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COMPARATIVE STUDY OF ACYCLOVIR SOLID DISPERSION FOR BIOAVAILABILITY ENHANCEMENT

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ABSTRACT

The objective of present study is to improve the dissolution rate of Acyclovir a poorly water soluble drug by solid dispersion technique using a water soluble carrier, PEG-6000, urea, mannitol. The solid dispersions are prepared by physical method, co-grinding method and solvent evaporation method. The prepared solid dispersions showed an enhancement in dissolution rate and solubility compared to plain drug. In vitro release profiles of all SDs were comparatively evaluated and also studied against pure acyclovir. Faster dissolution was exhibited by solid dispersion containing 1:4 ratio of drug: PEG-6000. The increase in dissolution rate of the drug may be due to increase in wettability, hydrophilic nature of the carrier and due to reduction in drug crystallinity. The prepared solid dispersion was subjected for % practical yield, drug content, infrared (IR) spectroscopic, differential scanning calorimetry (DSC). FT-IR spectra revealed no chemical incompatibility between drug and PEG-6000.Drug– polymer interaction was investigated using differential scanning calorimetry (DSC) studies.

Key words: Solid dispersions, carriers, solubility enhancement, poorly soluble drugs, bioavailability

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INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously. There are various techniques available to improve the solubility of poorly soluble drugs[1, 2] such Micronization, Nanosuspension, Modification of the crystal habits, Eutectic mixtures, Solid dispersions, Micro emulsions, Self micro emulsifying drug delivery systems, cyclodextrin inclusion and lipid based delivery systems etc. SDs is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The concept of solid dispersions (SDs) was introduced in 1961 by Sekiguchi[3, 4] in which the drug is dispersed in inert water - soluble carrier at solid state. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone (PVP) and polyethylene glycols are used as carriers for SDs[4-7,]

Acyclovir is a purine nucleoside (deoxiguanosine) analogue, has activity against human herpes viruses. One of the most commonly used antiviral drugs; it is primarily used for the treatment of herpes simplex virus infections, as well as in the treatment of herpes zoster. Acyclovir was seen as the start of a new era in antiviral therapy, as it is extremely selective and low in cytotoxicity. It acts as an antimetabolite and very potent inhibitor of viral DNA polymerase.

The major drawback of this drug is its low aqueous solubility that delays its absorption and has poor oral bioavailability (15-30%), hence intravenous administration is necessary if high concentrations are required. When orally administered, peak plasma concentration occurs after 1–2 hours. Therefore the absorption and its dissolution rate are increased by formulating solid dispersions. The present study is aimed to formulate solid dispersion of acyclovir to overcome its low bioavailability (15-30%).

The main objective of my work is to compare the efficacy of several methods such as physical mixing, co-grinding method and solvent evaporation method in improving the solubility and dissolution rate of acyclovir by preparing solid dispersion with various water soluble polymers such as mannitol, PEG 6000 and urea. The solid dispersion are evaluated for % yield, drug content, in- vitro and in-vivo dissolution rate studies and interaction between the drug and polymers using IR spectral studies and DSC[8, 9].

MATERIAL AND METHOD

Materials

Acyclovir was obtained as a gift sample from Arochem Industries, Thane, Mumbai. PEG-6-000 Mannitol, and Urea of pharmacopoeial grade were purchased from Parched from Central Drug House, New Delhi, India. All reagents were of A.R. grade. Double distilled water was used for all the experiments.

Preparation of solid dispersions

Solid dispersions were prepared by mixing various polymers[10] and using different methods[11, 12] as shown in Table1, 2, and 3.

Physical mixture

The physical mixtures of Acyclovir with polymer were prepared by, weighing the calculated amount of drug and carriers and then thoroughly mixing them in a glass mortar for 30 min by constant triturating. Then resultant physical mixtures were passed through sieve # 60 and stored in desiccators until used for further studies[13, 14].

Table 1: Formulation Chart for Physical Mixture Method

S. No.	Formulation code	Ingredients	Composition
1	PMU1	Drug : Urea	1 : 1
2	PMU2	Drug : Urea	1 : 2
3	PMU3	Drug : Urea	1 : 3
4	PMU4	Drug : Urea	1 : 4
5	PMM1	Drug : Mannitol	1 : 1
6	PMM2	Drug : Mannitol	1 : 2
7	PMM3	Drug : Mannitol	1 : 3
8	PMM4	Drug : Mannitol	1 : 4
9	PMP1	Drug : PEG-6000	1 : 1
10	PMP2	Drug : PEG-6000	1 : 2
11	PMP3	Drug : PEG-6000	1 : 3
12	PMP4	Drug : PEG-6000	1 : 4

Co-grinding Method

The calculated amounts of drug and carriers where weighed and mixed together with one ml of water. The damp mass obtained was passed through a sieve # 60. The resultant granules were dispersed in Petri dishes and dried at 60°C under vacuum, until a constant weight was obtained. The granules obtained were stored in desiccators until used for further studies[15, 16].

Solvent Evaporation Method

The calculated amount of drug and polymer were dissolved in few ml of solvent dichloromethane with constant stirring. Then the solvent was completely evaporated at 40°C under vacuum, until the solid mass dried. Then dried mass was pulverized, passed through sieve # 60 and stored in desiccators until used for further studies[17]

Table 2: Formulation Chart for Co-grinding Method

S. No.	Formulation code	Ingredients	Composition
1	CGU1	Drug : Urea	1 : 1
2	CGU2	Drug : Urea	1 : 2
3	CGU3	Drug : Urea	1 : 3
4	CGU4	Drug : Urea	1 : 4
5	CGM1	Drug : Mannitol	1 : 1
6	CGM2	Drug : Mannitol	1 : 2
7	CGM3	Drug : Mannitol	1 : 3
8	CGM4	Drug : Mannitol	1 : 4
9	CGP1	Drug : PEG-6000	1 : 1
10	CGP2	Drug : PEG-6000	1 : 2
11	CGP3	Drug : PEG-6000	1 : 3
12	CGP4	Drug : PEG-6000	1 : 4

Table 3: Formulation Chart for Solvent evaporation Method

S. No.	Formulation code	Ingredients	Composition
1	SEU1	Drug : Urea	1 : 1
2	SEU2	Drug : Urea	1 : 2
3	SEU3	Drug : Urea	1 : 3
4	SEU4	Drug : Urea	1 : 4
5	SEM1	Drug : Mannitol	1 : 1
6	SEM2	Drug : Mannitol	1 : 2
7	SEM3	Drug : Mannitol	1 : 3
8	SEM4	Drug : Mannitol	1 : 4
9	SEP1	Drug : PEG-6000	1 : 1
10	SEP2	Drug : PEG-6000	1 : 2
11	SEP3	Drug : PEG-6000	1 : 3
12	SEP4	Drug : PEG-6000	1 : 4

EVALUATION OF ACYCLOVIR SOLID DISPERSIONS

Percent practical yield (PY)

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation. The results was shown in Figure 1, 2, 3.

PY (%) = [Practical Mass (Solid dispersion) / Theoretical Mass (Drug + Carrier)] × 100

Drug Content

The solid dispersions of drug prepared by physical mixture method, co-grinding method and solvent evaporation method were assayed for drug content by dissolving specific amount of solid dispersions in 10 ml of distilled water. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbance of solutions were determined at 252 nm by UV-visible spectrophotometer. Three replicates were prepared and average value was reported. The results was shown in Figure 4, 5, 6. The actual drug content

% Drug content = Actual amount of drug in solid dispersion/ Theoretical amount of drug in solid dispersion x 100

Aqueous Solubility Study

The solubility[18]of Acyclovir as pure drug and its solid dispersion were determined in distilled water. Acyclovir and solid dispersion equivalent to 10 mg of drug was taken and to this 10 ml of respective medium was being added in 100 ml stoppered volumetric flask and shaken for 25 hrs at RT on magnetic stirrer. The entire samples were protected from light by wrapping the flask by aluminum foil. After 24 hr samples were filtered through Whatman filter paper no. 42 and aliquots were suitably diluted and assayed spectroscopically at 252 nm. Each solubility was determined in triplicate and average values were reported. The results was shown in Table 4,5, 6.

***In-vitro* Dissolution Studies**

Dissolution study of pure drug and its solid dispersion was carried out by using USP XXIII basket type dissolution apparatus for 2 hr. the stirring rate was 60 rpm. The dissolution medium was 900 ml 7.4 pH phosphate buffer kept at 37°C ± 0.5°C. The solid dispersions containing 10 mg equivalent of Acyclovir was taken in a muslin cloth and kept in the basket of dissolution apparatus. Samples of 5 ml were withdrawn at specified time intervals, filtered and analyzed spectrophotometrically at 252 nm using Shimadzu-1700 UV-visible spectrophotometer. The samples withdrawn were replaced by fresh buffer solution. Each preparation was tested in triplicate and then means values were calculated. The values were calculated for cumulative %

drug release and the same was used while plotting the release curves. The percent drug release at various time intervals calculated and plotted against time.

Stability Study

Stability study for selected solid dispersions was carried out by storing 1 gm of solid dispersions in an amber colored screw capped bottle at different temperatures and relative humidity, accelerated (50 ± 2°C/75 ± 5 % RH) and ambient (25 ± 2°C/60% RH) for a period of 3 months. Samples are withdrawn at 0, 15, 30 and 60 days periods. These samples were visually examined for any physical changes, percent drug content and *In-vitro* dissolution study.

CHARACTERIZATION OF SOLID DISPERSION

Fourier Transform Infra Red Spectral studies

FTIR spectra were obtained on FTIR spectrometer (Perkin Elmer BX) from 4000 cm^{-1} to 400 cm^{-1} using KBr pellets method. Samples were mixed with KBr powder in ratio of 3:97 (sample: KBr) in glass mortar. Pellets of sample of 10mm disc are prepared at pressure 10 tons for 30 seconds at a resolution of 4 cm^{-1}.

Differential Scanning Calorimetry studies

The DSC measurement were performed by differential scanning calorimeter[19] (Mettler Toledo Star System, Switzerland) in Central Instrumentation Lab, NIPER (National Institute of Pharmaceutical Education and Research) Mohali, Chandigarh. Temperature and enthalpy were calibrated with the standard materials Indium (melting point =156.6ºC) and Zinc (melting point =419.5ºC) at a heating rate of 5ºC/min. Sample (3-4 mg) were accurately weight and sealed in aluminum pans and heated at a rate of 5ºC/min. Heating scans by 10ºC/min. were applied with a nitrogen purge of 20ml/min. over a temperature range of 30ºC to 285ºC. An empty aluminum used as reference.

RESULT AND DISCUSSION

Percent practical yield (PY)

The percentage practical yield for all the formulations of solid dispersions was found to be between the range of 86.50 ± 0.72 % to 98.35 ± 0.88 % (n = 3). Maximum yield was found to be 98% of formulation CGP4. This is because there is minimum loss of formulation occur in preparation of solid dispersions via co-grinding method, as mixing done in presence of distilled water. The evaporation is less in case of D. W. as compare to solvent used in solvent evaporation method. So this method shows good % practical yield. The results are shown in Figure 1, 2, 3.

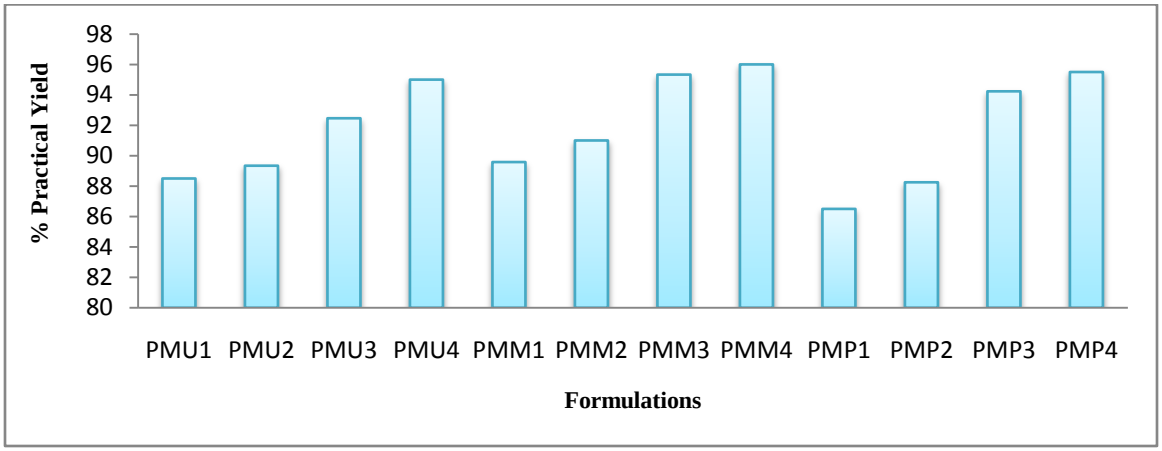

Figure 1: % Practical yield for physical Method

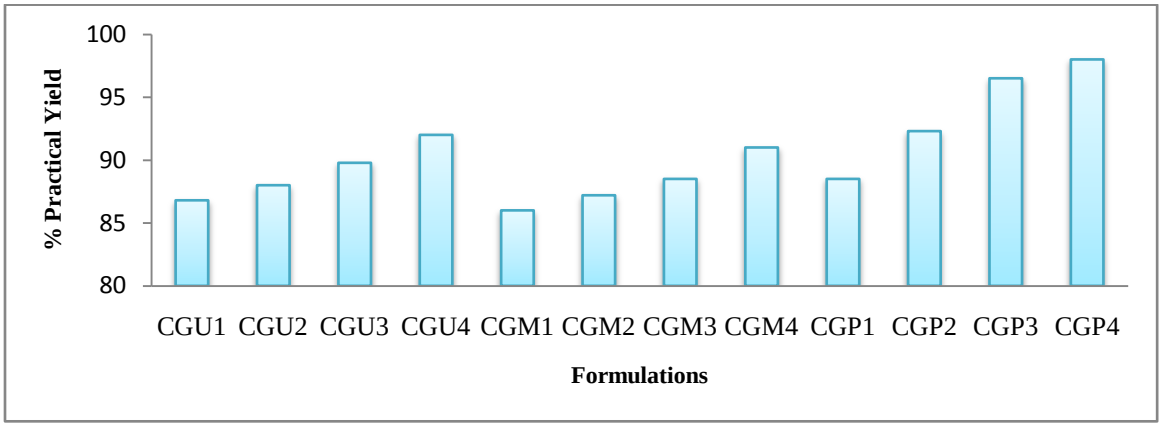

Figure 2: % Practical yield for co-grinding Method

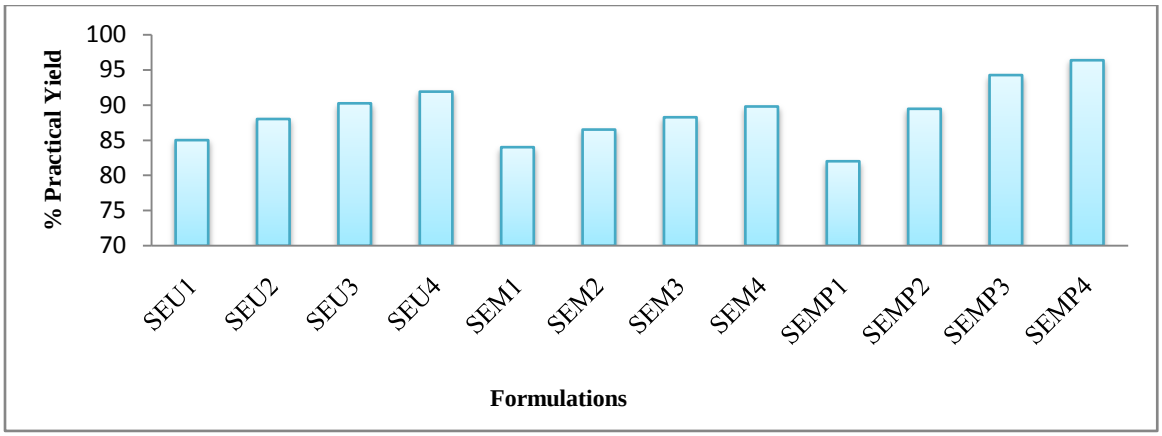

Figure 3: % Practical yield for Solvent Evaporation Method

Drug content

The percentage drug content for all the formulations of solid dispersions was found to be between the range of 56.50 ± 0.72 % to 91.35 ± 0.88 % (n = 3). Maximum yield was found to be 91.35 % of formulation SEP4. The solvent evaporation method of preparation results more

uniform dispersion with high content uniformity than formed by physical and co-grinding method. So it shown higher % drug content. The results are shown in Figure 4, 5, 6.

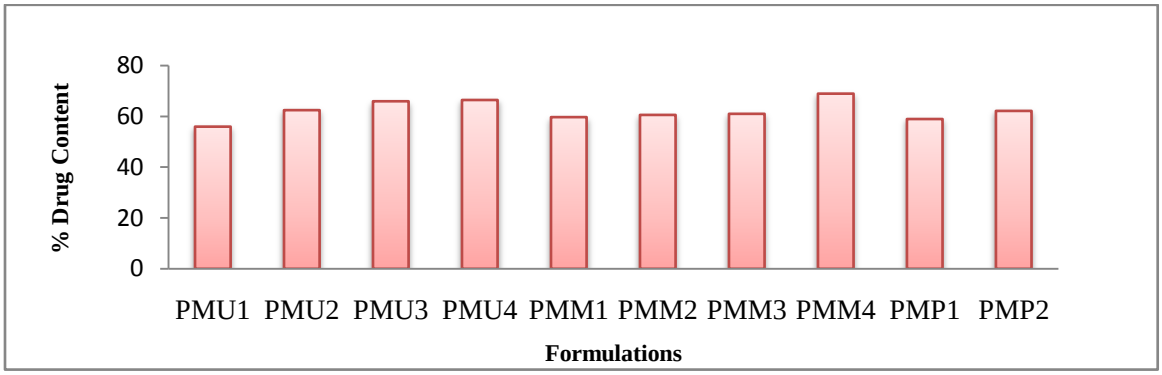

Figure 4: % Drug Content for Physical Method

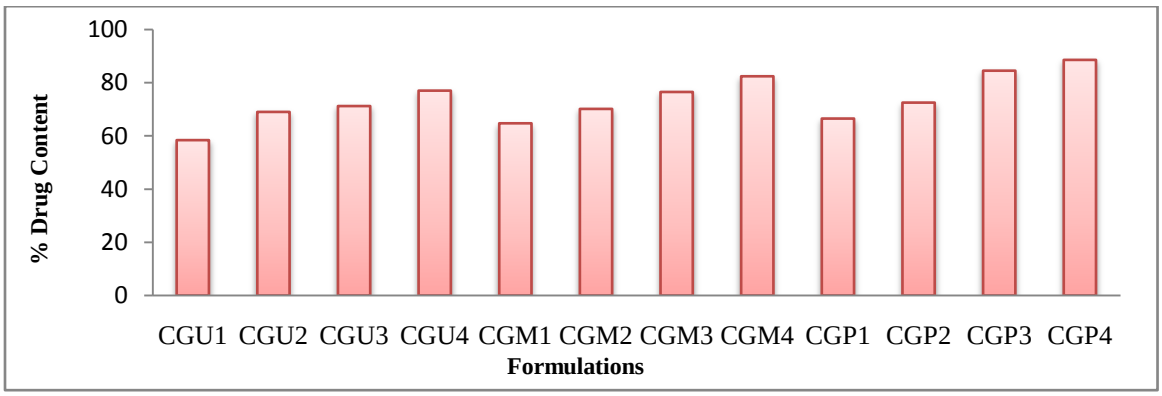

Figure 5: % Drug Content for Co-grinding Method

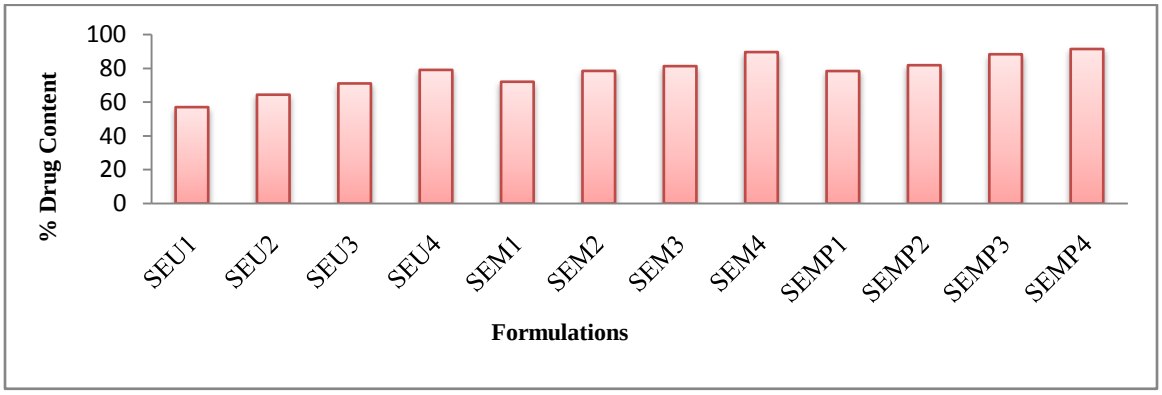

Figure 6: % Drug Content for Solvent Evaporation Method

Aqueous Solubility Study

At the end of 48 hrs the aqueous solubility of acyclovir was found to be 1.05 ± 0.081 mg/ml. Where in physical method of preparation it was 1.10 ± 0.063 to 2.87 ± 0.028 mg/ml, for co-grinding method of preparation it was 2.22 ± 0.064 to 4.12 ± 0.078 mg/ml and for solvent evaporation method of preparation it was 2.75 ± 0.084 to 8.32 ± 0.054. The solubility of drug increased in linear function of carrier concentration. All the solid dispersion were shows enhance

solubility but higher in case of formulation SEP4 (1:4 ratio). In case of solvent evaporation method it observed higher and comparative low in case of co-grinding and physical mixture methods. It was due to fact that solid dispersion prepared by solvent evaporation method results more uniform dispersion of drug in hydrophilic carrier matrix as compare to those prepared by co-grinding and physical mixture methods. In case of physical mixture, a small increase in solubility of drug was obtained which can be explained due to the formation of a minimum quantity of the complex as compare to other two methods. The effect of different carriers on the aqueous solubility of acyclovir was showed that the concentration of acyclovir in water increased in presence of PEG 6000, mannitol and urea. But in case of PEG 6000 (1:4) the solubility is more because it has higher solubilizing effect than mannitol and urea. The results confirmed that the extent of disruption of crystallinity[20-22] of acyclovir by PEG 6000 was higher than that by mannitol and urea. The results are shown in Table 4, 5, 6.

Table 4: Aqueous Solubility for Physical Method

S. No.	Formulations	Aqueous Solubility (mg/ml)
1	Pure drug	1.05 ± 0.081
2	PMU1	1.10 ± 0.063
3	PMU2	1.20 ± 0.037
4	PMU3	1.42 ± 0.042
5	PMU4	1.60 ± 0.033
6	PMM1	1.19 ± 0.016
7	PMM2	2.03 ± 0.052
8	PMM3	2.37 ± 0.011
9	PMM4	2.68 ± 0.039
10	PMP1	1.59 ± 0.084
11	PMP2	1.90 ± 0.023
12	PMP3	2.63 ± 0.045
13	PMP4	2.87 ± 0.028

Results have been expressed as mean ± S.D. (n = 3)

Table 5: Aqueous Solubility for Co-grinding Method

S. No.	Formulations	Aqueous Solubility (mg/ml)
1	CGU1	2.22 ± 0.064
2	CGU2	2.69 ± 0.080
3	CGU3	3.17 ± 0.016
4	CGU4	4.32 ± 0.056

5	CGM1	2.50 ± 0.033
6	CGM2	2.74 ± 0.037
7	CGM3	3.15 ± 0.050
8	CGM4	4.64 ± 0.021
9	CGP1	2.36 ± 0.054
10	CGP2	3.14 ± 0.019
11	CGP3	3.87 ± 0.034
12	CGP4	4.12 ± 0.078

Results have been expressed as mean ± S.D. (n = 3)

Table 6: Aqueous Solubility for Solvent Evaporation Method

S. No.	Formulations	Aqueous Solubility
1	SEU1	2.75 ± 0.084
2	SEU2	3.83 ± 0.033
3	SEU3	4.33 ± 0.042
4	SEU4	4.52 ± 0.078
5	SEM1	5.32 ± 0.034
6	SEM2	6.50 ± 0.022
7	SEM3	6.78 ± 0.017
8	SEM4	7.10 ± 0.056
9	SEP1	5.55 ± 0.049
10	SEP2	6.60 ± 0.083
11	SEP3	7.88 ± 0.062
12	SEP4	8.32 ± 0.054

Results have been expressed as mean ± S.D. (n = 3)

***In-vitro* dissolution studies**

The in vitro studies of drug was done in phosphate buffer of pH 7.4. Percentage drug dissolved within 120 min. in phosphate buffer pH 7.4 were reported in figure 7-21. The percentage drug released data from various formulations was found in the range of 42.02 ± 0.61 % to 92.05 ± 0.19 % within 120 minutes. The pure drug exhibited only 33.53 ± 0.45 % of release. *In vitro* release studies reveal that there is marked increase in the dissolution rate of acyclovir from all solid dispersions as compare to pure drug. The dissolution of drug increase with increase in the carrier ratio in the formulations. The maximum drug release was found in the formulation SEP4 (1:4 ratio of drug: PEG-6000) is 92.05 ± 0.19 %. The order of drug dissolution from different carriers is PEG 6000 > mannitol > urea. The solubility of drug increase due to increase wettability of drug in presence of hydrophilic polymers. The solid dispersion prepared by physical and solvent evaporation methods showed a significant increase in dissolution rate with

increase in the amount of PEG-6000. Formulation SEP4 shows maximum release 92.05 ± 0.19 % in 120 min. (Figure 15) and also formulations PMU4 PMM4, PMP4, CGM4 and CGP4 showed maximum release in 120 min. (Figure 7, 10, 13, 11, 14) among the other preparation of solid dispersions prepared by physical mixture method and co-grinding method respectively. In general the dispersion prepared by solvent evaporation method showed faster release of acyclovir fallowed by dispersion obtained by physical mixture. Co-grinding method generally did not give good results. This is due to the fact that solid dispersions prepared by solvent evaporation method and physical mixture method result in more uniform dispersion of the drug in hydrophilic carrier matrix as compared to those prepared by co-grinding method. The enhanced dissolution rates of SDs may be due to many factors such as decreased particle size of drug, specific form of drug in these SDs, in addition to the increase in drug wettability[22] and preventing of drug aggregation by each polymer. Furthermore, all polymers affected the crystallinity of the drug could be considered as an important factor in enhancement the dissolution rate. It is known that amorphous drug represents the most ideal case for fast dissolution. Thus *in-vitro* drug release was best for solid dispersion SEP4.

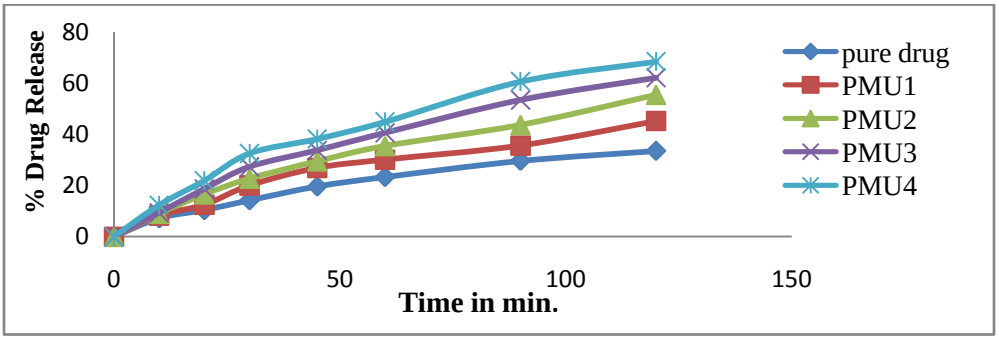

Figure 7: In vitro release profile of pure drug & formulations (PMU1, PMU2, PMU3, PMU4) in PBS pH 7.4

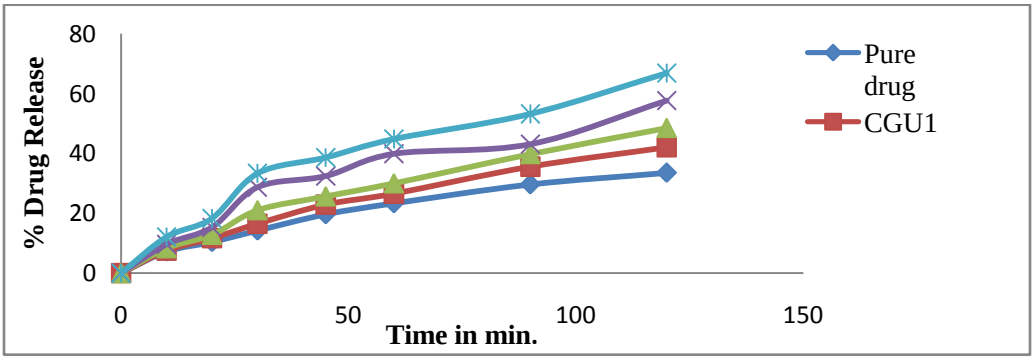

Figure 8: In vitro release profile of pure drug & formulations (CGU1, CGU2, CGU3, CGU4) in PBS pH 7.4

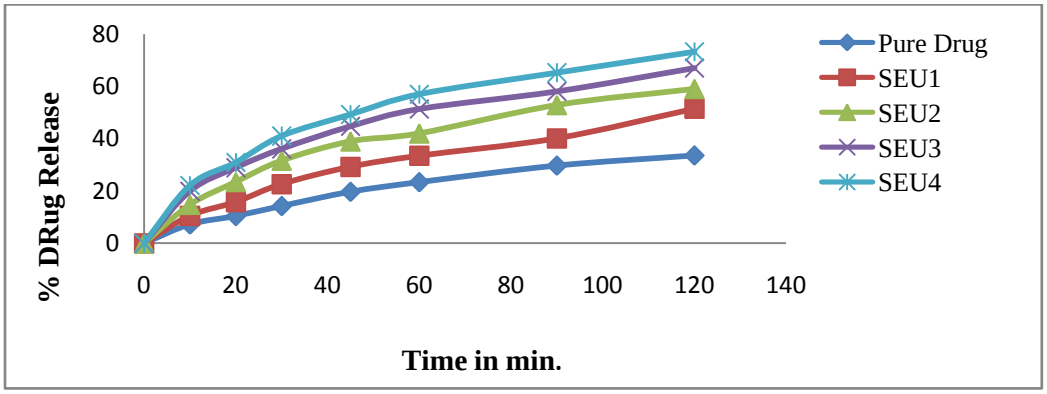

Figure 9: In vitro release profile of pure drug & formulations (SEU1, SEU2, SEU3, SEU4) in PBS pH 7.4

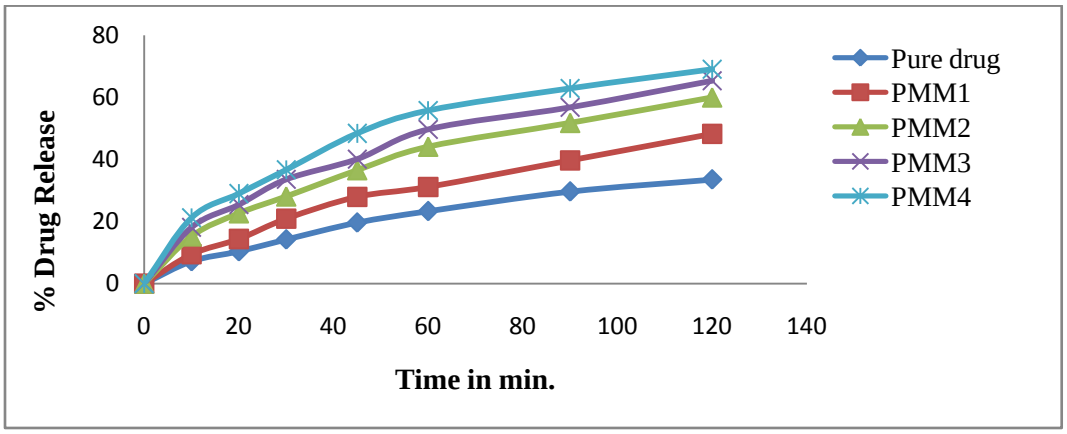

Figure 10: In vitro release profile of pure drug & formulations (PMM1, PMM2, PMM3, PMM4) in PBS pH 7.4

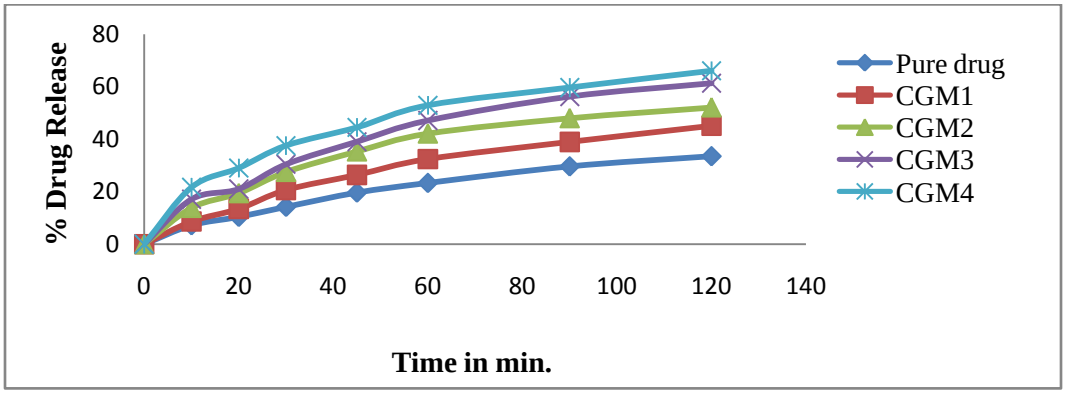

Figure 11: In vitro release profile of pure drug & formulations (CGM1, CGM2, CGM3, CGM4) in PBS pH 7.4

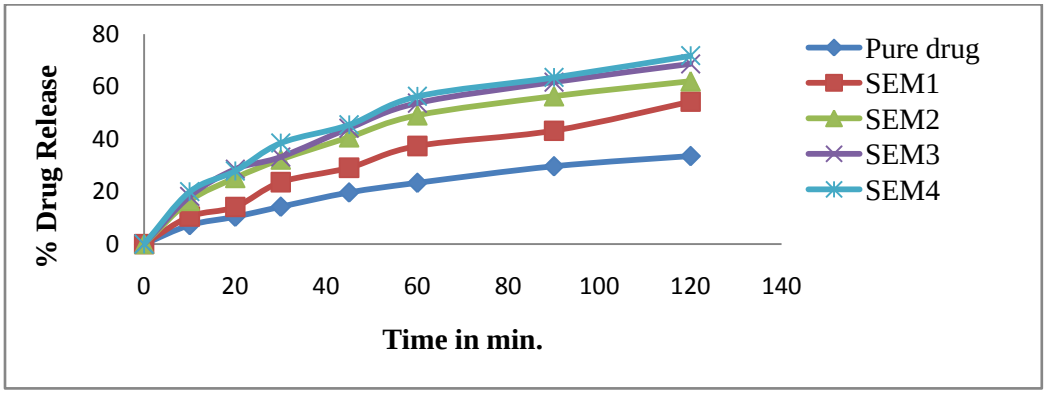

Figure 12: In vitro release profile of pure drug & formulations (SEM1, SEM2, SEM3, SEM4) in PBS pH 7.4

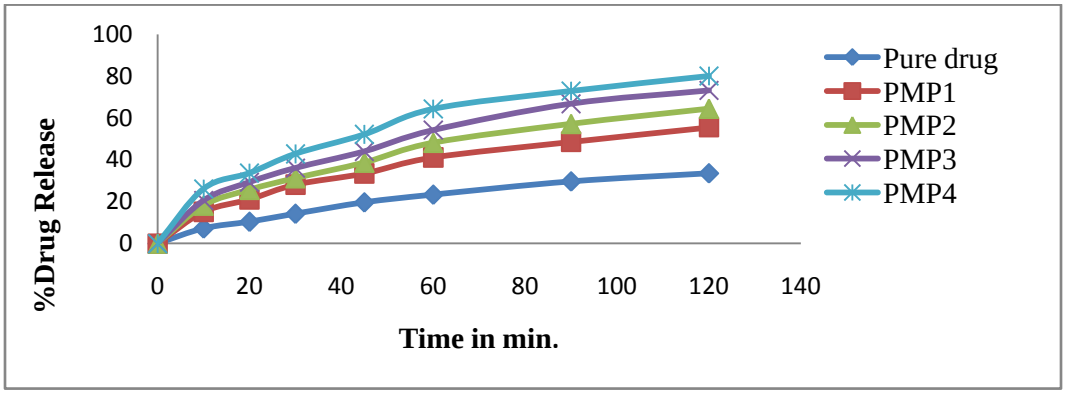

Figure 13: In vitro release profile of pure drug & formulations (PMP1, PMP2, PMP3, PMP4) in PBS pH 7.4

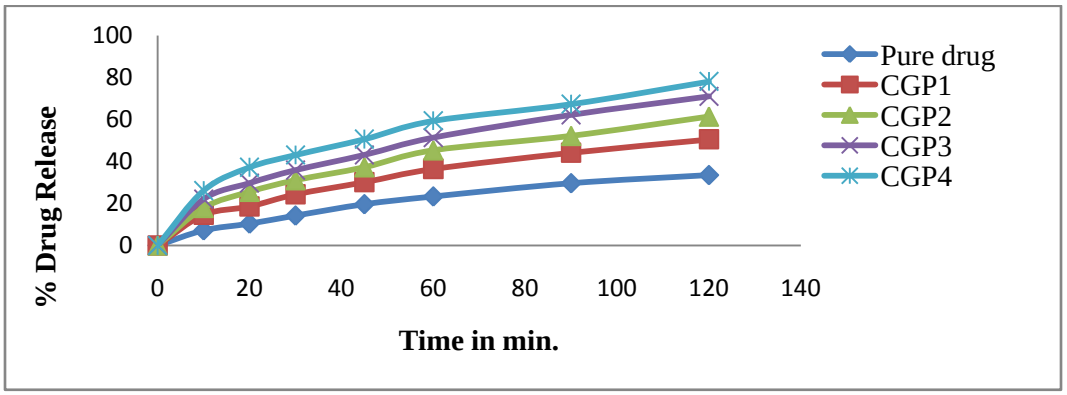

Figure 14: In vitro release profile of pure drug & formulations (CGP1, CGP2, CGP3, CGP4) in PBS pH 7.4

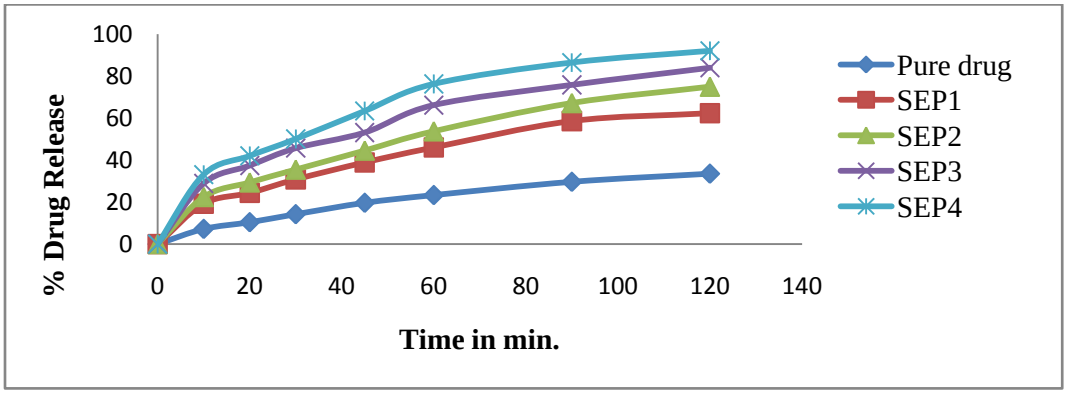

Figure 15: In vitro release profile of pure drug & formulations (SEP1, SEP2, SEP3, SEP4) in PBS pH 7.4

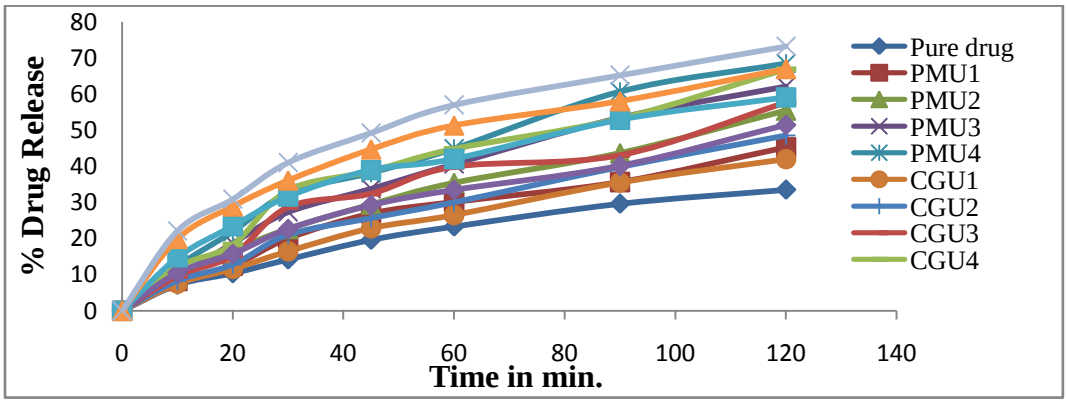

Figure 16: In vitro release profile of pure drug & formulations (PMU1, PMU2, PMU3, PMU4, CGU1, CGU2, CGU3, CGU4,) in PBS pH 7.4

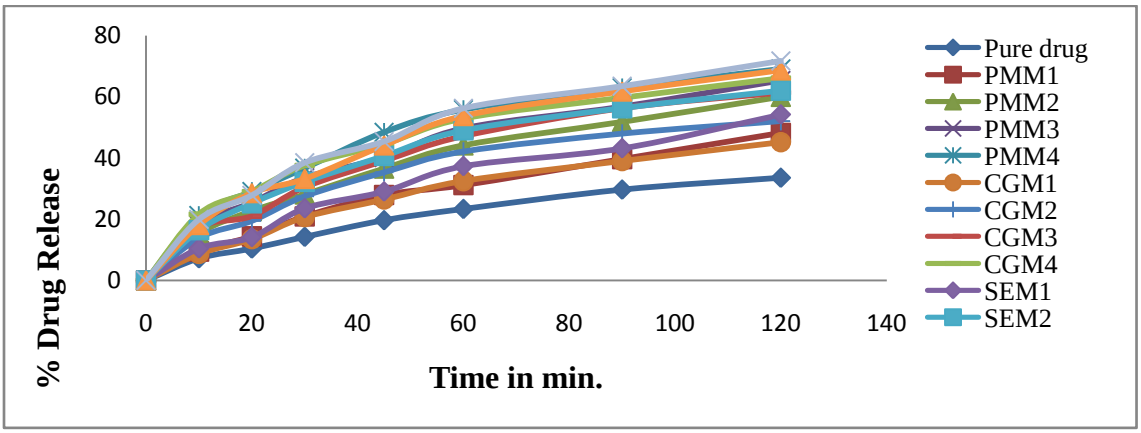

Figure 17: In vitro release profile of pure drug & formulations (PMM1, PMM2, PMM3, PMM4, CGM1, CGM2, CGM3, CGM4, SEM1, SEM2,) in PBS pH 7.4

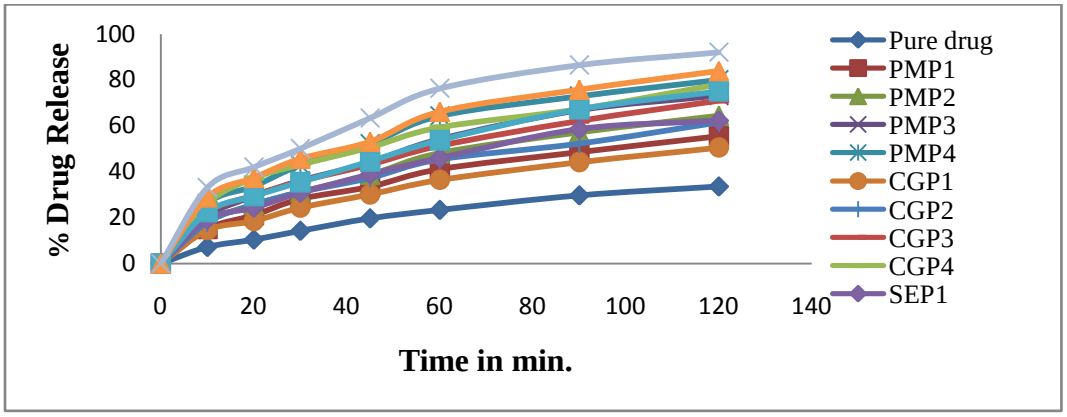

Figure 18: In vitro release profile of pure drug & formulations (PMP1, PMP2, PMP3, PMP4, CGP1, CGP2, CGP3, CGP4, SEP1) in PBS pH 7.4

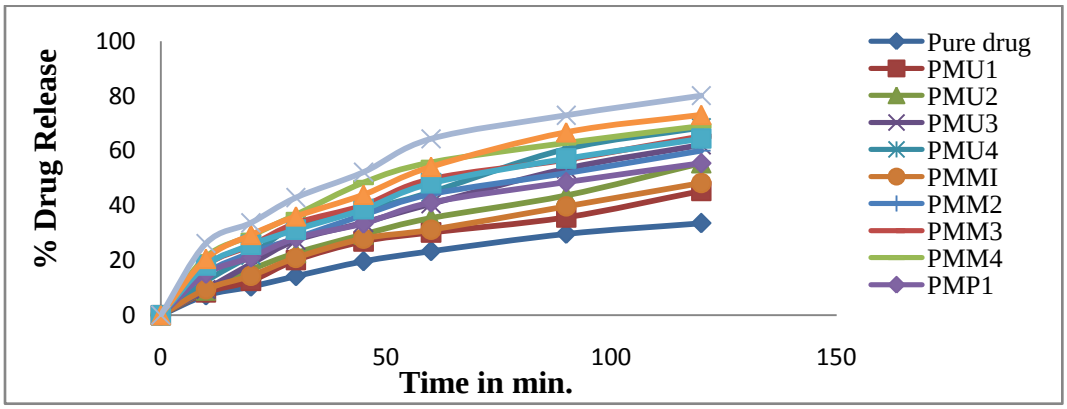

Figure 19: In vitro release profile of pure drug & formulations (PMU1, PMU2, PMU3, PMU4 PMM1, PMM2, PMM3, PMM4, PMP1,) in PBS pH 7.4

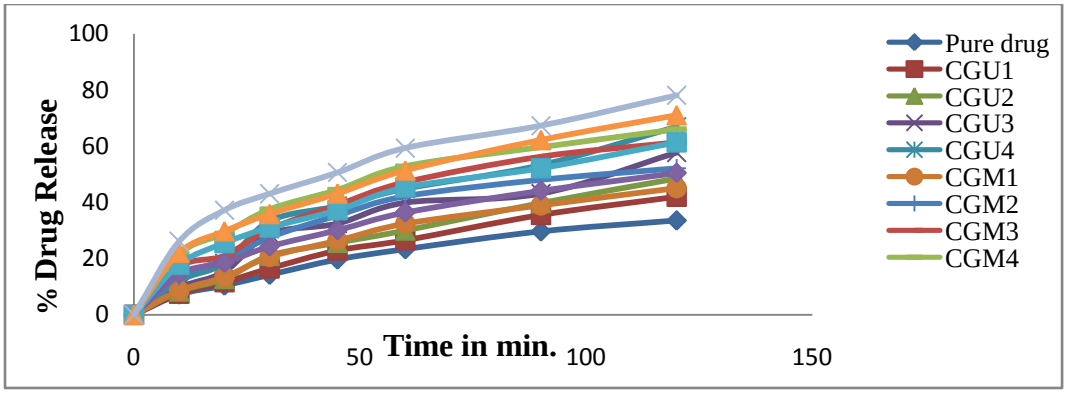

Figure 20: In vitro release profile of pure drug & formulations (CGU1, CGU2, CGU3, CGU4, CGM1, CGM2, CGM3, CGM4) in PBS pH 7.4

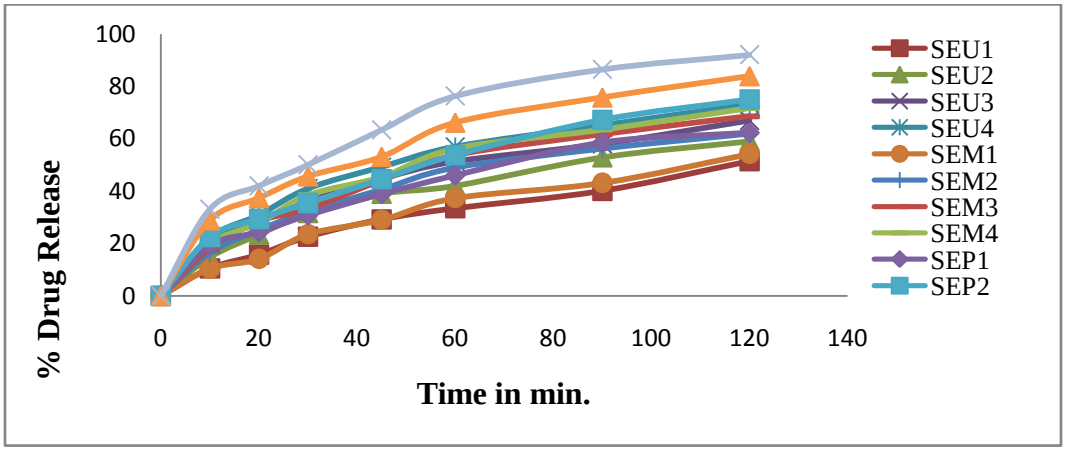

Figure 21: In vitro release profile of pure drug & formulations (SEU1, SEU2, SEU3, SEU4, SEM1, SEM2, SEM3, SEM4, SEP1, SEP2) in PBS pH 7.4

Fourier Transform Infra Red Spectral studies

The FTIR spectrum of pure drug, PEG-6000 and formulation SEP4 is represented in figure 22-24. The important peaks in IR spectra of acyclovir were 750 cm^{-1} for N-H bending of primary amine and 1635 cm^{-1} for C=O stretching. In IR spectra of PEG-6000 peak obtained at 1110.26cm^{-1} for C-C and 3449.69 cm^{-1} for O-H stretching. In case of solid dispersion of drug and PEG-6000, both drug and polymers peaks were present. Thus indicating that there is no significance evidence of chemical interaction between drug and polymer, which confirm the stability of drug with its solid dispersion. The interpretation of spectra is given in the table 7.

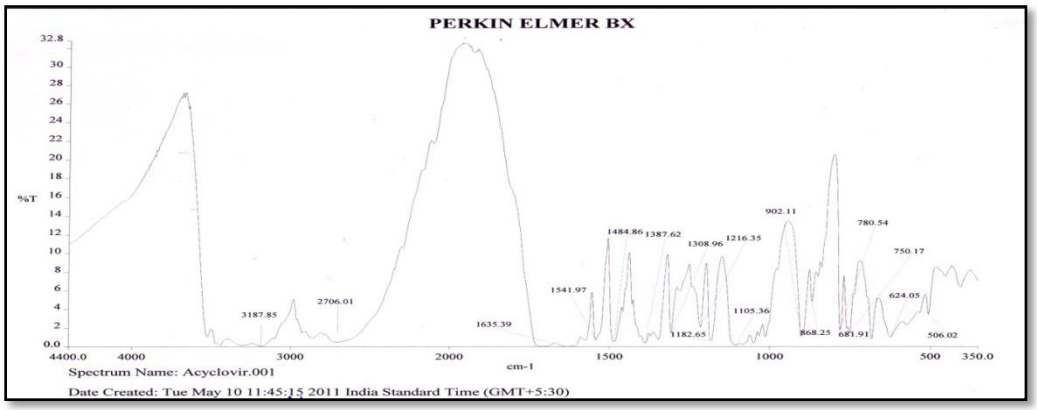

Figure 22: FTIR spectra of acyclovir

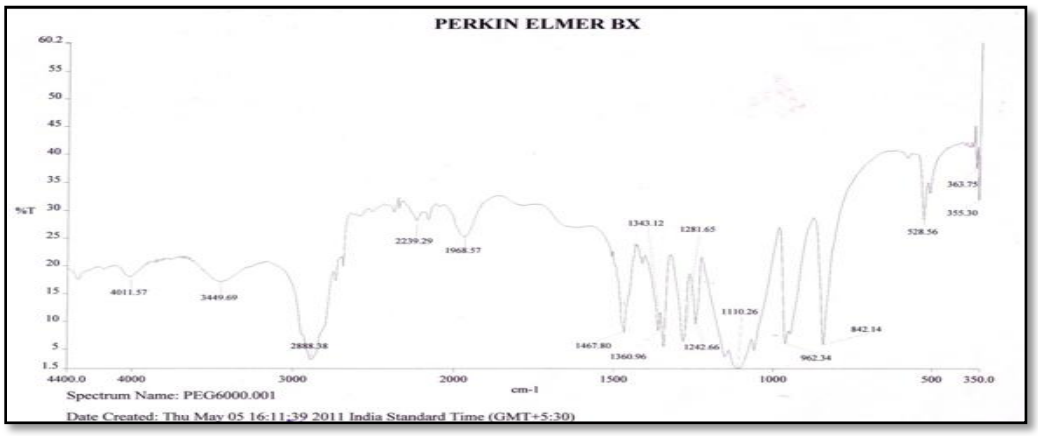

Figure 23: FTIR spectra of PEG-6000

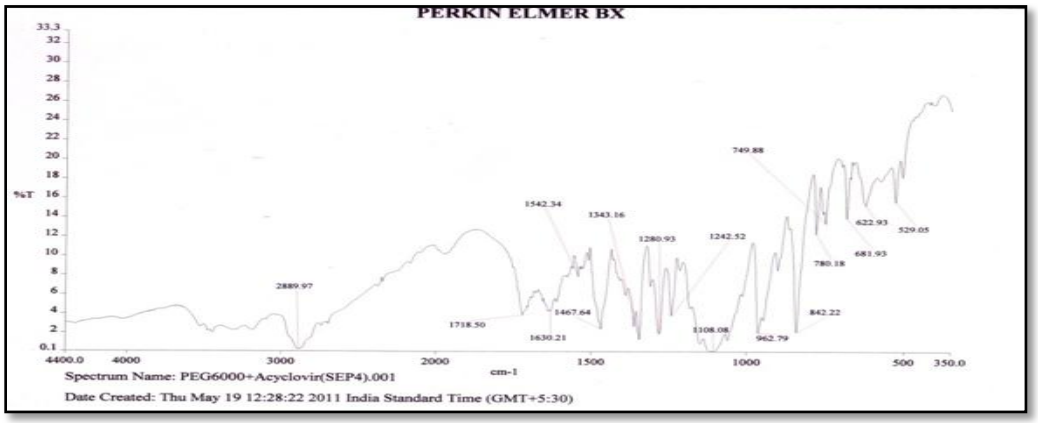

Figure 24: FTIR spectra of Formulation

Table 7: Interpretation of FTIR spectra of formulation

S. No.	Peak (cm^{-1}) (Pure drug)	Peak (cm^{-1}) (Formulation SEP4)	Interpretation
1.	750	749.88	N-H bending (1°amine)
2.	1635	1630.21	C=O stretching
3.	1308	1308.34	C=N stretching
4.	1541	1542.34	N-H bending (2° amine)

Differential Scanning Calorimetry studies

The DSC enables the quantitative detection of all the process in which energy required or produced (i.e. endothermic or exothermic phase transformations).The thermal behavior of prepared solid dispersion of acyclovir with PEG-6000 was studied by DSC. The thermograph of pure acyclovir, PEG-6-000 and formulation (SEP4) are shown in Figure 25-27. In case of acyclovir one endothermic curve was observed at 253 °C which were near to its melting point 256 °C.

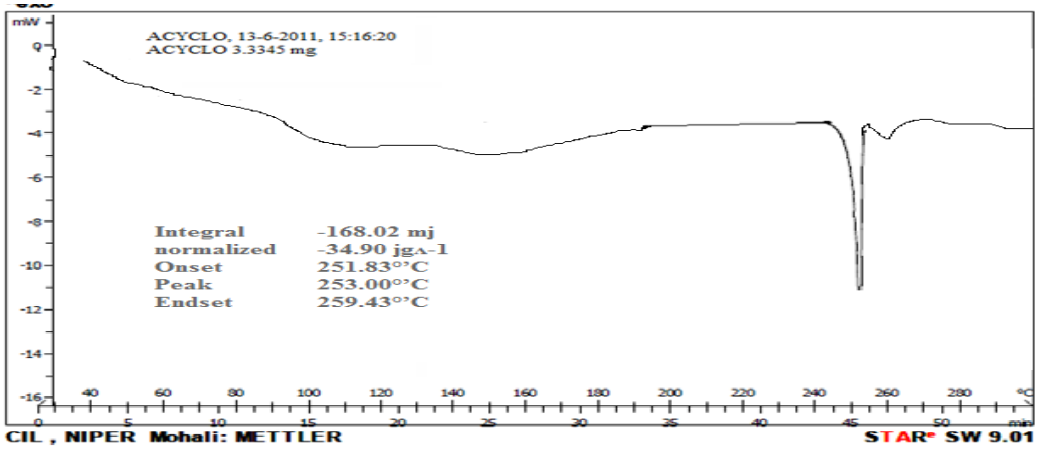

Figure 25: DSC thermograph of pure acyclovir

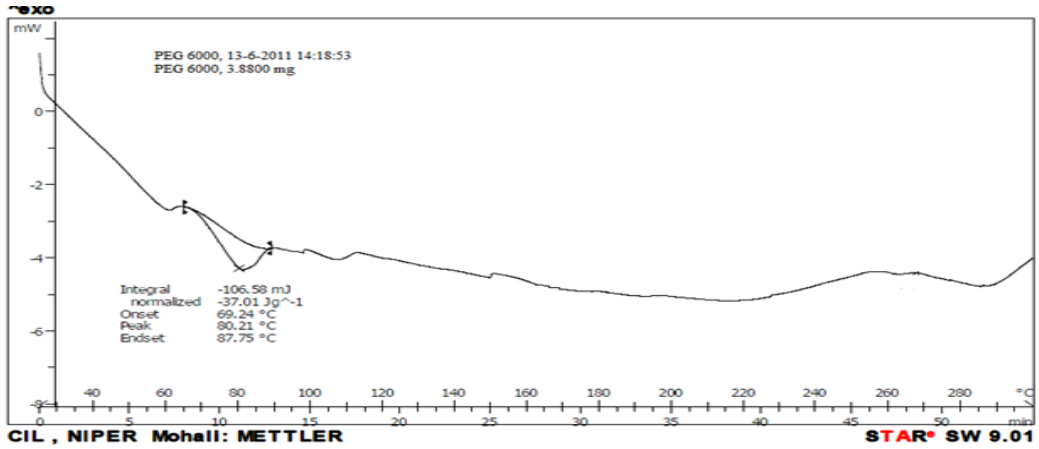

Figure 26: DSC thermograph of pure PEG-6000

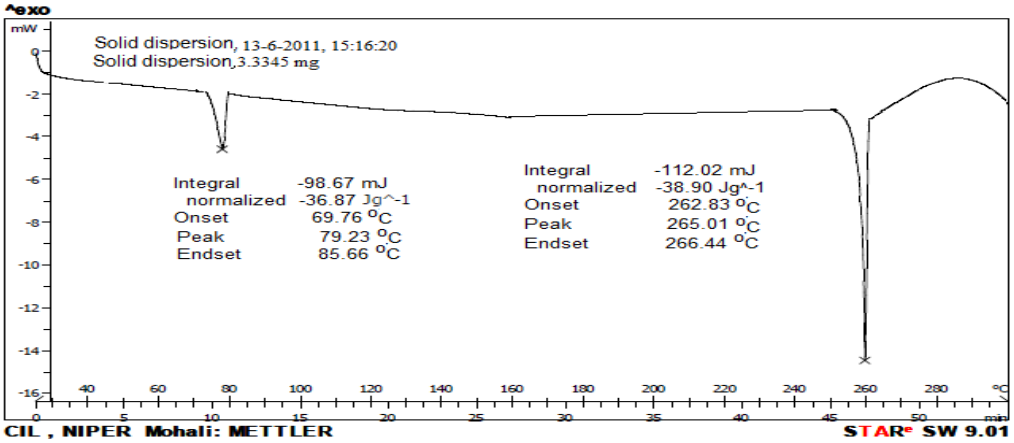

Figure 27: DSC thermograph of formulation SEP4

***In-vivo* Release Study**

The average plasma concentration time curve in rabbits after a single dose of acyclovir as free solution and solid dispersion were shown in figure 28. The pharmacokinetic parameters of acyclovir were calculated from the individual curve and the mean value was presented in table

13. The solid dispersion formed showed significantly ($P < 0.05$) higher values for AUC nearly 5 times (391 ± 1.21 mg/ml*h) as compared to drug solution (71.32 ± 1.32). In addition the formulation showed the ability to maintain the plasma concentration throughout the period, as compared to the drug that only for 2-3 hr. the results confirming the a prolonged release of drug and increase in the concentration of drug hence increase in the solubility and bioavailability of drug from solid dispersion prepared by using PEG-6000. Hence the overall better pharmacokinetics performance of solid dispersion of drug with PEG-6000 as compare to pure drug. Result was shown in Table 8,9.

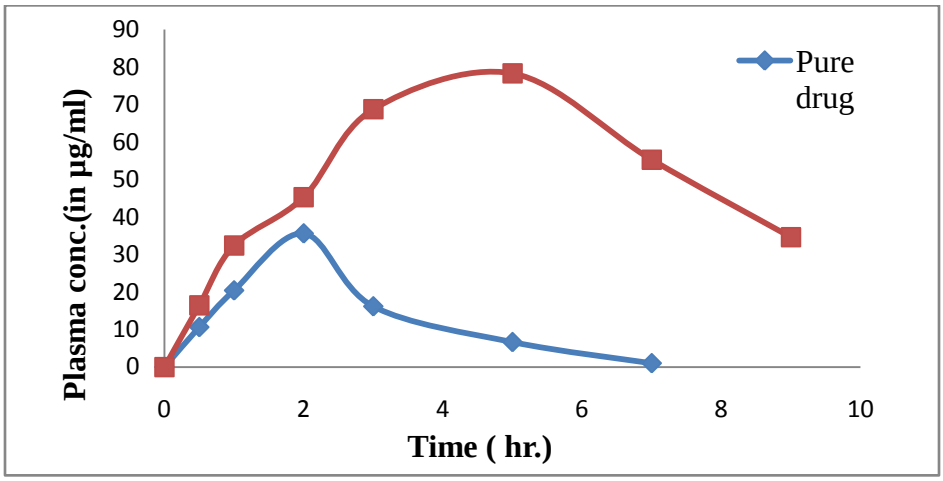

Figure 28: Plasma concentration time profile

Table 8: Blood plasma concentration of drug and formulation SEP4

S. no.	Time (hr.)	Plasma Concentration(µg/ml)	
		Pure Drug	SEP4
1	0.0	0.0	0.0
2	0.5	10.66 ± 1.33	16.47 ± 1.23
3	1	20.45 ± 1.10	32.44 ± 1.32
4	2	35.66 ± 1.23	45.32 ± 1.65
5	3	16.20 ± 2.34	68.78 ± 1.11
6	5	6.67 ± 2.12	78.33 ± 1.48
7	7	1.03 ± 1.12	55.32 ± 2.01
8	9	-----	34.65 ± 3.21

Results have been expressed as mean ± S.D. (n = 3)

Table 9: Pharmacokinetic parameter of drug and formulation (SEP4)

System	Cmax (µg/ml)	Tmax (hr)	AUC(µg/ml*hr)
Acyclovir	35.66 ± 1.23	2.0 ± 2.4	71.32 ± 1.32
SEP4	78.33 ± 1.48	5.0 ± 4.6	391 ± 1.32

Accelerated Stability Studies

The solid dispersions were subjected to short term accelerated stability testing. Stability study for selected solid dispersions was performed at (50 ± 2°C/75 ± 5 % RH) and ambient (25 ± 2°C/60% RH) for a period of 3 months. There were no significance changes occurs in physical appearance, % practical yield, % drug content, *in-vitro* drug release and weight gain/loss at 25°C. Slight changes observed at 50°C in physical appearance, weight but no change in *in-vitro* drug release profile and drug content[23, 24,25]. Result was shown in Table 10,11.

Table 10: Effect of storage at room temperature (25±°2C) on the formulation at the end of different time interval

Parameters	Time (in days)				
	00	15	30	60	90
Physical appearance	White	White	White	White	White
% PY	96.34±0.035	96.34±0.035	96.34±0.035	96.34±0.035	96.34±0.035
% DC	91.35±0.064	91.35±0.064	91.35±0.064	91.35±0.064	91.35±0.064
***In-vitro* drug release (After 120 min.)**	92.05 ± .032	92.05 ±0.032	92.05 ±0.032	92.05±0.032	92.05±0.032
Wt. gain/loss	0.00	0.00	0.00	0.00	0.00

Results have been expressed as mean ± S.D. (n = 3)

Table 11: Effect of storage at temperature (50±2°C) on the formulation at the end of different time interval

Parameters	Time (in days)				
	00	15	30	60	90
Physical appearance	White	White	White	White	Off -White
% PY	96.34±0.035	96.34±0.035	96.34±0.035	96.34±0.035	96.34±0.035
% DC	91.35±0.064	91.35±0.064	91.35±0.064	91.35±0.064	91.35±0.064
***In-vitro* drug release (After 120 min.)**	92.05 ± 0.032	92.05 ±0.032	92.05 ± 0.032	92.05 ± 0.032	92.05 ± 0.032
Wt.gain/loss	0.00	0.00	0.00	0.06 %	1 %

Results have been expressed as mean ± S.D. (n = 3)

CONCLUSION

Solid dispersion of acyclovir with different polymers (polyethylene glycol-6000, mannitol and urea) were prepared by physical method, co-grinding method and solvent evaporation in drug: polymer ratio of 1:1, 1:2, 1:3, and 1:4. The best formulation is confirmed by FTIR and DSC study. The solid dispersion prepared by different methods help to improve aqueous solubility. *In-*

vitro and *in-vivo* release profile. Overall formulation SEP4 prepared by solvent evaporation method using PEG-6000 showed superior dissolution profile when compared to other method. These findings are extremely important from a commercial point of view as the prepared formulation remove the drawback of poor dissolution profile of Acyclovir.

REFERENCES

1. Shinde AJ. Solubilization of Poorly Soluble Drugs: A Review. pharmainfo.net 2007; 5: 1-19
2. Ghaste R., Dhanyakumar CD., Shah R, Ghodke S. Solid Dispersions: An Overview. Pharmainfo net 2009; 1-28
3. Sekiguchi K, Obi N. Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. Chem Pharm 1961; 9: 866-872.
4. Sekiguchi K, Obi N. Studies on Absorption of Eutectic Mixture II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. Chem Pharm 2006; 12: 134-144.
5. Chiou WL, Riegelman S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J Pharm Sci 1969; 1505-1510.
6. Leunner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000; 50: 47-60.
7. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. II. Experimental evaluation of eutectic mixture: urea-acetaminophen system. J Pharm Sci. 1966; 55:482-487.
8. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. III. Experimental evaluation of griseofulvin-succinic acid solution. J Pharm Sci. 1966; 55:487-492
9. Jafar M, Dehghan M, Shareef A. Enhancement of dissolution and anti-inflammatory effect of meloxicam. Int J Applied Pharma 2010; 2(1): 22-27
10. Chiou WL, Riegelman S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J Pharm Sci 1969; 1505-1510.

11. Narang A, Shrivastava A. Melt extrusion solid dispersion technique. Drug Dev Ind Pharm 2002; 26(8);111-115

12. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm 2002; 54; 107-117.

13. Serajuddin A. solid dispersion technique. J Pharm Sci 1999; 88(10); 891-900.

14. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000, 50: 47-60.

15. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int J Pharm 2004, 274: 65-73.

16. Jafar M, Dehghan M, Shareef A. Improving Dissolution of Meloxicam Using Solid Dispersions. Iranian J Pharm Res 2006; 4: 231-238.

17. Galia E, Nicolaides E, Hoerter D, Loebenberg R, Reppas C and Dressman JB. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. Pharm Res 1998; 15: 698-705.

18. Maa YF, Zhao L, Payne LG and Chen D (2003). Stabilization of alum-adjuvanted vaccine dry powder formulations: mechanism and application. J. Pharm.Sci., 92(2): 319-33

19. Ghaderi R, Artursson P,Carifors J. Preparation of biodegradable microparticles using solution enhanced dispersion by supercritical fluids (SEDS). Pharm Res 1999, 16: 676-681

20. Kerc J, Srcic S. Thermal analysis of glassy pharmaceuticals. Thermochim Acta 1995, 248: 81-95.

21. Sekiguchi K, Obi N. Studies on Absorption of Eutectic Mixture II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. Chem Pharm Bull (Tokyo), 12: 134-144.

22. Wadke DA, Serajuddin A, and Jacobson H, Preformulation testing, Lieberman HA, Lachman L and Schwartz JB, eds. Pharmaceutical Dosage Forms: Tablets. New York, NY: Marcel Dekker; 1989:1-73.

23. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics A Treatise. 1st Edn, Vallabh Prakashan, Delhi, 1995: 171-172.

24. Hume-RW, Raynor GV. The Structure of Metals and Alloy, Institute of Metals, London, 1954. Res 1998; 15: 698-705.

25. Wadke DA, Serajuddin A, Jacobson H. Preformulation testing, Lieberman HA, Lachman L and Schwartz JB, eds. Pharmaceutical Dosage Forms: Tablets. New York, NY: Marcel Dekker; 1989:1-73.