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Enhancement of Solubility of Acyclovir by Solid Dispersion And Inclusion Complexation Methods

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ABSTRACT

Solid dispersions of acyclovir in PEG 6000 and PVP K30 containing five different ratios were prepared by the solvent evaporation method. Inclusion complexes were prepared by kneading method by dissolving acyclovir and β-CD, HP β-CD at 5 different ratios in distilled water. The optimized batches of solid dispersions (AS_4, BS_5) and inclusion complexes (CI_5, DI_5) of acyclovir were analyzed by IR spectroscopy, SEM and DSC. The dissolution studies for solid dispersions (AS_4, BS_5) and inclusion complexes (CI_5, DI_5) were performed in 0.1 N HCl and PBS pH 7.4 for all optimized batches. The solubility of acyclovir was found to be more with inclusion complexation method as compare to solid dispersion technique. Hence, the results showed that hydroxypropyl β-cyclodextrin inclusion complex could possibly improve the dissolution characteristics of acyclovir and would provide better bioavailability as compare to conventional dosage form.

Key-Words: solid dispersion, inclusion complex, Acyclovir, solvent evaporation

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INTRODUCTION

The rate and extent of dissolution of the active ingredient from any solid dosage form determines the rate and extent of absorption of drug. In case of poorly water soluble drug, dissolution is the rate limiting step in the process of a drug absorption. Poorly soluble drugs have been shown to be unpredictable and slowly absorbed as compared to the drugs with higher solubility. Several methods have been employed to improve the solubility of poorly water soluble drugs. Acyclovir is a popular anti-Herpes drug among the antiviral category for the treatment of diseases including *Herpes simplex* (type 1) keratitis, orofacial, cuteneous Herpes, gential herpes, and varicella zoster infections. Among the Herpes viruses *H. simplex* (type I) is the most sensitive followed by *H. simplex* (type II) viruses. Acyclovir is the drug of choice for most of these cases but the

problem of using this drug is that it has poor oral bioavailability. The conventional routes and therapies available for the treatment of Herpes, keratitis, includes orally administered tablet but are associated with it is very low bioavailability ranging from 15-30%. Repeated administration of high doses result in infrequent nausea, diarrhoea, rash, and headache. This problem can be resolved by enhancing the solubility and hence dissolution of poorly water soluble drug acyclovir. Consequently, the rationale of this study is to improve the biological performance of Acyclovir through enhancing its solubility and dissolution rate by two systems: solid dispersion and inclusion complexation. In the present work we tried to prepare solid dispersion with polyethylene glycol (PEG 6000), polyvinylpyrrolidone (PVP K 30) and inclusion complexation with β-cyclodextrin and hydroxypropyl β-cyclodextrin to improve solubility and dissolution rate of acyclovir which would help to improve bioavailability. The solid dispersion and the inclusion complex techniques seems to pose great potential in significantly enhancing the solubility and dissolution rate of different formulations(1-7).

MATERIALS AND METHODS:

PEG-6000, PVP K-30, β-CD and HP β-CD were purchased from CDH (P) Ltd., New Delhi. Acyclovir was obtained as a gift sample from Alembic Pharmaceutical Pvt Ltd, Varodara. All other materials used were of pharmaceutical grade.

Preparation of physical mixtures

Acyclovir and excipients (PEG-6000, PVP K-30, β-CD and HP β-CD) were accurately weighed at different ratios (1:1, 1:2, 1:3), pulverized and mixed thoroughly in mortar with pestle until homogeneous mixture was obtained. The mixture was passed through the sieve, to get uniform size, for further experiments (Table I).

Preparation of solid dispersion

Solid dispersions of acyclovir in polyethylene glycol-6000(PEG-6000) and polyvinylpyrollidone K-30 (PVP K-30) containing five different ratios (1:1, 1:2, 1:3, 1:4, and 1:5 w/w) were prepared by the solvent evaporation method. Acyclovir and the polymer were dissolved in a minimum amount of methanol. The solvent was removed by evaporation on magnetic stirrer at the temperature 40°C for 1 h. The resulting residue was dried for 2 h and stored overnight in a desiccator. After drying, the residue was ground in a mortar and sieved through a mesh # 60. The resultant solid dispersions were stored in desiccator until further investigation (Table II).

Preparation of inclusion complexation

The inclusion complexation of acyclovir with β-cyclodextrin and HP β-cyclodextrin were prepared in different ratios (1:1, 1:2, 1:3, 1:4, and 1:5) by kneading method. Thick slurry was prepared by adding one third water by weight to excipients. Under stirring the appropriate quantity of drug was added to it and then dried in an oven at 45°C until dry. The dried mass was pulverized and sieved through mesh # 60 (Table II).

Characterization of solid dispersion and inclusion complex: (8-10)

Infra red (IR) studies

The optimized batches of solid dispersion (AS_4 and BS_5, fig.3) and inclusion complexation (CI_5 and DI_5, Fig. 4) were analyzed by IR spectroscopy (FTIR- Jasco-470 plus)

Scanning electron microscopy (SEM)
The surface morphology of optimized batches (AS_4 and BS_5) was determined by scanning electron microscopy (SEM, Leo 430, UK, fig.5.)

Differential scanning calorimetery (DSC) analysis
The optimized batches of inclusion complexation were subjected to differential scanning calorimetery (DSC) analysis (Fig.6). The change in endothermic peaks of acyclovir and excipients were observed, which confirms the interaction between drug and excipients.

Content uniformity
The content of acyclovir in PEG 6000 and PVP K30 solid dispersion and in inclusion complexation with β-cyclodextrin and HP β-cyclodextrin was estimated by UV spectrophotometric method using Shimadzu 1700 spectrophotometer. An accurately weighed quantity of solid dispersion (equivalent to 10 mg of acyclovir) was taken and dissolved in 100ml of 0.1N HCl, from this solution 1ml of solution was diluted to 10ml and assayed for drug content at 255 nm**.**

Dissolution studies
The dissolution studies of optimized batches of solid dispersion (AS_4 and BS_5). and inclusion complexation (CI_5 and DI_5) were performed in 900ml of 0.1 N HCl (Table III Fig.1)and PBS pH 7.4 Table IV, Fig.2) at 37ºC by the USP- II paddle apparatus at 50 rpm. In the present studies samples (equivalent to 400mg of drug) were dispersed in medium. Aliquots of 5 ml from the dissolution medium were withdrawn at different time intervals and replenished by an equal volume of fresh dissolution medium. The samples were filtered through whatman filter paper and analyzed for acyclovir contents by measuring its absorbance at 255 nm for 0.1NHCl and at 256 nm for PBS pH 7.4 using Shimadzu 1700 UV/visible Spectrophotometer.

RESULT AND DISCUSSION

The solubility of acyclovir in water was found to be 12.84 µg/ml. 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. The effect of different carriers on the aqueous solubility of acyclovir was shown in Table II. Solubility experiments showed that the concentration of acyclovir in water increased in presence of PEG6000, PVPK30, β-CD and HP β-CD. The solid dispersion (AS_4, BS_5) and inclusion complexes (CI_5, DI_5) of acyclovir were analyzed by IR spectroscopy (FTIR- Jasco-480 plus). The change in principle peaks of group acyclovir and excipients were found, which confirmed the complex formation between drug and excipients.The important peaks in IR spectra of acyclovir were, 3208.03 of N-H stretch of primary amine (NH2), 1785.94 of C=O stretching (Fig. 3). In IR spectra of PEG-6000 and PVP K-30, the important peaks were observed at 1665.23 and 1283.39, respectively for C=O stretch but in solid dispersion these peaks were absent and new peaks at 1291.11 and 1107.22 for asymmetric C-O-C stretch were observed.

In IR spectra of pure β-CD and HP β-CD (Fig.4) the important peaks were observed at 3321.78 and 3384.94, respectively for O-H stretch of primary alcohol. Whereas in IR spectra of inclusion complex all these important peaks were absent and instead of this, peak of symmetric and anti

symmetric peaks were observed at 1125.26 and 1291.11, respectively. These changes in IR peaks clearly suggested that the acyclovir-excipients complex had been formed in case of solid dispersion (PEG-6000 and PVPK30) and inclusion complex (β-CD and HP β-CD). The surface morphology of drug and solid dispersion (AS_4, BS_5) was determined by the use of scanning electron microscopy. Acyclovir existed as needle-like crystals, whereas PVP K30 seen as amorphous spherical or pieces of spherical particles and PEG 6000 consisted of large crystalline particles of rather irregular size. The solid dispersions appeared in the form of irregular particles in which the original morphology of both components disappeared and tiny aggregates of amorphous pieces of irregular size were present. Therefore, the reduced particle size, increased surface area, and the close contact between the hydrophilic carriers and acyclovir might be responsible for the enhanced drug solubility found for the solid dispersion particles (fig.5).

DSC curves obtained for pure material, β-CD, HP β and inclusion complexes are displayed in fig.6. In case of acyclovir one endothermic peak was observed at 251.8 which were near to its melting point 253°C. In the DSC curves of pure β-CD and HP β-CD, the peaks corresponding to the evaporation of water appeared in the temperature range of 50-150°C. Besides the endothermic peaks corresponding to the loss of water, the thermogram of β-CD displayed melting endotherm with a shoulder, which indicated the presence of more than one crystal form.
The inclusion complex of acyclovir with cyclodextrin showed spectra corresponding to superposition of their parent products. In the curve of inclusion complex with β-CD, it exhibits endotherms at 121.4 and 223°C. The inclusion complex of acyclovir with HP β-CD the all important peaks were absent and a peak was observed at 98.1 which show that all characteristic features of acyclovir peak and cyclodextrin were lost. The disappearance of the thermal features of the drug indicated that the drug penetrated into the cyclodextrin cavity replacing the water molecules. The change in endothermic peaks of acyclovir and cyclodextrin were observed, which confirms the interaction between drug and excipients. Content of acyclovir in solid dispersion (PEG 6000, PVP K-30), inclusion complex (β-CD, HP β-CD) was estimated and % drug content of formulations AS_4, BS_5, CI_5 and DI_5 was found to be 94.18, 94.87, 96.03 and 97.47 respectively. The maximum cumulative % drug release in 0.1 N HCl for AS_4, BS_5, CI_5 and DI_5 batch was 80.11%, 83.23%, 89.45% and 94.25% respectively (Table.III and Fig.1). The drug release was also performed in phosphate buffer saline (pH 7.4) for 60 min. The maximum drug release from batches AS_4, BS_5, CI_5 and DI_5 was 71.63%, 73.12%, 74.12% and 83.24% respectively. (Table IV and Fig. 2).

The release of drug from the optimized batches was compared with marketed preparation (zovirax) in both medium. The dissolution rate of the drug in the solid dispersions and inclusion complexes was evidently higher than that of the marketed drug. This can be attributed to the increase in solubility as drug. (Table III-IV and Fig.1-2). Several mechanisms had been proposed to account for the increase in the dissolution kinetic of drugs from solid dispersions. Decreased crystallinity, increased wettability, and reduction of drug particle size were considered to be predominant factors. Increase of dissolution rates was obtained for the inclusion complexes. This behavior might be attributed to the high energetic amorphous state and inclusion complex formation.

A rapid and excellent dissolution behavior was obtained by forming solid dispersion with PVP K30 or PEG6000 and inclusion complex with β-CD or HP β-CD. Among these preparations HP β-CD inclusion complex (DI_5) shows higher solubility and dissolution rate.

Table I: Physical mix of drug and polymer

Carrier	Code	Drug /Carrier ratio	Mean absorbance	Conc.(mcg/ml)
PEG 6000	AP1	1:1	0.395	14.58
	AP2	1:2	0.487	17.97
	AP3	1:3	0.516	19.04
PVP K30	BP1	1:1	0.407	15.02
	BP2	1:2	0.488	18.01
	BP3	1:3	0.522	19.26
β CD	CP1	1:1	0.432	15.94
	CP2	1:2	0.498	18.38
	CP3	1:3	0.603	22.25
HPBCD	DP1	1:1	0.478	17.64
	DP2	1:2	0.545	20.11
	DP3	1:3	0.574	22.88

Table II : Solubility Of Solid Dispersion (As1-Bs5) And Inclusion Complex Of Drug (CI1-DI5) With Polymer

Carrier	Code	Drug /Carrier ratio	Mean absorbance	Conc.(mcg/ml)
PEG 6000	AS1	1:1	1.428	52.694
	AS2	1:2	1.569	57.897
	AS3	1:3	1.779	65.646
	AS4	1:4	1.815	66.974
	AS5	1:5	1.788	65.978
PVP K30	BS1	1:1	1.491	55.018
	BS2	1:2	1.611	59.446
	BS3	1:3	1.806	66.642
	BS4	1:4	1.890	69.742
	BS5	1:5	1.917	70.738
PEG 6000	CI1	1:1	1.715	63.292
	CI2	1:2	1.974	72.856
	CI3	1:3	2.073	76.517
	CI4	1:4	2.285	84.317
	CI5	1:5	2.307	85.137
PVP K30	DI1	1:1	2.077	76.657
	DI2	1:2	2.366	87.321
	DI3	1:3	2.450	90.406
	DI4	1:4	2.495	92.089
	DI5	1:5	2.505	92.465

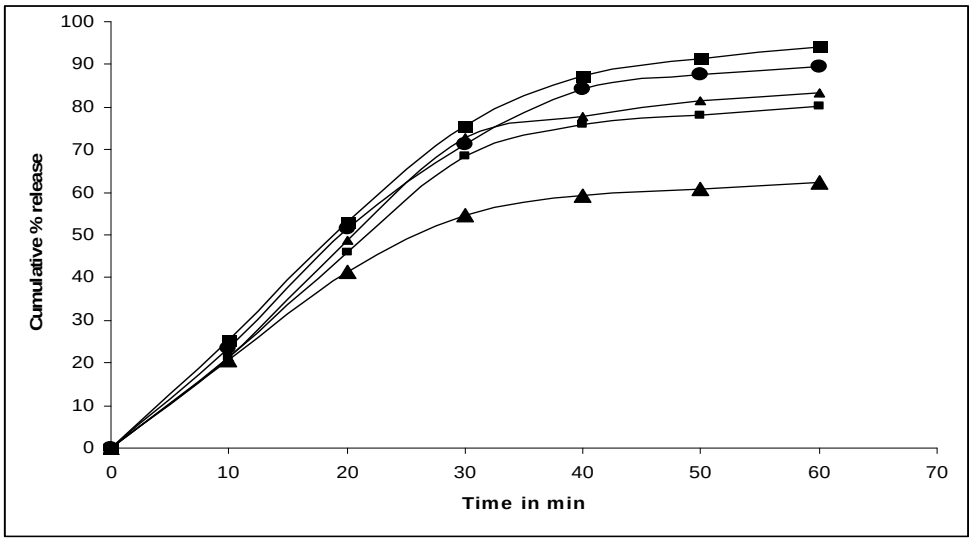
Table III : Dissolution profile of optimised batches of solid dispersion, inclusion complex and marketed preparation in 0.1N HCl.

TIME (MIN)	CUMULATIVE % DRUG RELEASE				
	AS4	BS5	CI5	DI5	Marketed
10	21.35	21.44	23.56	25.31	20.64
20	45.89	48.68	51.62	53.24	41.22
30	68.46	72.99	71.34	75.56	54.74
40	75.81	77.91	84.22	87.36	59.11
50	78.23	81.55	87.59	91.32	60.69
60	80.11	83.23	89.45	94.25	62.36

Table IV : Dissolution profile of optimised batches of solid dispersion, inclusion complex and marketed preparation in PBS pH 7.4.

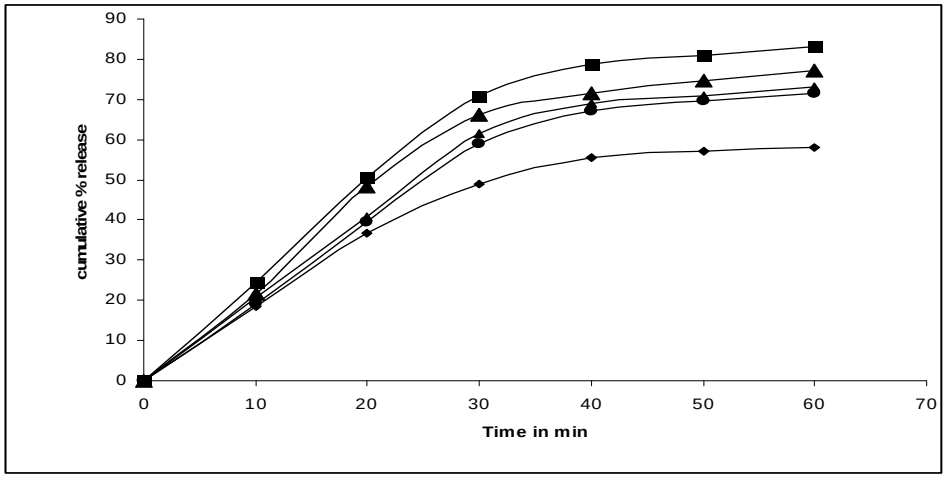
TIME (MIN)	CUMULATIVE % DRUG RELEASE				
	AS4	BS5	CI5	DI5	Marketed
10	19.11	20.71	21.61	24.31	18.63
20	39.56	40.89	48.22	50.51	36.56
30	58.91	61.52	66.25	70.84	48.94
40	67.26	69.11	71.63	78.61	55.66
50	69.77	70.83	74.56	80.86	57.11
60	71.63	73.12	74.12	83.24	58.02

Fig. 1: Comparison of dissolution profile of optimized batches of solid dispersion and inclusion complexation with marketed formulation in 0.1 N HCl



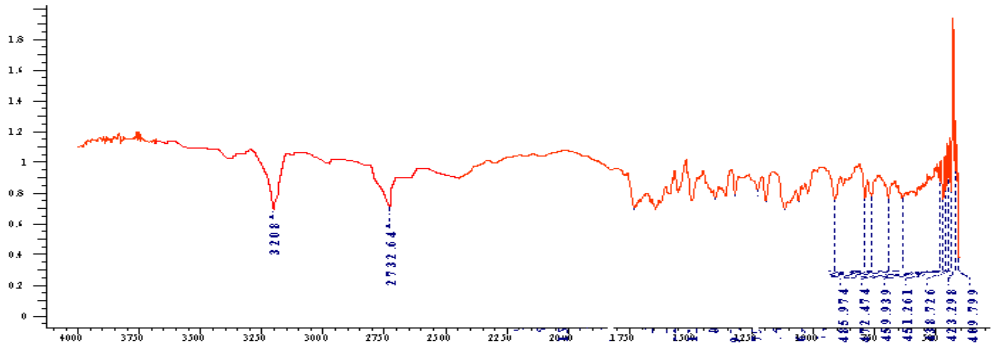
-----■--- Batch DI5; -----●----Batch CI5; ------▲---- Batch BS5; ----- ▪---- BatchAS4
---- ▲ --- Marketed

Fig. 2: Comparison of dissolution profile of optimized batches of solid dispersion and inclusion complexation with marketed formulation in PBS pH (7.4)

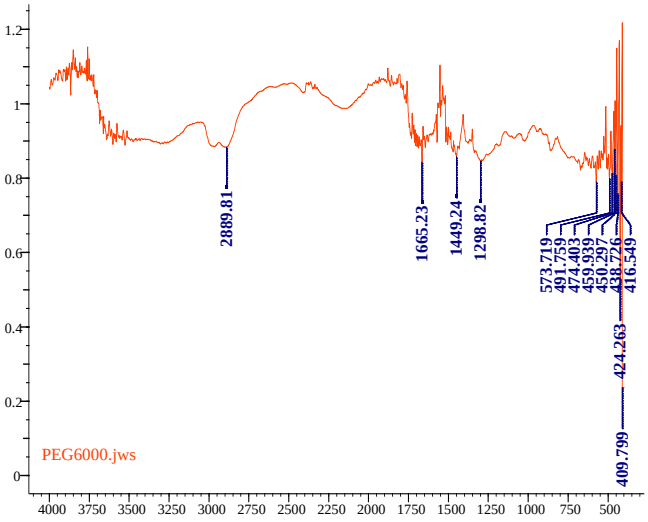


----■--- Batch DI5; ----▲---Batch CI5; ----- ▲------ Batch BS5; --- ●---- Batch AS4
-----▪-----Marketed

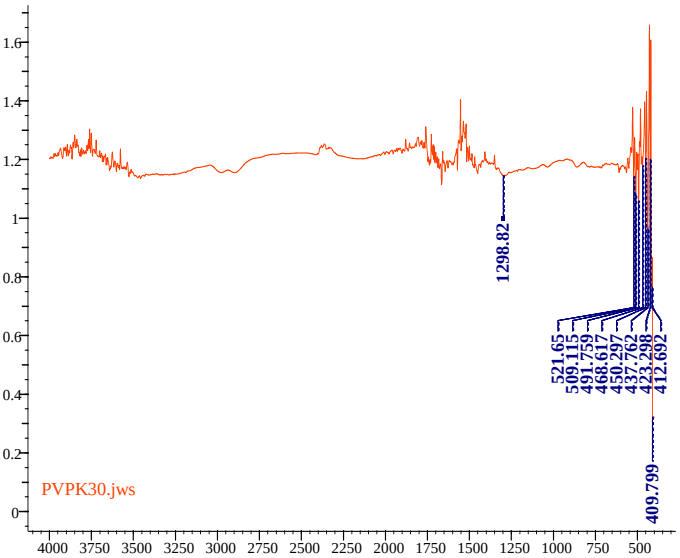
Fig. 3: IR spectra of solid dispersion



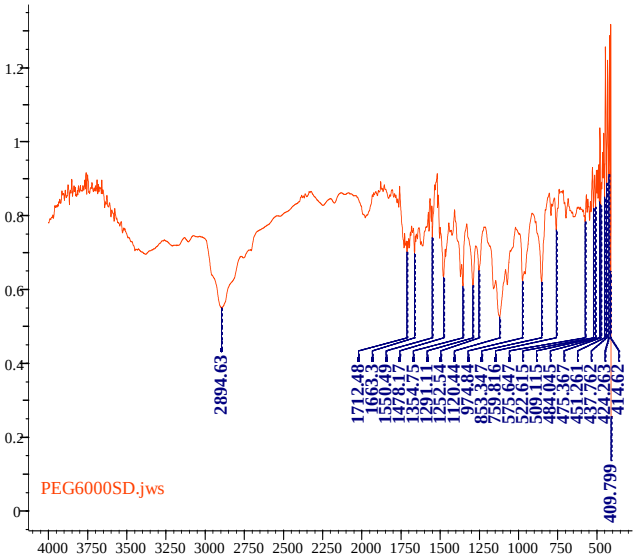
(a) Acyclovir



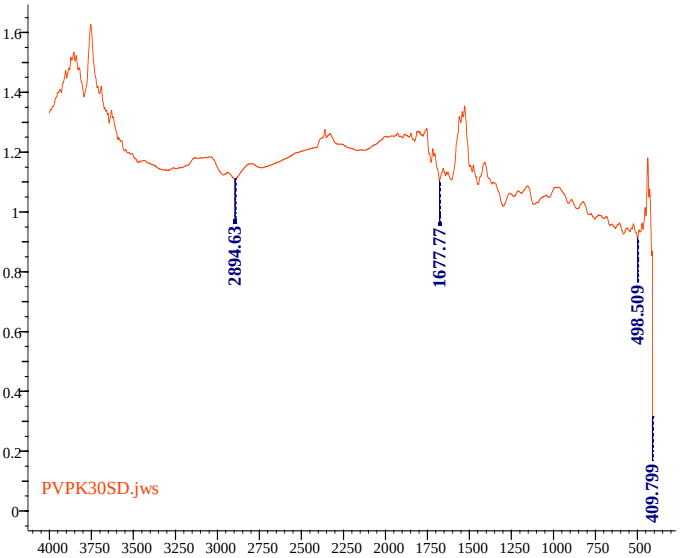
(b) polyethylene glycol -6000 (PEG 6000)



(c) polyvinylpyrollidone K-30 (PVP K30)

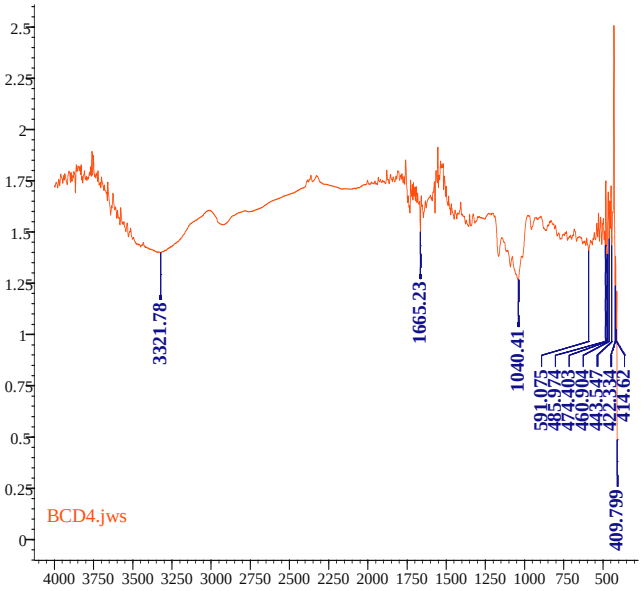


(d) Solid dispersion of acyclovir and polyethylene glycol -6000 (AS_4)

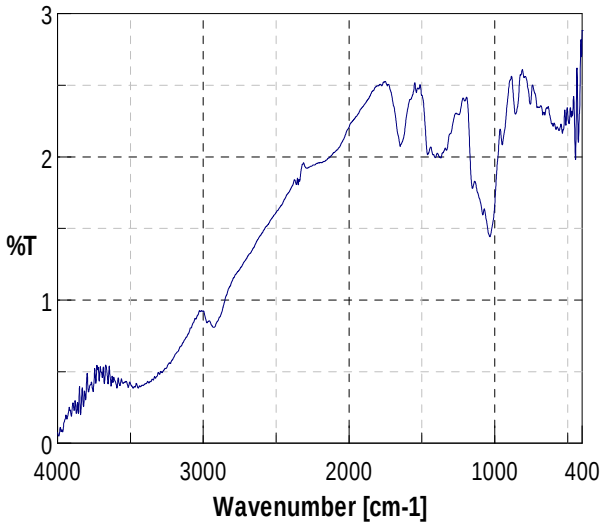


(e) Solid dispersion of acyclovir and polyvinylpyrollidone K-30 (BS_5)

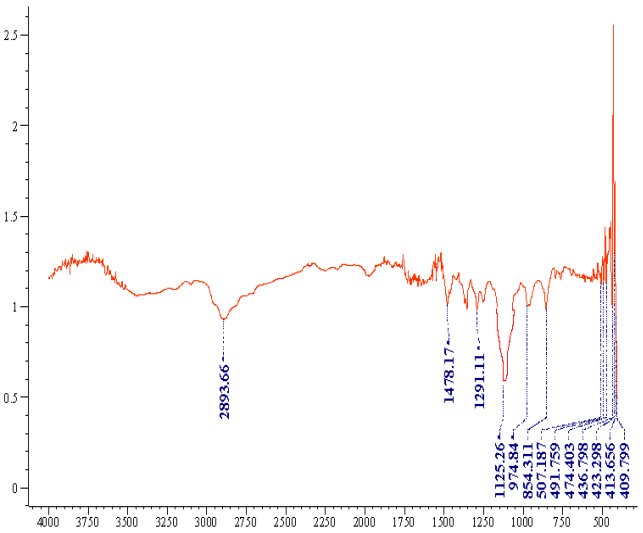
Fig. 4: IR spectra of inclusion complex



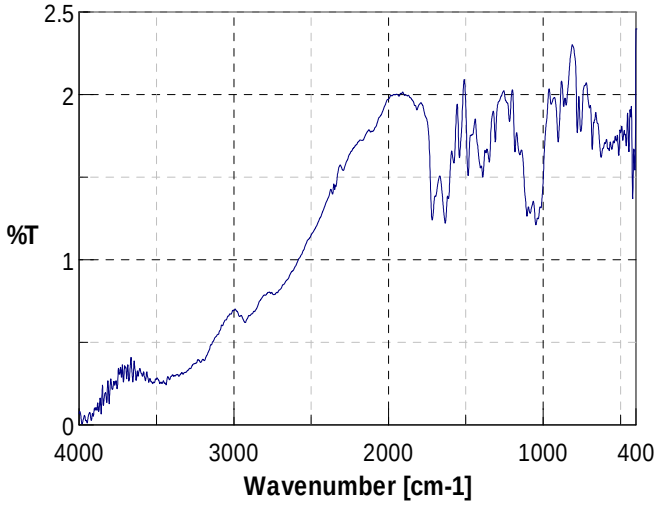
(a) β-cyclodextrin (β-CD)



(b) Hydroxypropyle β-cyclodextrin (HP β-CD)

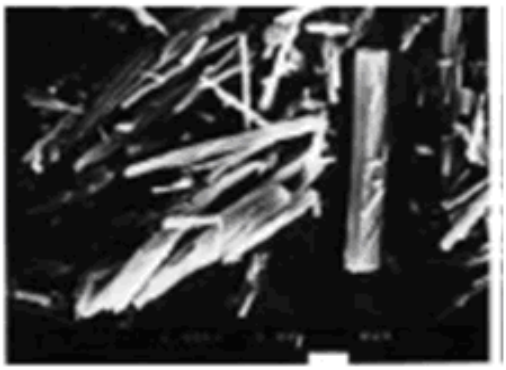


(c) Inclusion complex of acyclovir and β-cyclodextrin (CI_5)

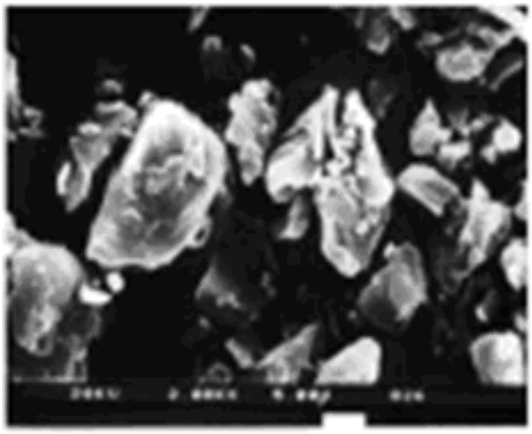


(d) Inclusion complex of acyclovir and hydroxypropyle β-cyclodextrin (DI_5)

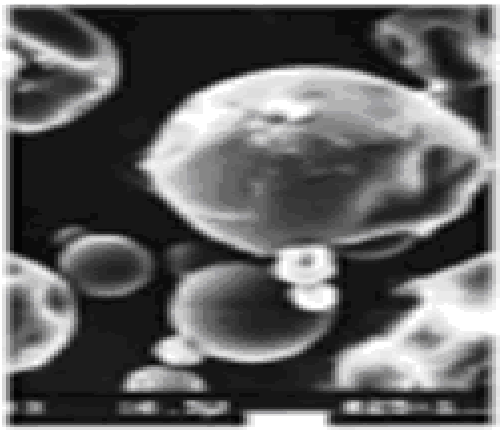
Fig. 5 : SEM micrographs



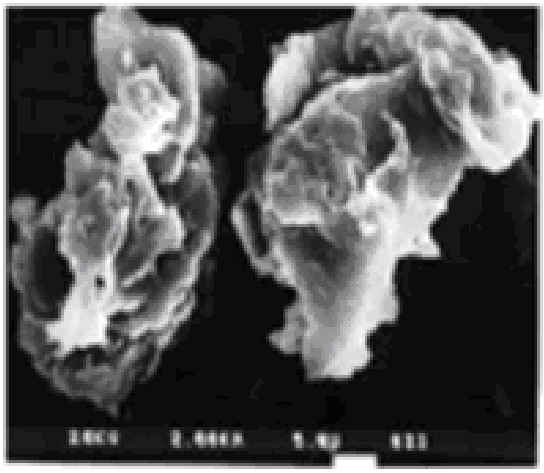
(a) Acyclovir



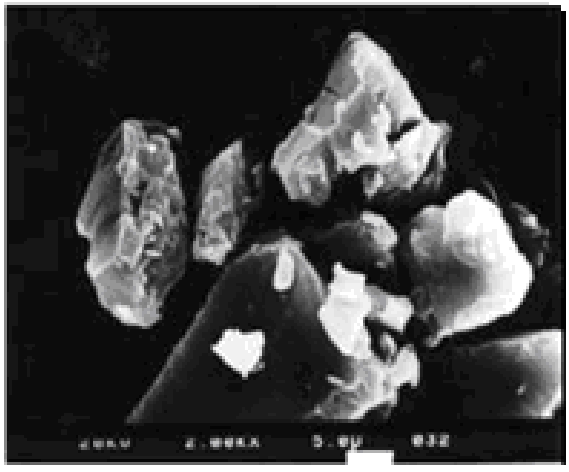
(b) polyethylene glycol-6000 (PEG6000)



(c) polyvinylpyrollidone K-30 (PVPK30)

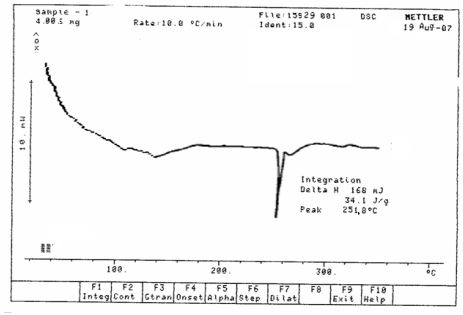


(d) Solid dispersion of acyclovir and polyethylene glycol -6000 (AS_4)

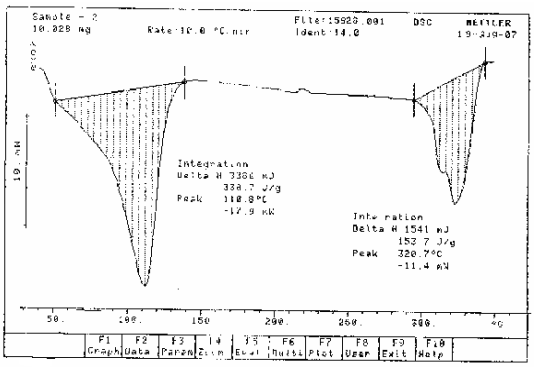


(e) Solid dispersion of acyclovir and polyvinylpyrollidone K-30 (BS_5)

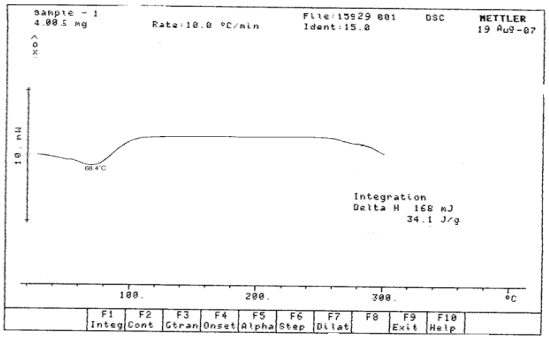
Fig. 6: DSC Curves



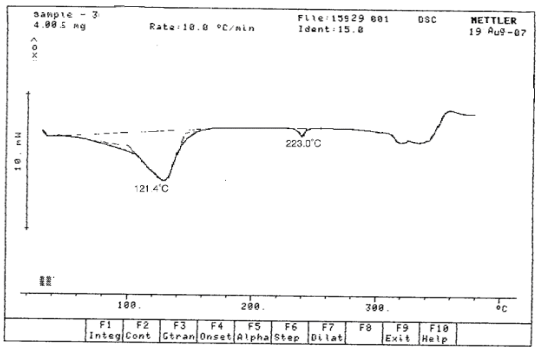
(a) Acyclovir



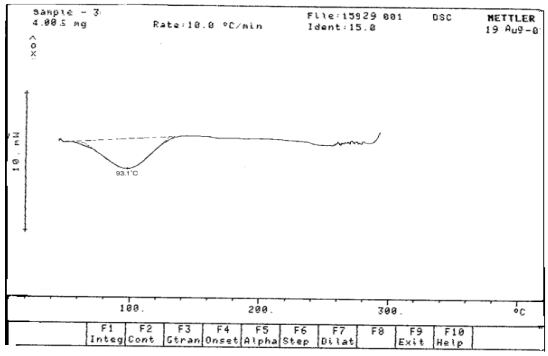
(b) β-cyclodextrin (β-CD)



(c) Hydroxypropyle β-cyclodextrin (HP β-CD)



(d) Inclusion complex of acyclovir and β-cyclodextrin (CI_5)



(e) Inclusion complex of acyclovir and hydroxypropyle β-cyclodextrin (DI_5)

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