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ENHANCEMENT OF DISSOLUTION OF TELMISARTAN BY SURFACE SOLID DISPERSION TECHNIQUE

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ABSTRACT

Telmisartan is an Angiotensin Receptor Blocker (ARB) used for the treatment of hypertension. It belongs to BCS class–II i.e. low solubility and high permeability and exhibits variable bioavailability. The objective of the present study was to prepare surface solid dispersions of telmisartan to improve its aqueous solubility and dissolution rate. Water insoluble carriers like Avicel pH 101, Crospovidone, Sodium starch glycolate, Cab-o-sil, Pregelatinised starch and Potato starch were used to form surface solid dispersion (SSD) of Telmisartan by solvent evaporation method. The surface solid dispersion prepared with Cab-o-sil in the drug : carrier ratio of 1:10 showed highest dissolution rate as compared to pure drug and physical mixture. The SSD on Cab-o-sil was characterized by Powder X-ray diffractometry, Differential scanning calorimetry, Fourier transform infrared spectroscopy and Scanning electron microscopy. DSC studies revealed that there was no chemical interaction between drug and the carrier and XRD studies demonstrated that there was a significant decrease in crystallinity of pure drug .The optimized surface solid dispersion was compressed into tablets and evaluated for Weight variation, Hardness, friability, Drug content, Disintegration time and Dissolution rate. These tablets exhibited higher rates of dissolution and dissolution efficiency as compared to marketed tablets.

Key words: *Crospovidone; Sodium starch glycolate; Pregelatinised starch; Potato starch; Avicel pH 101.*

INTRODUCTION

Dissolution acts as a rate limiting step in the absorption of drugs from oral route, therefore it is necessary to enhance the dissolution for maximum therapeutic efficacy. Various methods employed to improve the dissolution characteristics of poorly water soluble or insoluble drugs are solubilization, pH adjustment[1], cosolvency[2], microemulsion[3], self emulsification[4], polymeric modification[5], drug complexation[6], micronization[7], use of surfactant as a solubilizing agent[8], pro-drug approach[9] and solid dispersion[10]. Among the various approaches, solid dispersion has shown promising results in improving the solubility, dissolution rate and subsequently the bioavailability of drugs [11]. The surface solid dispersion overcomes some of the shortcomings of the conventional solid dispersions. Surface solid dispersion is a technique of dispersing one or more active ingredients on a water insoluble carrier of high surface area in order to achieve increased dissolution rates and bioavailability of poorly and practically insoluble drugs.

This technique has been extensively used to increase the solubility, dissolution and the bioavailability of poorly water soluble drugs such as ibuprofen[12], piroxicam[13-14], meloxicam[15], itraconazole[16] and ketoprofen[17]. The carriers used in surface solid dispersions are water-insoluble, porous materials which are hydrophilic in nature[12]. Some of the common tablet excipients like Avicel, Cab-o-sil, crospovidone and pregelatinised starch have been used as carriers for surface solid dispersions[14]. The release of drug from carrier material depends on the hydrophilic nature, particle size, porosity and surface area of the carrier[18]. Larger the surface area of carrier available for adsorption of drug better is the release rate. Carriers that have large surface area like silicon-dioxide can improve the dissolution rate if used in less quantity[19].

Telmisartan is an Angiotensin Receptor Blocker (ARB) having high affinity for the angiotensin II type 1 (AT1) receptors, has a long duration of action and has the longest half-life of any ARB (24 hours)[20]. It is used to treat high blood pressure (hypertension) by blocking the hormone angiotensin, thereby relaxing the blood vessels. High blood pressure reduction helps prevent strokes, heart attacks and kidney problems.

It is practically insoluble in water and solutions of pH range 3 to 9, sparingly soluble in strong acid except hydrochloric acid and soluble in strong base[21]. The solubility of Telmisartan has been improved by using polymers like Gelucire 43/01, Poloxamer 407, PVP K-30 and HPMC E4 and PEG 6000. Solid dispersions were prepared by fusion method. Saturation solubility studies, *in-vitro* dissolution of pure drug, physical mixtures and solid dispersions were carried out. All the polymers were found to be effective in increasing the

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dissolution rate of Telmisartan in solid dispersions as compared to pure drug[22]. Dry emulsions were also prepared by using oleic acid in which drug is highly soluble, lactose as water soluble carrier and aerosil as an adsorbent. Dry emulsion was evaluated for drug content, globule size determination and dissolution studies. *In vitro* drug release of dry emulsion was studied by USP type II dissolution apparatus. The solubility of the drug increased with increase in the concentration of the carrier [23].

Dissolution of other antihypertensive drugs has been improved by various novel techniques. The dissolution rate of the poorly soluble drug Valsartan was improved by formulating the drug as liquisolid compacts. Liquisolid compacts were prepared with propylene glycol as solvent, Avicel PH102 as carrier, and Aerosil 200 as the coating material. Dissolution efficiency of valsartan at 15 min was increased from 4.02% for pure drug and 13.58% for marketed product to 29.47% for the liquisolid formulation[24].

Irbesartan is a non peptide specific competitive antagonist of the angiotensin II receptor (AT1 subtype) used orally for treatment of hypertension. It is slightly soluble in, alcohol and methylene chloride and practically insoluble in water. The solid dispersions were prepared by co-grinding and melt fusion method and evaluated by dissolution studies. The results obtained showed that the rate of dissolution of Irbesartan was considerably improved in solid dispersions as compared to pure drug [25].

Felodipine is a second generation calcium channel blocker, belonging to BCS class II category and widely used as antihypertensive and antianginal drug. Hence, its low water solubility limits the pharmacological effect. Spherical agglomerates of felodipine were prepared by Quasi emulsion solvent diffusion technique to improve the dissolution rate using acetone, water and dichloromethane as good solvent, poor solvent and bridging liquid respectively[26].

Olmesartan medoxomil is a novel antihypertensive drug having low aqueous solubility and poor micromeritic properties. The effect of different polymers such as polyvinyl pyrollidone (PVP K30) and hydroxypropyl-â-cyclodextrin (HPâCD) on solubility, dissolution rate and flowability of olmesartan medoxomil has been studied by crystallo-co-agglomeration technique [27].

Oral bioavailability of practically insoluble drug Candesartan cilexetil [CC] was improved by preparing nanosuspensions. The nanosuspensions were prepared by media milling using zirconium oxide beads and converted to solid state by spray drying. The spray dried nanosuspension of CC was evaluated for particle size, zeta potential, saturation solubility, crystallanity, surface morphology and dissolution behaviour [28].

The aim of this study was to enhance the solubility of telmisartan. The carriers used were Avicel, Cab-o-sil, crospovidone, sodium starch glycolate, pregelatinized starch and potato starch. The SSDs were prepared with different drug to carrier ratios by solvent evaporation method. The drug release was studied by using USP 2 dissolution test apparatus at pH 1.2 and dissolution rates of SSDs were compared to that of pure drug and marketed tablets.

MATERIALS AND METHODS

Materials

Telmisartan was obtained as a gift sample from Ranbaxy Laboratories, Poanta Sahib (India). Avicel PH 101, Aerosil 200(Cab-o-sil), Sodium starch glycolate (SSG), Pregelatinized starch, Potato starch and Crospovidone (CP) were obtained as generous gift samples from Park Pharma, Baddi (India). All the reagents used were of analytical grade.

Preparation of calibration curve

20 mg of drug was dissolved in methanol in a volumetric flask and volume made up to 100 ml with methanol (200 ì g/ml). From this stock solution, dilutions of different concentrations were prepared with 0.1N HCL (pH 1.2) and absorbance measured at 296 nm using systronics UV-VIS Spectrophotometer. Beer–Lambert law was obeyed in the concentration range of 2 to 16ì g/ml.

Preparation of surface solid dispersion and physical mixture

The Surface solid dispersions of telmisartan were prepared by solvent evaporation method using different hydrophilic carriers such as Avicel, Cab-o-sil, Crospovidone, Sodium starch glycolate, Pregelatinized starch and Potato starch. Surface solid dispersion and physical mixtures were prepared with drug to carrier ratios of 1:6, 1:9, 1:10, 1:12 and 1:15. The required amount of drug was dissolved in methanol to get a clear solution. Water insoluble carrier was added to this clear drug solution and dispersed. The solvent was removed by continuous trituration until a dry mass was obtained. The obtained mass was further dried at 50°C for 4 hrs in an oven. This product was crushed, pulverized and sifted through a 120# sieve. The obtained product was stored in desiccators containing fused $Cacl_2$. Physical mixtures (PM) containing one part of drug and different parts of carrier were prepared by mixing in a porcelain mortar. The prepared mixtures were sifted through #120 sieve and evaluated.

Evaluation of Surface Solid Dispersion

Solubility Studies

Saturation solubility was determined by the shake-flask method. Excess quantity of drug and SSDs were kept in conical flasks containing 10 ml of distilled water. The samples were placed in an orbital shaker at 37 °C and

100 rpm until equilibrium was achieved (24 h). The solutions were diluted and their concentration analysed by UV- VIS spectrophotometer at 296 nm.

Drug Content

Surface solid dispersion equivalent to 40 mg of telmisartan was weighed accurately and dissolved in 100 ml of methanol. This solution was further diluted with 0.1N HCL (pH 1.2) and analyzed by UV-VIS spectrophotometer at 296 nm.

SSD having maximum solubility and drug release was characterized by XRD, DSC, FTIR and SEM and compared with the pure drug.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy was used to study the structural changes and possible interactions between the drug and carrier in the SSD. IR spectra of drug and SSD mixture were recorded using an FTIR spectrophoto - meter [BRUKER (Alpha E)]. The samples were scanned over the frequency range 4000–400 cm^{-1}. The resultant spectra were compared for any spectral changes.

Powder X-Ray Diffractometry (PXRD)

XRD was necessary to study the polymorphic changes of drug in SSD. XRD spectra of samples were recorded using a high-power powder x-ray diffractometer (XPERT_PRO, USA) with Cu as target. The samples were analyzed at a 2è angle range of 2–45°. Operating voltage and current were 40 kV and 55 mA respectively.

Differential Scanning Calorimetry (DSC)

DSC was used to study the drug excipient interaction in surface solid dispersions. Thermograms of drug, physical mixture and SSD mixture were recorded using a differential scanning calorimeter. Accurately weighed sample was heated in a pierced aluminium pan from 30 to 300 °C at a heating rate of 10 °C/min under a stream of nitrogen at a flow rate of 50 ml/min.

Scanning Electron Microscopy (SEM)

Drug and SSD were all mounted onto copper stubs with double-sided adhesive tape and coated with gold using the coated sputter. The samples were examined under a JSM-6100 electron probe microanalyzer (Jeol, USA).

Gas Chromatography

The residual solvent concentration of the prepared solid dispersion of drug was studied by GC. GC analysis was performed using Agilent GC with head space sampler fitted with a flame ionization detector and employing nitrogen as carrier gas. Headspace GC is used to detect solvent residues.

Dissolution rate study

In-vitro dissolution studies for drug telmisartan and prepared SSDs were carried out using USP Apparatus 2 (Paddle type). Sample equivalent to 40 mg of telmisartan was placed in the dissolution vessel containing 900 ml of 0.1N HCL (pH 1.2) at 37 ± 0.5°C and stirred at 75 rpm [29]. Aliquots of 5 ml were withdrawn at specified time intervals and replaced with an equal volume of dissolution medium. The filtered samples were analyzed spectrophotometrically at 296 nm. The dissolution of pure drug and physical mixture was also carried out as shown in Fig 1. The amount of drug released at 5, 15 and 30 minutes were calculated and tabulated respectively. Dissolution data obtained was fitted into zero order, first order, Hixson-Crowell cube root and Higuchi model to analyze the mechanism of drug release rate kinetics from the prepared SSD and physical mixtures. Correlation Coefficient (r) values are given in Table 1.

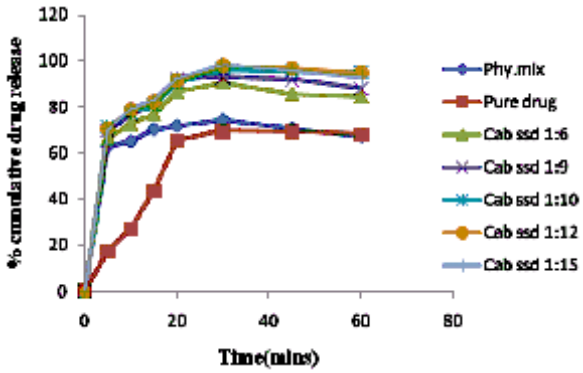


Fig. 1: *Dissolution profile of pure drug, physical mixture and various drug to carrier ratios of telmisartan on Cab-o-sil*

Table 1: Correlation *Coefficient (r) values of telmisartan surface solid Dispersions*

S.No	Formulation	Correlation Coefficient (r) Values			
		Zero order	First order	Higuchi	Hixson-Crowell
1	Drug+SSG	0.508	0.653	0.797	0.607
2	Drug+CP	0.288	0.339	0.583	0.321
3	Drug+Avicel PH101	0.361	0.551	0.661	0.483
4	Drug+Cab-o-sil	0.418	0.706	0.714	0.627
5	Drug+Starch	0.605	0.674	0.841	0.654
6	Drug+Pregelatinized Starch	0.594	0.629	0.820	0.620

Preparation and evaluation of tablets with surface solid dispersions

SSD with Cab-o-sil as the carrier was selected for the preparation of tablets on the basis of dissolution profile. The amount of SSD equivalent to unit dose of drug (40 mg) was incorporated into each tablet. The main ingredients, drug and carrier were thoroughly mixed in a mortar and pestle for 5 minutes. Talc and magnesium stearate were added to this mixture and the blend was compressed into 450 mg tablet by direct compression method with a punch size of 9 mm. The prepared and marketed tablets were evaluated for parameters such as hardness, friability, disintegration time, content uniformity and drug release.

Evaluation of Tablets

All tests were carried out according to the USP compendial specifications.

Uniformity of Weight

Twenty tablets were taken randomly and weighed individually and the average weight, standard deviation and the coefficient of variation calculated.

Hardness and Friability

Hardness and friability of prepared tablets were measured using a Monsanto hardness tester and Roche type apparatus respectively.

Disintegration time

DT was determined at 37°C using disintegration apparatus (EI products, India).

Dissolution Studies

In-vitro release profile of SSD tablets was obtained using a dissolution test USP Apparatus 2 (Electro Lab). Dissolution was carried out in 900 ml of 0.1N HCL buffer (pH 1.2) as the dissolution medium at 37ÚC ± 2ÚC at 75 rpm. (Fig 2)

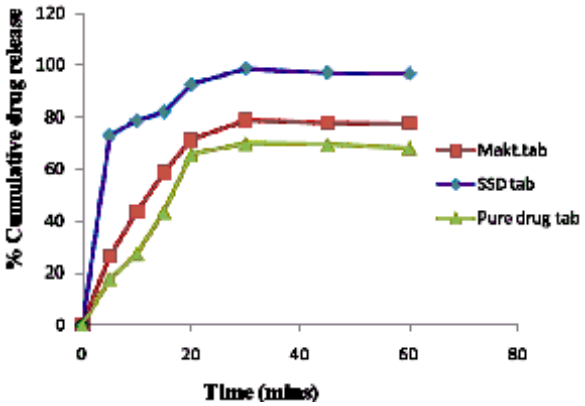


Fig. 2: *Dissolution profile of SSD tablets, Marketed tablet and Pure drug tablet*

RESULTS AND DISCUSSION

Water dispersible carriers like Cab-o-sil, crospovidone, Avicel, sodium starch glycolate, Potato starch and Pregelatinised starch were selected for the study. All SSDs were found to be fine and free flowing powders. Cab-o-sil and Avicel showed higher dissolution of telmisartan (Table 2). The order of increasing dissolution rate observed with various carriers studied were Cab-o-sil>Avicel>Sodium starch glycolate> Potato starch> Crospovidone> Pregelatinised starch. Improvement in the dissolution with 1:12 and 1:15 ratios was marginal as compared to 1:10 ratio, hence a drug:carrier ratio of 1:10 was considered optimum. Telmisartan tablets were prepared by direct compression method with 1:10 SSD of Drug: Cab-o-sil (Table 3). All the tablets were prepared as per GMP guidelines. (Table 4).

Solubility Studies

Cab-o-sil SSD showed highest solubility (0.826±0.008mg/ml), an 80 fold increase in solubility as compared to pure drug (0.0015±0.009mg/ml) as shown in Fig 3. This may be due to either reduction in the crystallinity of drug or improved wetting of the drug particles due to increase in surface area.

Table 2 : *Comparison studies of Dissolution profiles of different SSD*

S. No	Excipients	Ratio	% Cumulative release in 5, 15 and 30mins		
			t5± SD	t15± SD	t30± SD
1	Drug		17.64±1.37	48.56±0.35	69.75±0.22
2	Mixed Tab		26.47±0.65	58.86±0.32	78.87±0.18
3	SSG	1:9	43.07±1.61	54.65±0.87	69.30±0.66
		1:9	44.55±1.31	60.64±0.72	79.75±0.56
		1:10	46.32±0.95	65.30±0.69	79.98±1.23
		1:12	47.36±0.65	66.64±1.22	77.08±1.54
		1:15	48.52±0.45	69.75±0.64	78.65±1.11
4	CP	1:6	40.19±0.49	59.36±1.44	71.53±1.02
		1:9	56.47±1.21	70.12±1.27	73.64±0.71
		1:10	57.57±1.17	71.59±0.76	73.86±0.46
		1:12	57.75±1.12	75.08±1.07	75.31±0.94
		1:15	58.23±0.76	72.64±0.84	76.20±0.34
5	Avicel pH101	1:6	50.95±1.21	72.61±1.54	82.66±0.75
		1:9	65.73±0.75	79.09±0.72	89.55±0.89
		1:10	67.94±1.11	81.54±0.81	87.59±0.73
		1:12	68.60±1.18	83.10±0.96	88.22±1.24
		1:15	68.82±0.96	82.87±1.13	88.00±0.76
6	Cab-o-sil	1:6	66.39±1.83	76.64±1.43	90.45±0.66
		1:9	69.52±0.77	81.09±1.44	93.12±0.68
		1:10	71.47±0.56	85.65±0.86	96.24±0.41
		1:12	70.58±1.14	81.98±1.25	97.80±1.52
		1:15	70.36±0.59	82.87±0.48	98.25±0.29
7	Potato starch	1:6	9.26±0.96	38.68±1.57	65.75±1.23
		1:9	19.41±1.62	37.09±0.39	71.75±0.87
		1:10	20.29±1.45	38.42±0.41	73.08±0.73
		1:12	21.27±0.43	39.86±0.74	75.31±0.82
		1:15	22.27±0.89	37.09±0.83	76.87±0.63
8	Pregelatinized Starch	1:6	12.23±1.22	35.36±0.21	63.31±1.34
		1:9	19.41±1.14	41.97±0.29	70.42±1.25
		1:10	20.95±0.99	36.42±1.13	70.86±0.42
		1:12	21.39±0.87	34.87±1.26	71.58±0.39
		1:15	33.97±1.08	56.20±0.98	74.86±0.54

Process yield with 1:9 was very less as compared to 1:10, therefore 1:10 was selected as the optimum formulation.

Table 3: *Composition for Tablets (450 mg)*

INGREDIENTS	Amt(mg)/Tablet(SSD)
SSD (1:10)	440
Avicel pH 102	2
Magnesium stearate	4
Talc	4

Table 4: *Evaluation of tablets of Surface solid dispersion*

S.No	Evaluation Tests	SSD tablets
1	Disintegration Time	1.2 minutes
2	Hardness	4.95±0.02 Kg/cm^2
3	Friability	0.576%
4	Weight Variation	451.6±4.39
5	Content uniformity	97.5%±1.52

Each value represents mean ±SD (n=6)

Drug Content

Drug content for all SSD were in the range of 95-105%, complying with the USP standards as shown in Fig 4.

FT-IR spectra

The IR spectrum of Telmisartan and SSD are shown in Fig 5. These spectrum observations indicated no interaction between drug and the carrier used in SSD.

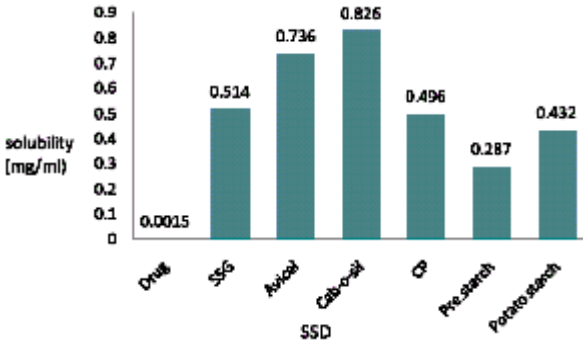


Fig. 3: Solubility studies of Drug and various SSD

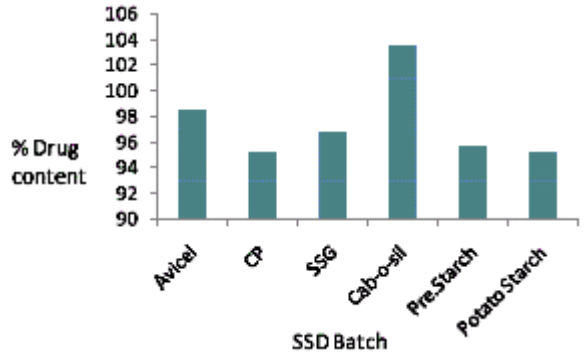


Fig. 4: Drug content of various SSD batches

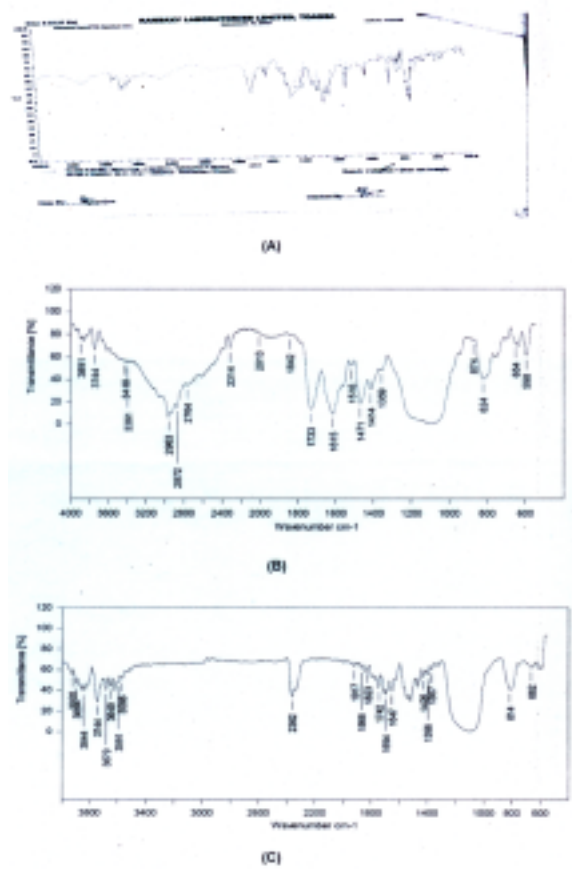


Fig. 5: Characterization of Telmisartan(A), Cab-o-sil polymer(B) and Cab-o-sil SSD(C) by FTIR spectroscopy

X-ray Diffraction

The changes in the physical state of drug in the SSD were evaluated by XRD. X ray diffractogram of Telmisartan and SSD's of drug with Cab-o-sil were recorded as shown in Fig 6. The diffraction pattern of pure drug telmisartan showed a highly crystalline nature indicated by the numerous distinctive peaks at a diffraction angle of 2è (6.77°, 14.21°, 15.04°, 22.25°) throughout the scanning range. XRD of surface solid dispersions showed disappearance of sharp distinctive peaks at a diffraction angle of 2è (6.84°, 14.24°, 22.37°). The diffraction patterns of the SSD indicated changes in the crystalline nature of the drug. The relative 2è angle of telmisartan peaks remained unchanged but relative intensity of the peaks was decreased which can be attributed to the changes in orientation during the surface deposition phase.

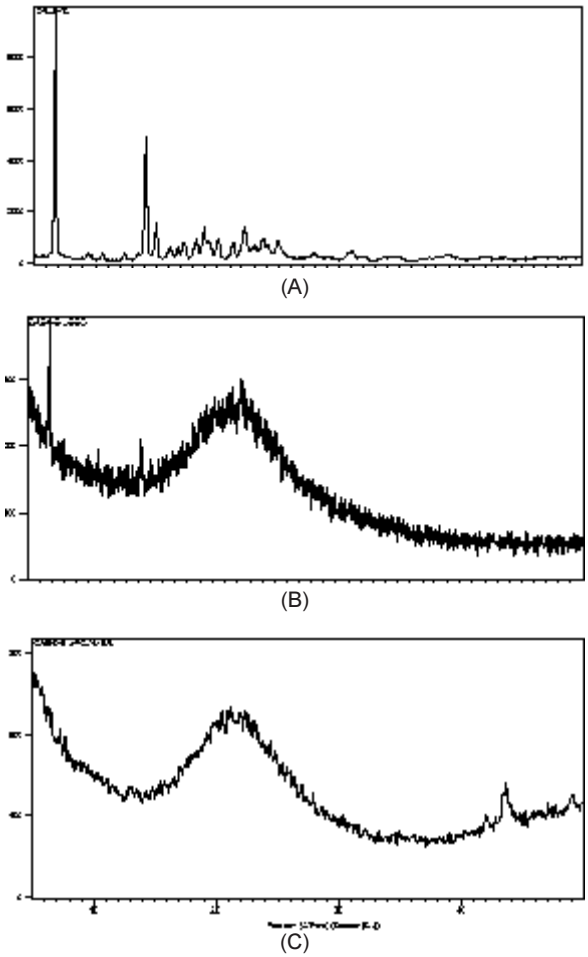
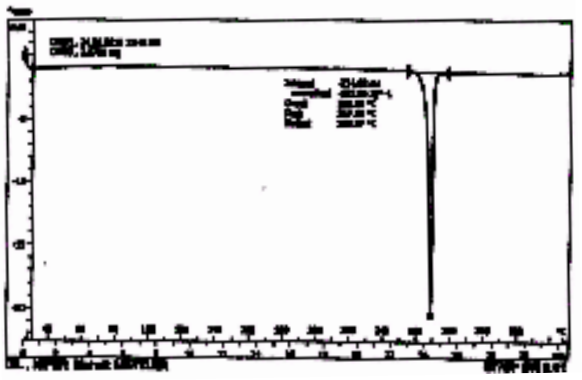


Fig. 6: Characterization of Telmisartan (A), Cab-o-sil SSD (B) and Cab-o-sil polymer (C) by XRD

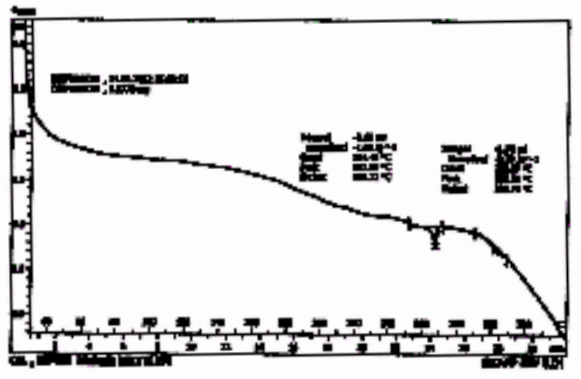
Differential Scanning Calorimetry

DSC was used to evaluate drug excipient interaction in prepared surface solid dispersions. DSC of drug, physical mixture and SSD prepared are shown in Fig 7. The DSC curve of Telmisartan showed a single

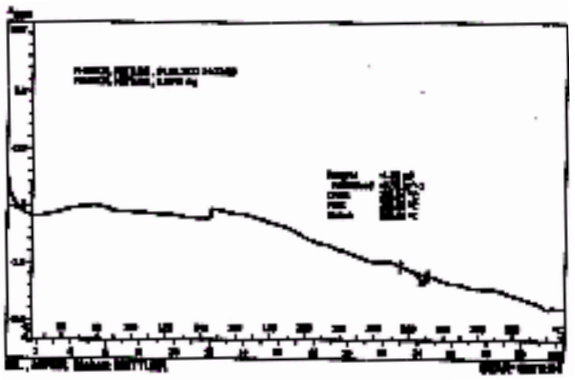
endothermic peak at 267°C. The SSD and physical mixture also show melting point at same temperature indicating no interaction between drug and excipients. Change in the crystalline structure of drug in the surface solid dispersion resulted in an increase in the solubility of drug which was reflected by the enhanced dissolution rate of drug from the solid dispersion.



(A)



(B)

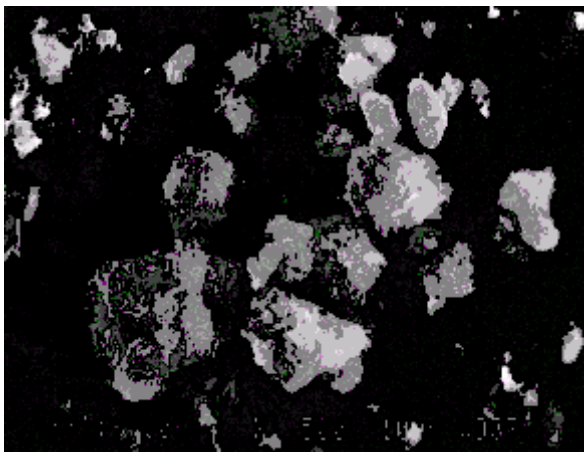


(C)

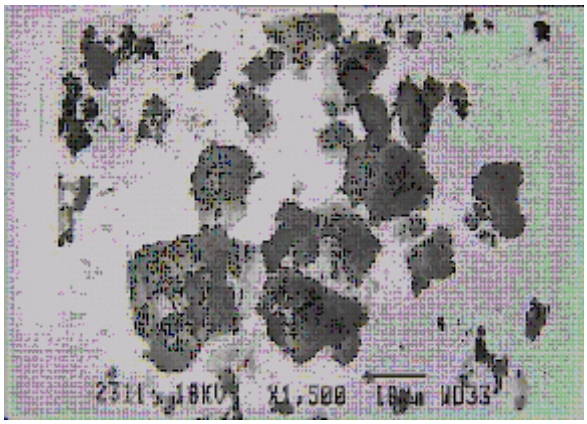
Fig. 7: *Characterization of Telmisartan (A), Cab-o-sil dispersion(B) and physical mixture (C) by DSC*

Scanning Electron Microscopy

The surface morphology of Telmisartan SSD on Cab-o-sil (1:10) were observed by scanning electron microscope (SEM), as seen in Fig 8. The Figure shows SSDs having irregular matrices due to the porous nature of the carrier and fine particles of the drug deposited on it. SEM studies explained the surface morphological properties of the SSD indicating that the solid dispersion is in amorphous state.



(A)



(B)

Fig. 8: *Scanning Electron Microscopy of Telmisartan: Cab-o-sil (1:10) formulation (A and B)*

Telmisartan tablets from surface solid dispersion

Telmisartan tablets of drug with SSG as carrier were prepared by direct compression method (Table 4). The prepared tablets have acceptable physical properties according to the USP. The uniformity of weight fulfills the requirement with less than ±5% in all cases.

Dissolution Studies

Tablets prepared from SSD having Cab-o-sil as the carrier exhibited higher dissolution rate as compared to marketed tablets and prepared pure drug tablets as shown in Fig 2. 78.87% drug was released from marketed tablets in 30 minutes whereas tablets prepared from SSD with Cab-o-sil as the carrier showed 98.70 % drug release.

CONCLUSION

Surface solid dispersion technique was successful in improving the dissolution rate of poorly water-soluble drugs like telmisartan. SSDs of drug with Cab-o-sil as the carrier showed significantly higher dissolution rate as compared to pure drug and physical mixture. The nature and amount of carrier used played an important role in the enhancement of dissolution rate. FTIR and DSC studies showed no evidence of chemical interaction between the drug and carrier. SSD tablets prepared with Cab-o-sil as the carrier showed an enhancement of dissolution rate of drug as compared to marketed tablets.

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