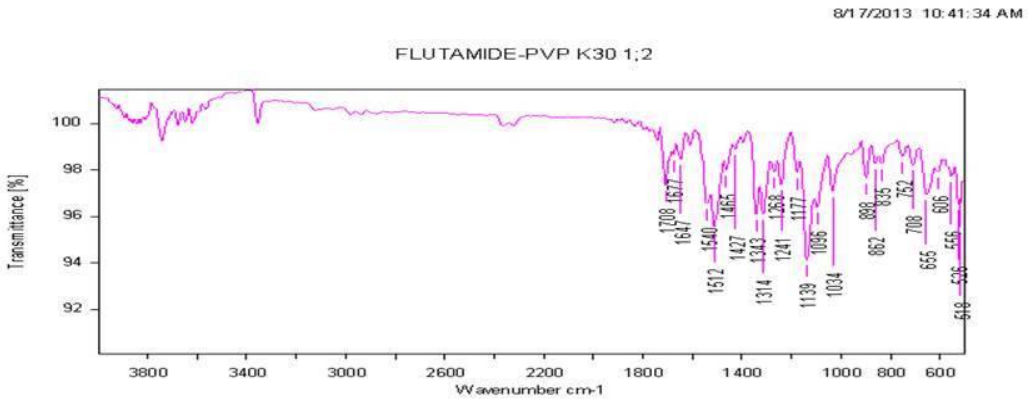


Fig. 5: IR spectra studies of physical mixture of Flutamide and PVP in the ratio 1:2

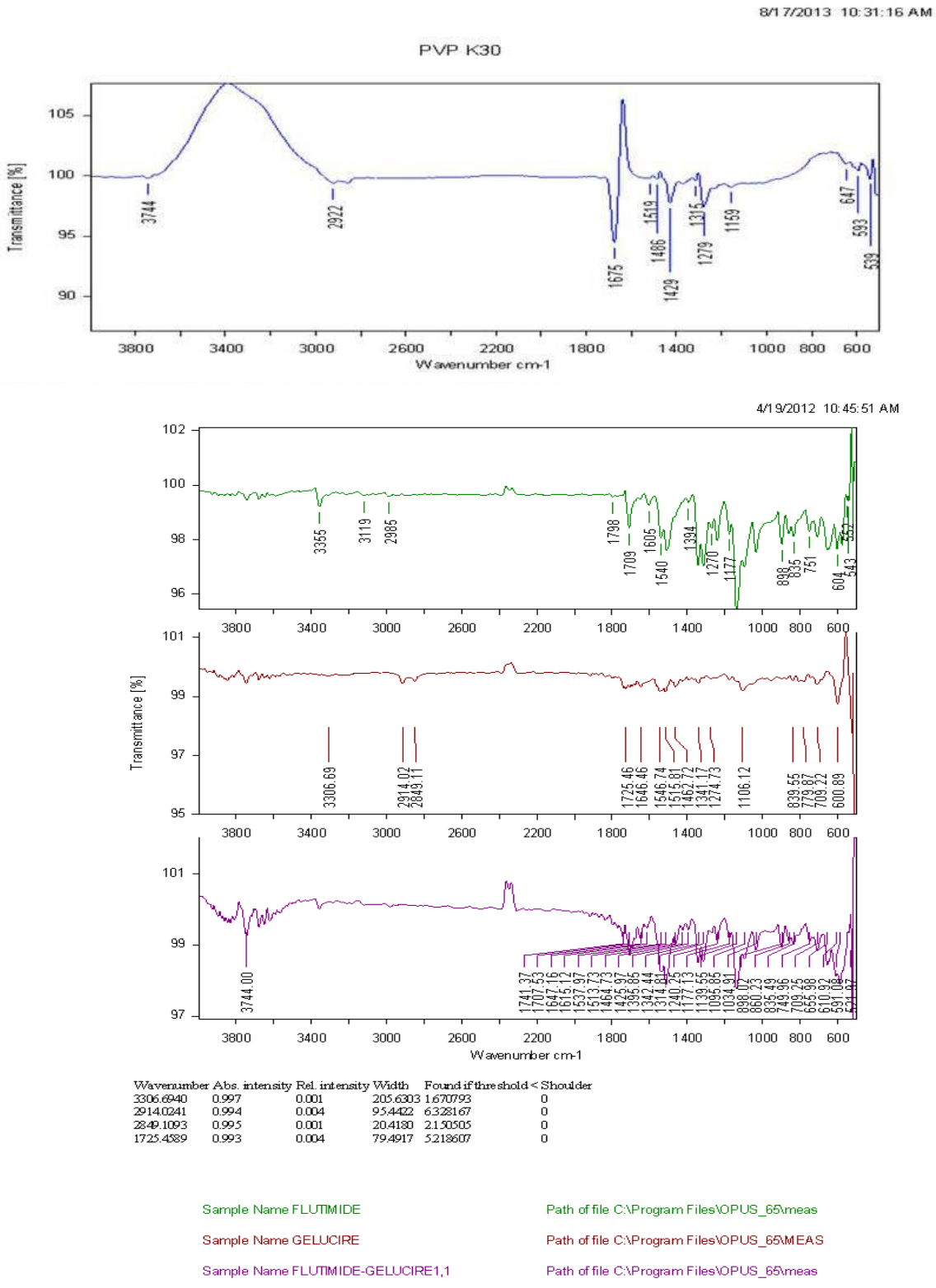


Fig. 6: IR spectra studies of Gelucire 50/13 and physical mixtures of Flutamide and Gelucire 50/13 in ratio 1:1

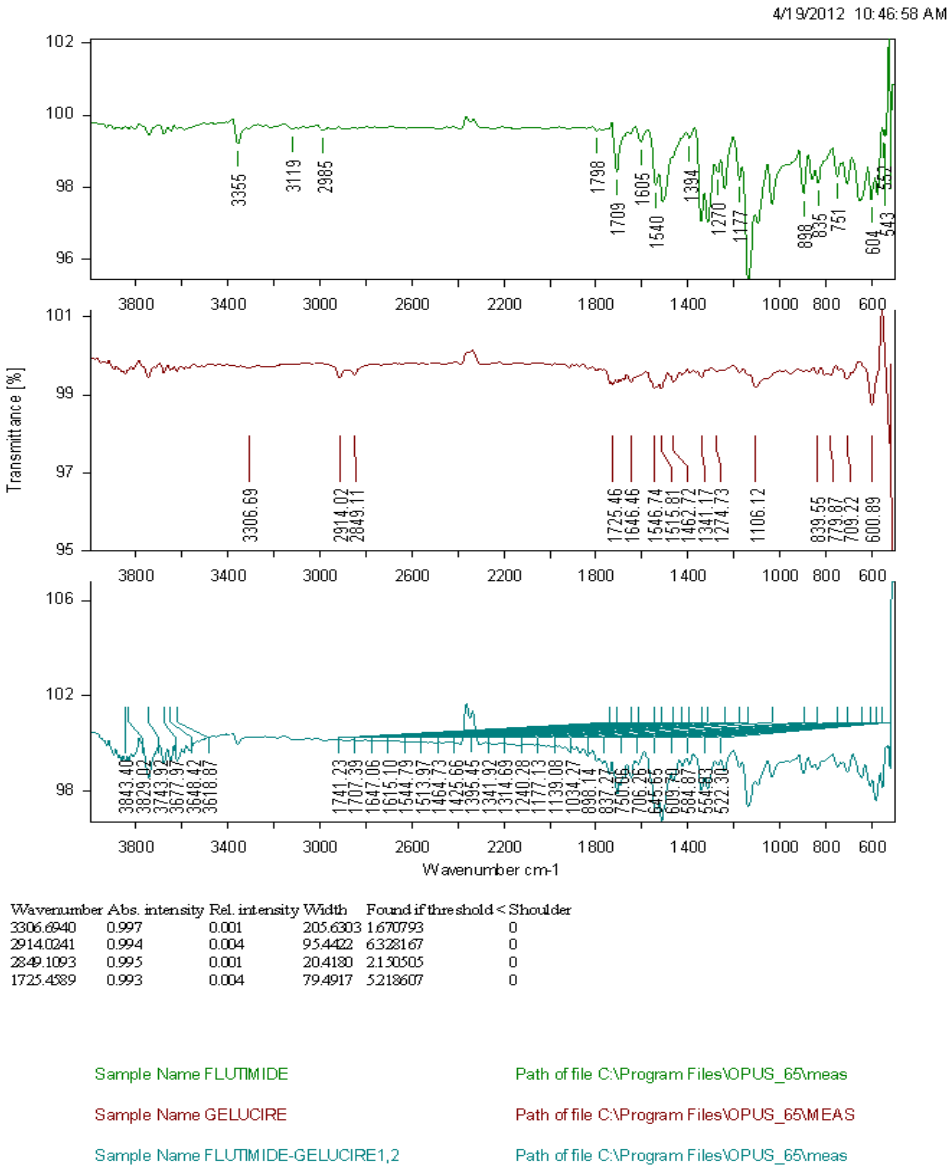


Fig. 7: IR spectra studies of Gelucire 50/13 and physical mixtures of Flutamide and Gelucire 50/13 in ratio 1:2

From the results, the functional groups such as N-H, C=O, C-F_3, N=O, C-N and it has been observed that the N-H stretching, C=O stretching, N=O stretching, C-F_3 stretching, C-N stretching of pure drug Flutamide shows unchanged in the spectra of Flutamide physical mixture. All the six spectrums show following absorption of Flutamide. Due to similar peaks it clearly indicates that there is no interaction between drug and the polymers. So we can use polymers PVP and Gelucire 50/13 for the formulation of solid dispersions.

Determination of drug content

The amount of drug content was tabulated in the Table 3 and 4. With Flutamide to Gelucire 50/13 and PVP in ratio 1:2.

Slope of the standard graph of Flutamide, (a) =0.987

Total amount of solid dispersions =150 mg

Dilution factor, (d.f.) =100

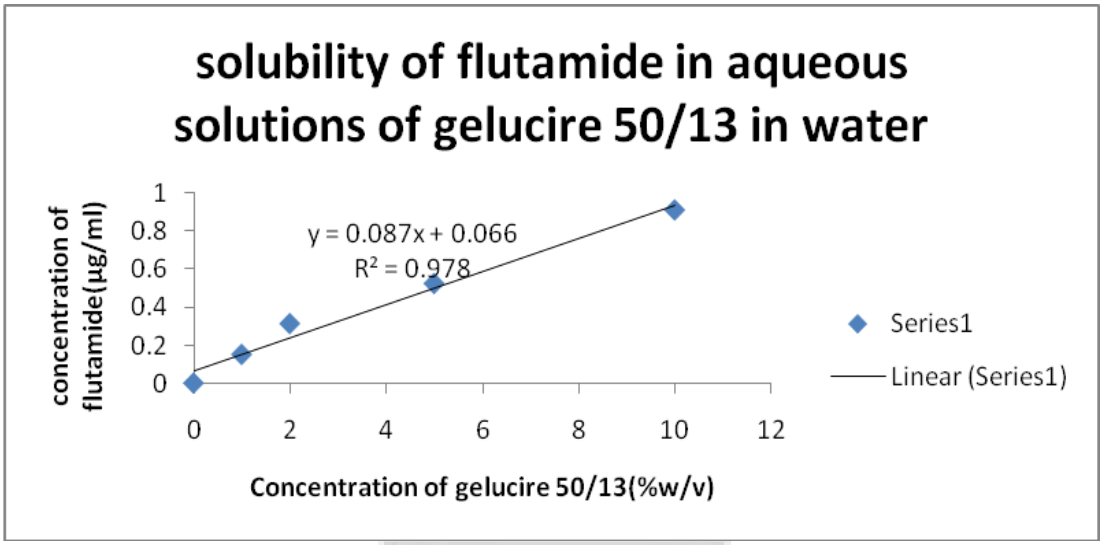


Table 3: Percentage drug loading data of solid dispersions of Flutamide using Gelucire 50/13 in ratio 1:2

Method	Absorbance of dilute extract of 10 mg of Flutamide, (b)	Concentration of Flutamide in µg/ml (b/a) x d.f.	Amount of drug containing in 100 mg of solid dispersions, (c)	Amount of drug in 150 mg of solid dispersions, (d)	Percentage drug loading, (c/d) x 100
Fusion	0.549	55.6231	0.55623	0.66	84.27±2
Solvent Evaporation	0.498	50.4559	0.50455	0.66	76.44±2
Co-Grinding	0.458	46.4032	0.46403	0.66	70.31±5
Co-Precipitation	0.428	43.3637	0.43363	0.66	65.70±1

Table 4: .Percentage drug loading data of solid dispersions of Flutamide using PVP in ratio 1:2

Method	Absorbance of dilute extract of 10 mg of Flutamide, (b)	Concentration of Flutamide in µg/ml (b/a) x d.f.	Amount of drug containing in 100 mg of solid dispersions, (c)	Amount of drug in 150 mg of solid dispersion, (d)	Percentage drug loading, (c/d) x100
Fusion	0.444	44.9848	0.4498	0.66	68.16±1
Solvent Evaporation	0.401	40.6281	0.4062	0.66	61.55±4
Co-Grinding	0.380	38.5005	0.3850	0.66	58.33±2
Co-Precipitation	0.330	33.434	0.3343	0.66	50.65±2

From the above results, the percentage of drug loading of solid dispersions of Flutamide using Gelucire 50/13 was found to be in the range of 65.70 % to 84.27 % and solid dispersions of Flutamide using PVP was found to be in the range 65.52 % to 72.73 %. From the results it was observed that, the percentage drug loading was found to be more in Gelucire 50/13 than PVP and it was found to be best at fusion technique.

Morphological Studies

Scanning electron microscopy (SEM)

The surface morphology of all the formulations was determined by SEM for characterization of shape and size of microspheres and the scanned SEM images are shown in photomicrograph 8 to 13. The result shows that native Flutamide powder has rectangular flaky appearing particles. The incorporation of Gelucire 50/13 in the solution gave rise to spongy scaly appearing particles with relatively blunt margins, these gives a waxy appearing particle with the disappearance of the Flutamide particle shape showing spongier appearance and higher void spaces. The SEM micrograph of solid dispersion formulation suggests that particle size of the drug might have been reduced than the pure drug which accelerates solubility and dissolution.

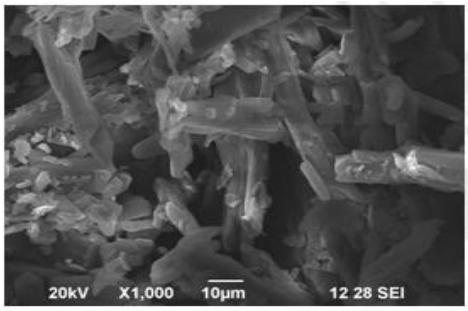


Fig. 8 SEM image of pure drug flutamide

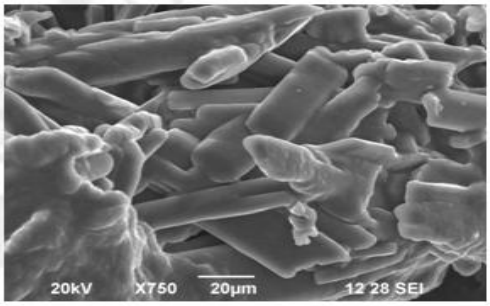


Fig. 9 SEM image of physical mixtures of gelucire 50/13 and flutamide with drug to polymer ratio 1:2

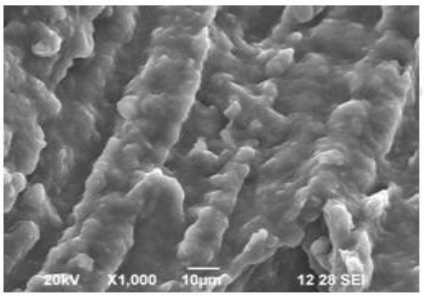


Fig.10 SEM image of solid dispersion of flutamide with drug to polymer ratio 1:2 using co grinding method

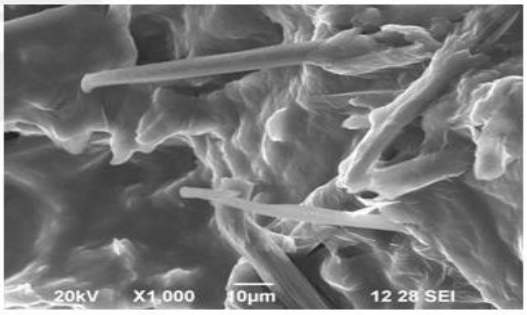


Fig.11 SEM image of solid dispersion of flutamide with drug to polymer ratio 1:2 using co precipitation method

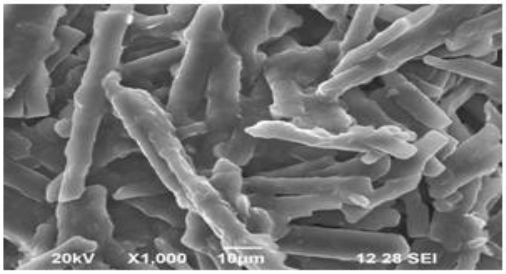


Figure 12 SEM image of solid dispersion of flutamide with drug to polymer ratio 1:2 using fusion method

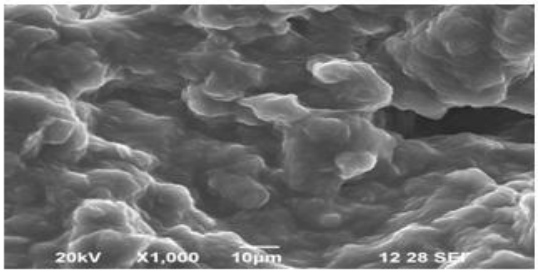


Figure 13 SEM image of solid dispersion of flutamide with drug to polymer ratio 1:2 using solvent evaporation method

In vitro release studies

The release profiles of various solid dispersions were studied for six hours using phosphate buffer 7.2. The *in vitro* release of all batches of formulations of solid dispersions were shown in Table 5 to Table 13 and comparative *in vitro* release curve of all batches given below.

Table 5: *In vitro* drug release studies data of pure drug Flutamide

Time in hours	Absorbance (nm)	Concentration (µg/ml)	Cumulative amount released (mg in 900 ml)	Cumulative percentage drug release
1	0.034	3.4447	3.1003	6.2006
2	0.051	5.1671	4.6504	9.3009
3	0.077	7.8014	7.0212	14.0425
4	0.101	10.2330	9.2097	18.4194
5	0.124	12.5633	11.3069	22.6139
6	0.149	15.0962	13.5866	27.1732

Table 6: *In vitro* drug release studies data using physical mixture of ratio Drug and PVP 1:1

Time in hours	Absorbance (nm)	Concentration (µg/ml)	Cumulative amount released (mg in 900 ml)	Cumulative percentage drug release
1	0.044	4.4579	4.0121	8.0243
2	0.071	7.1935	6.4741	12.9483
3	0.092	9.3211	8.3890	16.7781
4	0.109	11.0435	9.9392	19.8784
5	0.132	13.3738	12.0364	24.0729
6	0.165	16.7173	15.0455	30.0911

Table 7: *In vitro* drug release studies data using physical mixture of ratio Drug and PVP 1:2

Time in hours	Absorbance (nm)	Concentration (µg/ml)	Cumulative amount released (mg in 900 ml)	Cumulative percentage drug release
1	0.084	8.5106	7.6595	15.3191
2	0.104	10.5369	9.4832	18.9665
3	0.128	12.9685	11.6717	23.3434
4	0.149	15.0962	13.5866	27.1732
5	0.17	17.2239	15.5015	31.0030
6	0.181	18.3383	16.5045	33.0091

Table 8: *In vitro* drug release studies data using physical mixture of ratio Drug and Gelucire 50/13 1:1

Time in hours	Absorbance (nm)	Concentration (µg/ml)	Cumulative amount released (mg in 900 ml)	Cumulative percentage drug release
1	0.048	4.8632	4.3768	8.7537
2	0.071	7.1935	6.4741	12.9483
3	0.089	9.0172	8.1155	16.2310
4	0.117	11.8541	10.6686	21.3373
5	0.143	14.4883	13.0395	26.0790
6	0.199	20.1621	18.1458	36.2917

Table 9: *In vitro* drug release studies data using physical mixture of ratio Drug and Gelucire 50/13 1:2

Time in hours	Absorbance (nm)	Concentration (µg/ml)	Cumulative amount released (mg in 900 ml)	Cumulative percentage drug release
1	0.057	5.7750	5.1975	10.3951
2	0.08	8.1053	7.2948	14.5896
3	0.101	10.2330	9.2097	18.4194
4	0.122	12.3606	11.1246	22.2492
5	0.151	15.2988	13.7689	27.5379
6	0.21	21.2765	19.1489	38.2978

Comparative *in vitro* drug release studies

The comparative *in vitro* drug release data of various solid dispersions were shown in Table below. And also comparative *in vitro* drug release plot of formulations of various solid dispersions using different method were shown in Figure 14 and 17.

Table 10: Comparative cumulative percentage of drug release data of Drug and PVP ratio 1:1

Time in Hours	Pure Drug	Physical mixture	Co-precipitation method	Co-grinding Method	Solvent Evaporation Method	Fusion Method
1	6.2006	8.0243	12.5835	17.6899	22.0668	23.8905
2	9.3009	12.9483	16.9604	21.7021	26.8085	29.5440
3	14.0425	16.7781	19.5136	27.1732	32.8267	35.7446
4	18.4194	19.8784	24.4376	31.7325	35.3799	39.0273
5	22.6139	24.0729	32.6443	36.6565	38.2978	42.3100
6	27.1732	30.0911	40.1215	42.1276	43.5866	45.7750

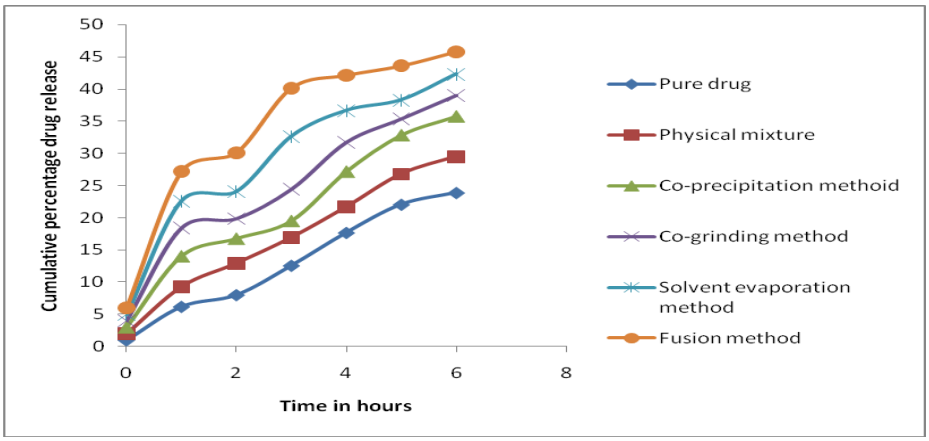


Fig. 14: Comparative *in vitro* drug release plot of Flutamide-PVP solid dispersions with ratio 1:1

Table11: Comparative cumulative percentage of drug release data of Drug to PVP ratio 1:2

Time in Hours	Pure Drug	Physical mixture	Co-precipitation method	Co-grinding Method	Solvent Evaporation Method	Fusion Method
1	6.2006	15.3191	19.8784	22.2492	26.8085	27.1732
2	9.3009	18.9665	25.3495	24.4376	27.7203	28.6322
3	14.0425	23.3434	26.9908	29.7264	31.1854	36.1094
4	18.4194	27.1732	33.5562	37.5683	37.9331	40.3039
5	22.6139	31.0030	38.4802	40.3039	41.5805	44.498
6	27.1732	33.0091	43.9516	47.5987	49.6048	51.9756

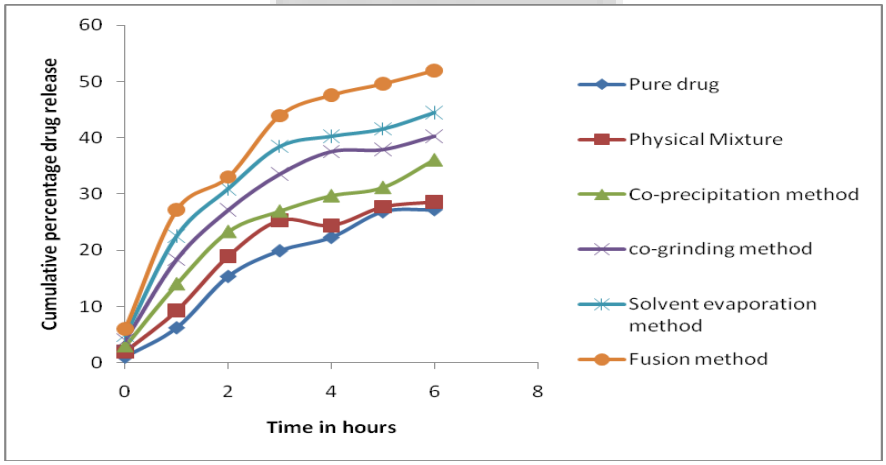


Fig. 15: Comparative *in vitro* drug release plot of Flutamide-PVP solid dispersions with ratio 1:2

Table 12: Comparative cumulative percentage of drug release data of drug to Gelucire 50/13 in ratio 1:1

Time in Hours	Pure Drug	Physical mixture	Co-precipitation method	Co-grinding Method	Solvent Evaporation Method	Fusion Method
1	6.2006	8.7537	28.449	35.3799	38.2978	42.1276
2	9.3009	12.9483	30.4559	40.8510	44.1337	47.5987
3	14.0425	16.2310	34.4680	48.1456	53.2522	58.3586
4	18.4194	21.3373	40.4863	54.8936	59.8176	64.9240
5	22.6139	26.0790	49.9696	58.3586	62.5531	68.5714
6	27.1732	36.2917	57.8115	63.6474	67.6595	74.4072

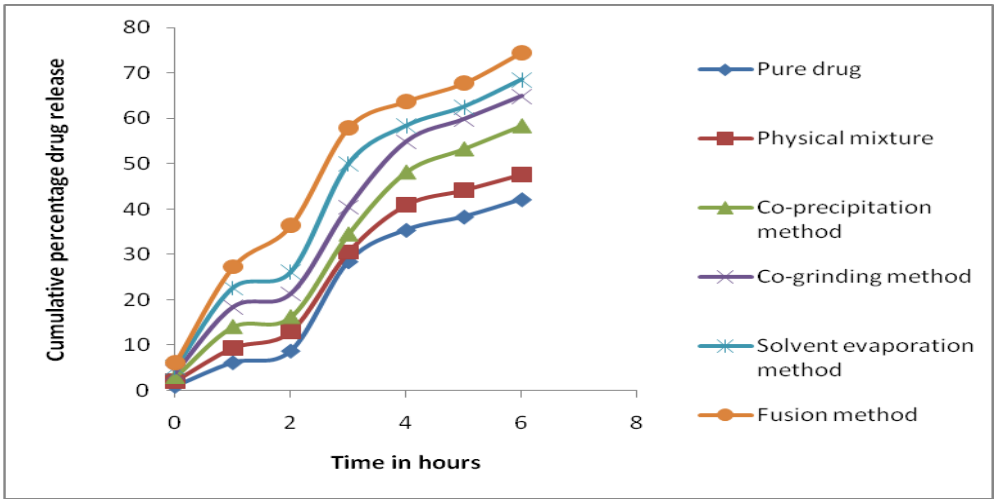


Fig. 16: Comparative *in vitro* drug release plot of Flutamide Gelucire 50/13 solid dispersions with ratio 1:1

Table 13: Comparative cumulative percentage of drug release data of Drug to Gelucire 50/13 in ratio 1:2

Time in Hours	Pure Drug	Physical mixture	Co-precipitation method	Co-grinding Method	Solvent Evaporation Method	Fusion Method
1	6.2006	10.3951	28.449	42.6747	56.5349	62.3708
2	9.3009	14.5896	30.4559	49.0577	63.4650	66.3829
3	14.0425	18.4194	34.4680	59.2705	70.5775	72.4012
4	18.4194	22.2492	40.4863	66.3829	76.4133	80.2431
5	22.6139	27.5379	49.9696	71.4893	80.2431	85.1671
6	27.1732	38.2978	57.8115	76.9604	86.4437	91.0030

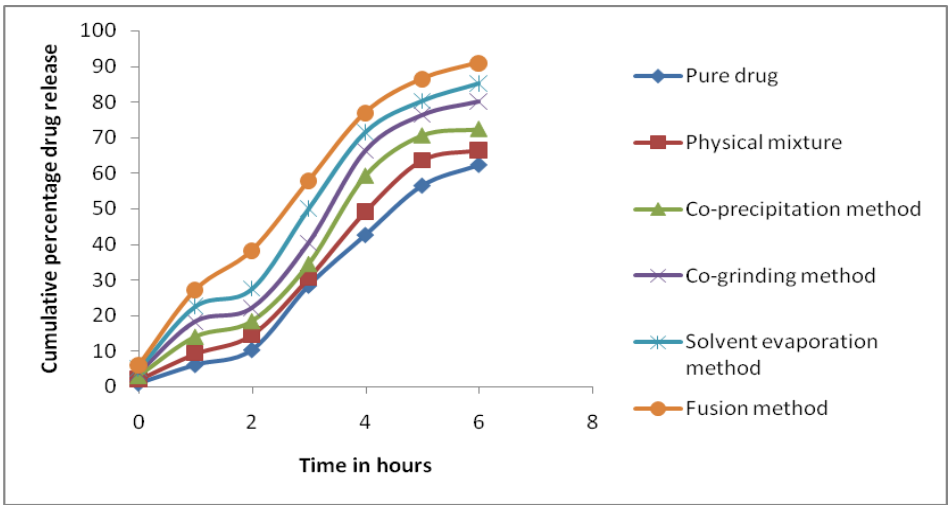


Fig.. 17: Comparative *in vitro* drug release plot of Flutamide Gelucire 50/13 solid dispersions with ratio 1:2

The dissolution pattern of solid dispersions of Flutamide was compared to that of pure drug and it was found that percentage drug release of solid dispersion was increased than pure drug. The release profile of all the formulations of solid dispersions was studied for 6 hours using phosphate buffer $_{P}$H 7.2.The *in vitro* release of all the batches of solid dispersion formulations were shown in Table 5 to 13 and *in vitro* release curves of all batches are shown in Figure 14 to 17. The dissolution rate profiles are plotted as the percentage release from the Flutamide from the various formulations of solid dispersions, physical mixture and pure Flutamide versus time in hours. The rate of dissolution of pure Flutamide was very slow compared with physical mixture and Flutamide formulation of solid dispersions. The results of release indicate more dissolution effect with increase in concentration of polymer. As compared to PVP the drug released from Gelucire 50/13 has more cumulative percentage of drug release. The percentage drug release from the prepared fusion method of solid dispersion of 1:2 Gelucire was found to be maximum (91.063 %) at the end of 6 hrs.

Stability studies

The stability studies were carried out as per the ICH Guidelines. The solid dispersion particles containing Gelucire 50/13 and PVP K30 ratio of 1:2 only taken for the stability studies, they were kept in small airtight glass containers and stored at different elevated temperature such as 4ºC, room temperature and 45ºC. There was no appreciable changes in drug content was

observed in 4ºC. So suitable storage condition was 4ºC. Table (14) showed the percentage of drug content.

Table 14 Accelerated stability analysis data

Parameter	Drug and carrier ratio	Temperature	Time (week)			
			Initial	1st	2nd	3rd
Drug content (%)	Flutamide and PVP K30 1:2 ratio Fusion method	4ºC	98±1	96±3	94±5	93±1
		Room temp	96±4	90±1	87±6	86±4
		45ºC	96±2	92±1	85±4	83±8
	Flutamide and Gelucire 50/13 1:2 ratio Fusion method	4ºC	99±3	98±3	98±5	97±3
		Room temp	98±5	96±5	94±6	90±4
		45ºC	98±1	95±3	92±1	90±3

CONCLUSION

Enhancement in the solubility and dissolution characteristics of poorly water soluble drug is important to achieve better bioavailability. Thus present study was aimed to enhance the solubility and dissolution rate of Flutamide with PVP K30 and Gelucire 50/13 prepared by different solid dispersion technique such as solvent evaporation method, co- precipitation, co grinding and fusion method. Finally it can be concluded that among the various methods, the fusion method shows the maximum drug release within 6 hours, found to be significant and simplest method. By SEM studies shows that the particles having spongier in nature with relatively blunt margins shows a waxy appearance in which enhances for obtaining large surface area in which particle size get reduced which could accelerate solubility and dissolution for enhancing the solubility of Flutamide, the most suitable carrier for enhancing the solubility of Flutamide was Gelucire 50/13. The drug dissolution rate was high at the drug-to-polymer composition ratio of 1:2 (w/w). The phosphate buffer pH 7.2 was found to be best dissolution medium for carrying out increase in dissolution rate of Flutamide.

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