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Research Article

Dissolution enhancement of Tacrolimus by surface solid-dispersion technique

Srikanth A*[1], Prasanna Raju Y[2], Devanna N[3]

[1]OTRI, JNTUA, Anantapuramu- 515001, Andhra Pradesh, India
[2]Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupati-517503, Andhra Pradesh, India
[3]JNTUA College of Engineering kalikiri, Chittor District, Andhra Pradesh, India

ABSTRACT

The work was aimed to increase the dissolution rate of tacrolimus by surface solid dispersion technique. being insoluble in water, tacrolimus exhibits very low drug dissolution profiles and hence it was planned to modify the surface area and thereby to increase the absolute surface area of tacrolimus by using insoluble and hydrophilic polymers. the surface modified solid mixture of tacrolimus were formulated by surface solid dispersion technique using polymers like sodium starch glycolate (ssg), microcrystalline cellulose (mcc), cross carmellose sodium (ccs), modified starch (ms) and gum karaya (gk). The various ratios of drug:polymer (1:0.5, 1:1, 1:2, 1:3, 1:4 and 1:5) were used to develop the solid mixtures. The obtained solid dispersions were evaluated for percentage yield, drug content and *in-vitro* drug release. *In-vitro* dissolution study for all surface solid dispersions was conducted in pH 6.8 pbs environment. Drug release patterns of tacrolimus from raw sample and surface solid dispersions were compared. The results were evidenced that all surface solid dispersions have shown profound increase in dissolution when compared with that of raw sample. Among all surface solid dispersions, the drug release was found to be highest in mixture of tacrolimus with mcc at 1:5 ratio in 120 minutes. Overall, surface dispersion technique can be employed to important naturally obtaining moieties without many hassles.

Keywords: *In-vitro* drug release; Solid dispersions; Tacrolimus; Surface solid dispersion technique.

INTRODUCTION

Tacrolimus, a macrolide isolated from an actinomycete *Streptomyces tsukubaensis* (Goto T.*et al*.,1987, Hane.*et al*.,1992, Hardman J.*et al*.,2001) It was soon found to be a potent alternative to cyclosporine in several experimental models. Absorption of tacrolimus is incomplete after oral administration. Its bioavailability ranges from 10 to 60%, with peak blood levels after 1 to 2 h and half-life of 8 to 24 h (Venkataramanan R.*et al*., 1987) The oral dose of tacrolimus needs to be higher than intravenous doses. Tacrolimus is highly bound to plasma proteins, e.g.,albumin, and to red blood cells and lymphocytes (Piekoszewski W. et al.,1993). The major part of the metabolism takes place in the intestinal wall and in the liver by the cytochrome P450 system (Sattler.M.et al.,1992) Tacrolimus comes under biopharmaceutical classification BCS-II having low solubility and high permeability, tacrolimus appears as white crystalline powder (Joe,J.H. *et a*l.,2010).It is practically insoluble in water, freely soluble in ethanol and very soluble in methanol and chloroform. tacrolimus bearing a empirical formula of $C_{44}H_{69}NO_{12}$. H_2O and having formula weight of 822.03.solid dispersions is the formulation that possibly enhances the dissolution rate, solubility, and oral absorption of a poorly water soluble drug (Cilurzo et al.,2002). The drug in solid dispersion often exists as amorphous form, amorphous form of a drug has a higher thermodynamic activity than crystalline form, this leads to the rapid dissolution of the drug (Craig, D.Q.M *et al*., 2001). The dissolution rate was increased by the following factors,

a) the reduction of the drug particle size to molecular level
b) solubilising effect on the drug by water soluble carrier
c) Enhancement of wettability and dispersibility of the drug by the carrier material (Yamashita e*t al*., 2003).

The chemical structure of tacrolimus was shown in the fig.1.

MATERIALS AND METHODS

Materials

Tacrolimus was procured as gift sample from DR.REDDY'S laboratories. Ltd, Hyderabad, gumkaraya, cross caramellose sodium, modified starch, sodium starch glycolate, microcrystalline cellulose were purchased from S.D.Fine Chem Ltd, Mumbai. All other chemicals used were of analytical grade.

* Corresponding Author
Email: srikanthvbcops@gmail.com
Contact: +91-9949959910
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Formulation of solid dispersions by Surface adsorption method

Tacrolimus was dissolved in dichloromethane (DCM) and add polymers (like SSG, MCC, CCS, Modified starch and gum karaya individually) to the tacrolimus solution. Then evaporate the solvent by using water bath. Tacrolimus and the selected polymers are weighed in the ratios of 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 respectively and prepared solid dispersions were used for further studies.

Evaluation of solid dispersion

Fourier transform infrared (FTIR) study

Fourier transform infrared spectrum of tacrolimus and solid dispersions (of highest ratios) using polymers and for individual polymers were recorded. On a thermo – IR 200 FTIR spectrophotometer (Perkin Elmer) potassium bromide pellet method was employed and back ground spectrum was collected under identical conditions. Each spectrum was derived from 32 single scans collected in the range of 4000 – 650cm^{-1} at the spectral resolution of 8 cm^{-1}.

Differential scanning calorimetry study

Thermal analysis of tacrolimus, solid dispersions using polymers of highest ratio and individual polymers were recorded using differential scanning calorimeter (Perkin Elmer-pyris 6). A heating rate of 20°C/min was employed over a temperature range of 50°C - 350°C with nitrogen purging. Powder sample was weighed into an aluminium pan was used as reference.

Scanning electron microscope (SEM) study

The SEM pictures were obtained by a scanning electron microscope (Hitachi-SU1510). The accelerating voltage is 15Kv at 500x.

Powder X-ray diffraction (XRD) measurement

The powder X-ray diffraction patterns of pure drug and solid dispersions and individual polymers were recorded using Xpert-pro panalytical diffractometer (Shimadzu-6005) .The samples were exposed to Cu-Kα radiation at 56Kv and 182Ma over the 2θ range from 0°C - 80°C.

Percentage yield

The percentage yield of solid dispersions were calculated by using the formula

$$\% \text{ yield} = \frac{\text{weight of solid dispersions}}{\text{weight of drug} + \text{weight of polymer}} \times 100$$

Drug content

Prepared tacrolimus solid dispersions equivalent to 20 mg of tacrolimus were accurately weighed and transferred to 100ml conical flask and the volume was made up to 100ml with methanol and absorbance was read at 233nm.

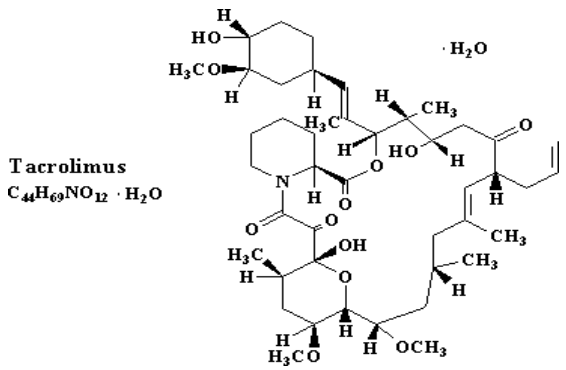

Figure 1: Chemical structure of Tacrolimus

Dissolution study

The dissolution test was carried out by using USP dissolution type-II appraratus (paddle). The dissolution conditions includes, dissolution medium (phosphate buffer pH 6.8), Temperature (37 ± 0.5°C), speed of rotation (50rpm) and volume (900ml).Tacrolimus containing solid dispersion equivalent to 20mg were placed in the basket of dissolution medium and the apparatus was run .the 5ml aliquots were withdrawn at intervals of 0, 5, 10, 15, 30, 45, 60, 75, 90 and 120 min and replace with 5ml of fresh dissolution medium. The samples were filtered through 0.45µm nylon filter and absorbance was recorded at 233nm and the % drug release was calculated. All the above mentioned methods was done for all the polymers shown in the table no.1

RESULTS AND DISCUSSION

Percentage yield and drug content of tacrolimus in different ratios of different polymers were shown in the table1 and the percentage practical yield was in the range of 68 to 91.88. Percentage yield was high with polymer microcrystalline cellulose and low with gum karaya.

Drug content was in the range of 70.5 to 99.25and drug content was decreased by increasing the polymer concentration and it was observed for all the polymers.fig.6. shows the SEM pictures of tacrolimus crystalline powder and fig.7. shows the SEM pictures of solid dispersions with polymer microcrystalline cellulose and SEM pictures of all other polymers were recorded. tacrolimus crystalline powder showed the prismatic shape and with the MCC showed the fibrous mass .these results suggest that solid dispersions prepared by surface solid dispersion technique is effective and the tacrolimus homogeneously dispersed with used polymers. The FTIR studies were carried out to investigate the interaction between the tacrolimus and polymers. The FTIR spectra of tacrolimus crystalline was shown in the fig.5 and absorption bands of O–H stretching vibration at3450 cm^{-1},C=O (ester and ketone) stretching vibrations at 1740, 1725 and 1693 cm−1,C=O (keto-amide)and C =C stretching vibration at 1637 cm^{-1}, C–O (ester) stretching vibration at 1194

Table 1: Percentage yield and drug content

S. No.	Drug : Polymer	Ratios	% yield (%)	Drug content	
				mg/ml	%
1.	Tacrolimus : Sodium starch glycolate	1:0.5	76.88	8.65	86.5
		1:1	85	9.15	91.5
		1:2	78.22	8.3	83
		1:3	77.5	8.175	81.75
		1:4	88	8.375	83.75
		1:5	87.55	8.1	81
2.	Tacrolimus : Microcrystalline cellulose	1:0.5	75.55	9.625	96.25
		1:1	83.33	9.225	92.25
		1:2	86.22	7.575	75.75
		1:3	89.33	7.35	73.5
		1:4	89.33	7.225	72.25
		1:5	91.88	7.05	70.5
3.	Tacrolimus : Cross carmellose sodium	1:0.5	72.44	8.45	84.5
		1:1	78.33	7.475	74.75
		1:2	84	7.925	79.25
		1:3	87.5	7.85	78.5
		1:4	86.13	8.6	86
		1:5	89.88	7.375	73.75
4.	Tacrolimus : Modified starch	1:0.5	86.33	9.925	99.25
		1:1	84.44	9.675	96.75
		1:2	87	7.45	74.5
		1:3	88.13	7.225	72.25
		1:4	89.11	7.2	72
		1:5		7.15	71.5
5.	Tacrolimus : Gum karaya	1:0.5	68	8.65	86.5
		1:1	76.66	7.15	71.5
		1:2	87.33	7.2	72
		1:3	89.66	7.025	70.25
		1:4	88	7.0	70.5
		1:5	88.55	7.6	76

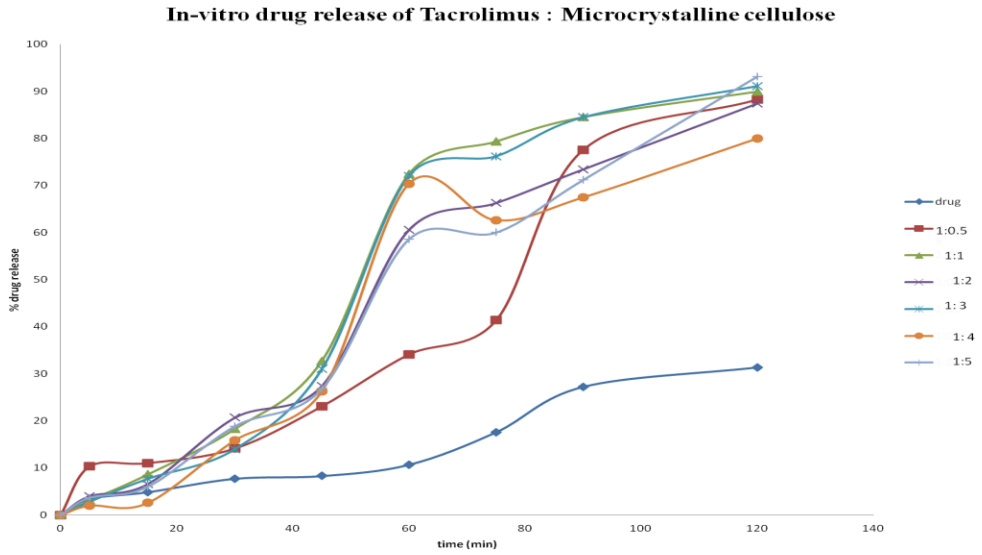

Figure 2: *In-vitro* Drug release of Tacrolimus : Microcrystalline cellulose

cm^{-1}, C–O–C (ether) stretching vibrations at 1176 and 1094 cm^{-1}were observed (Hane et al., 1992). These bands were also observed for the solid dispersions of tacrolimus with different polymers.fig.3and fig.4 shows the FTIR spectra of microcrystalline cellulose and Tacrolimus : Microcrystalline cellulose (1 : 5) respectively,

Table 2: % Drug release of Tacrolimus : Microcrystalline cellulose

S. No.	Time (min)	Tacrolimus : Microcrystalline cellulose (MCC)						
		Pure drug	1:0.5	1:1	1:2	1:3	1:4	1:5
1.	0	0	0	0	0	0	0	0
2.	5	3.42	10.34	3.10	4	2.85	2	3.71
3.	15	4.85	11.03	8.62	6.57	7.71	2.57	6
4.	30	7.71	14.13	18.27	20.68	14	15.86	18.85
5.	45	8.28	23.10	32.75	27.42	31.03	26.28	26.85
6.	60	10.68	34.13	72.41	60.57	72.06	70.34	58.57
7.	75	17.58	41.37	79.31	66.28	76.20	62.57	60.00
8.	90	27.24	77.58	84.48	73.42	84.48	67.42	71.17
9.	120	31.37	88.27	89.91	87.42	91.10	79.92	93.14

Figure 3: Ftir spectra of Microcrystalline cellulose

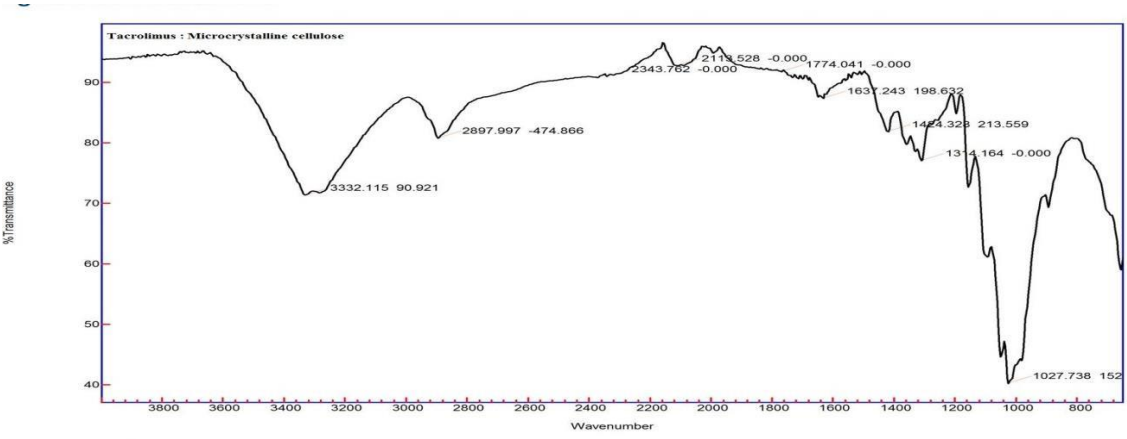

Figure 4: Ftir spectra of Tacrolimus : Microcrystalline cellulose

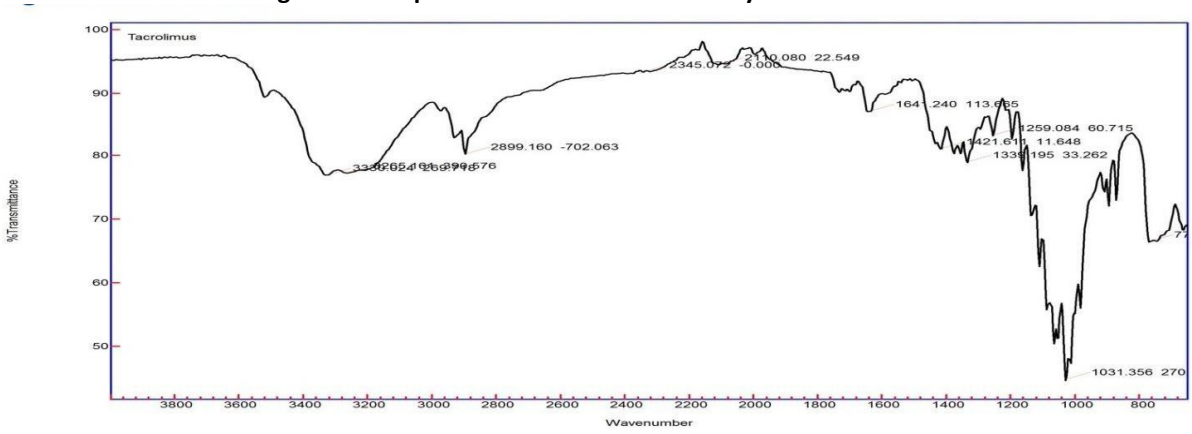

Figure 5: Ftir spectra of Tacrolimus

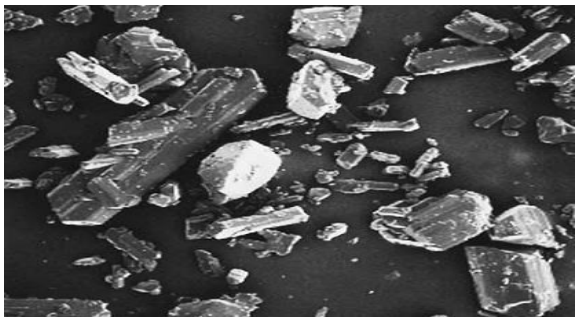

Figure 6: SEM of Tacrolimus

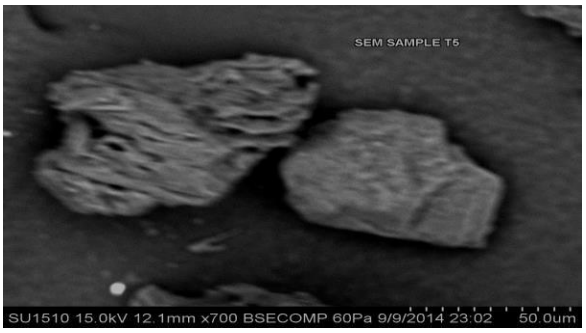

Figure 7: SEM of Tacrolimus: Microcrystalline cellulose

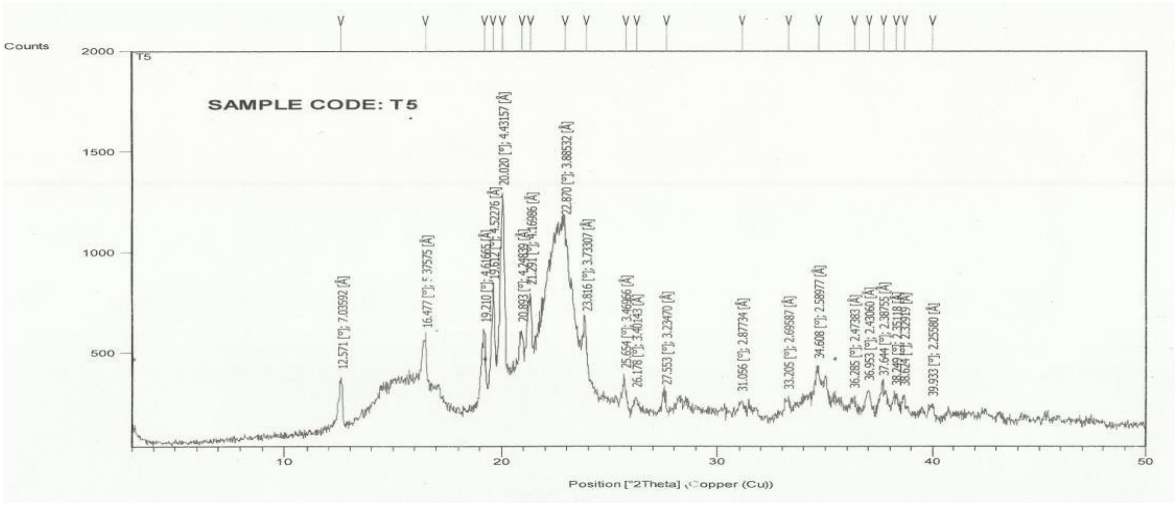

Figure 8: XRD of Tacrolimus: Microcrystalline cellulose

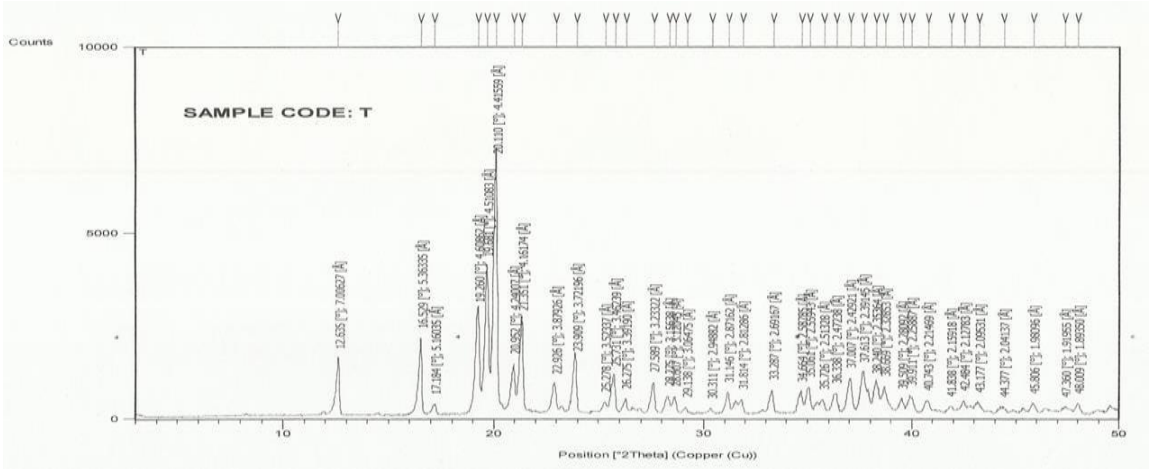

Figure 9: XRD of Tacrolimus

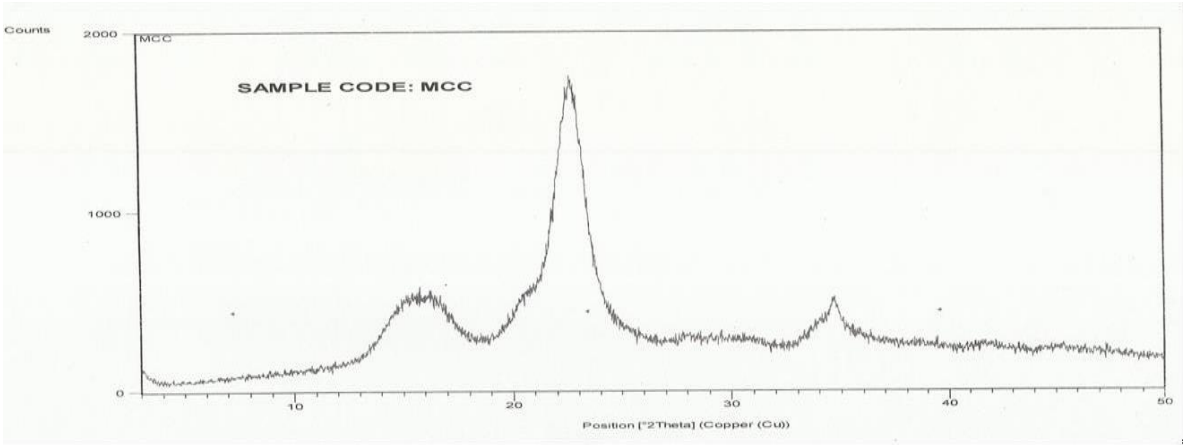

Figure 10: XRD of Microcrystalline cellulose

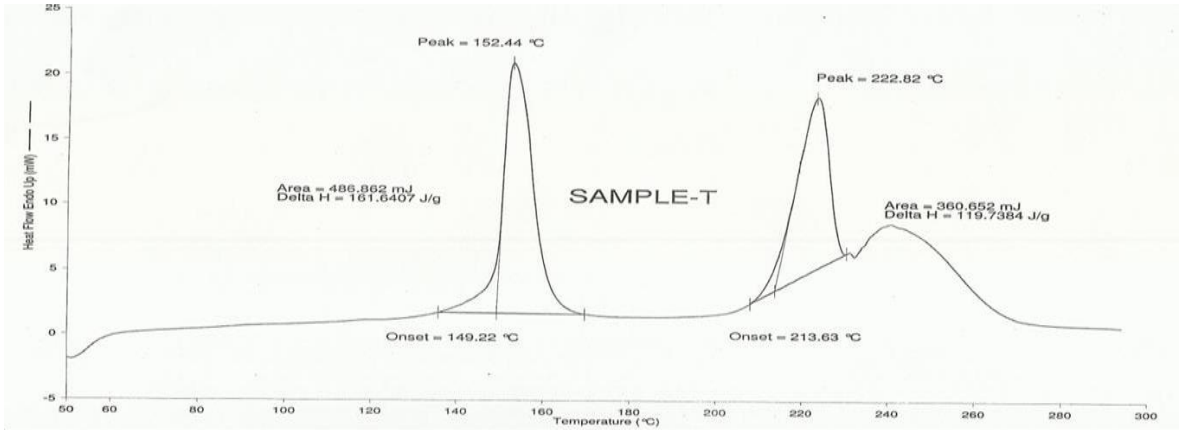

Figure 11: DSC thermo gram of Tacrolimus

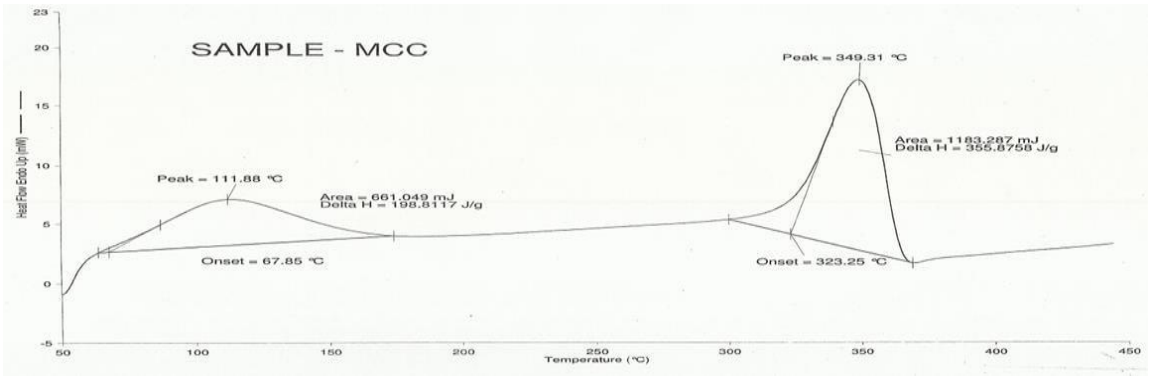

Figure 12: DSC thermo gram of Microcrystalline cellulose

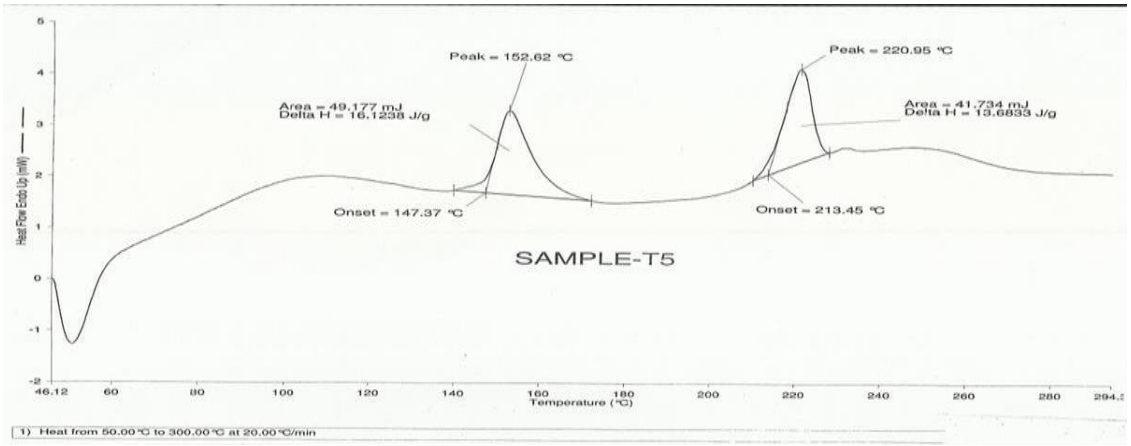

Figure 13: DSC thermo gram of Tacrolimus: Microcrystalline cellulose

these results suggest that there is no interaction between the drug and polymer. The crystallinity of tacrolimus in solid dispersions was checked by XRD. Fig.8, Fig.9, Fig.10, shows the XRD of Tacrolimus : Microcrystalline cellulose (1:5), XRD of Tacrolimus, XRD of Microcrystalline cellulose, XRD patterns suggests that pure tacrolimus is crystalline in nature and formulated solid dispersions are amorphous in nature, the amorphous form of a drug is having high thermodynamic activity than its crystalline form. The higher thermodynamic energy level of the drug leads to rapid dissolution property. The DSC thermo grams of pure tacrolimus, microcrystalline cellulose and Tacrolimus : Microcrystalline cellulose(1:5) were depicted in the Fig.11, Fig.12, Fig,13 respectively. The results depicted that there exists a slight variation in the endothermic peaks of tacrolimus to that of tacrolimus solid dispersions of mcc and also suggested that solid dispersions are amorphous in nature. *In-vitro* Drug release of pure tacrolimus and tacrolimus : microcrystalline cellulose in different ratios are tabulated in the Table no.2 and graphical representation of these results were shown in the Fig.2. It was observed that the increased dissolution profiles of tacrolimus solid dispersions than that of pure tacrolimus and the percentage drug release of tacrolimus and tacrolimus : microcrystalline cellulose (1:5) were 31.37 and 91.34 respectively after 120 minutes.

CONCLUSION

The surface solid dispersion technique is a most reliable method to increase the dissolution profiles of poorly water soluble drugs. The prepared solid dispersions can be used in designing a novel drug delivery systems used to alleviate the symptoms of different diseases. The surface dispersion technique can be employed to important naturally obtaining moieties without many hassles

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