ENHANCEMENT OF DISSOLUTION OF TELMISARTAN BY SURFACE SOLID DISPERSION TECHNIQUE

Sood Neha, Khatry Sadhna* and Arora Sandeep
Chitkara College of Pharmacy, Chitkara University, Rajpura-140401, Patiala (Punjab), India.

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, cosolvency, microemulsion, self emulsification, polymeric modification, micronization, use of surfactant as a solubilizing agent, pro-drug approach and solid dispersion. Among the various approaches, solid dispersion has shown promising results in improving the solubility, dissolution rate and subsequently the bioavailability of drugs. 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, piroxicam, meloxicam, itraconazole and ketoprofen. The carriers used in surface solid dispersions are water-insoluble, porous materials which are hydrophilic in nature. Some of the common tablet excipients like Avicel, Cab-o-sil, crospovidone and pregelatinised starch have been used as carriers for surface solid dispersions. The release of drug from carrier material depends on the hydrophilic nature, particle size, porosity and surface area of the carrier. 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.

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). 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. 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

*Correspondence: sadhna_khatry@yahoo.com, sadhna.khatry@chitkara.edu.in
ENHANCEMENT OF DISSOLUTION OF TELMISARTAN

Sood Neha et al

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 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 161 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 CaCl₂. 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
ENHANCEMENT OF DISSOLUTION OF TELMISARTAN

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 spectrophotometer (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 2θ 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. 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.

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

<table>
<thead>
<tr>
<th>No</th>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Hixson-Crowell</th>
<th>Higuchi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug</td>
<td>0.003</td>
<td>0.853</td>
<td>0.379</td>
<td>0.609</td>
</tr>
<tr>
<td>2</td>
<td>Drug and SSD</td>
<td>0.001</td>
<td>0.852</td>
<td>0.362</td>
<td>0.605</td>
</tr>
<tr>
<td>3</td>
<td>Drug and SSD and SSD</td>
<td>0.001</td>
<td>0.851</td>
<td>0.351</td>
<td>0.602</td>
</tr>
<tr>
<td>4</td>
<td>Drug and SSD and SSD</td>
<td>0.001</td>
<td>0.850</td>
<td>0.341</td>
<td>0.602</td>
</tr>
<tr>
<td>5</td>
<td>Drug and SSD and SSD</td>
<td>0.001</td>
<td>0.850</td>
<td>0.341</td>
<td>0.602</td>
</tr>
<tr>
<td>6</td>
<td>Drug and SSD and SSD</td>
<td>0.001</td>
<td>0.850</td>
<td>0.341</td>
<td>0.602</td>
</tr>
</tbody>
</table>

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.
ENHANCEMENT OF DISSOLUTION OF TELMISARTAN

Sood Neha et al

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 37ºC ± 2ºC at 75 rpm. (Fig 2)

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

<table>
<thead>
<tr>
<th>S. No</th>
<th>Excipients Ratio</th>
<th>% Cumulative release in 5, 15 and 30 mins</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug</td>
<td>116±4.37, 24.79, 45.6±2.95</td>
</tr>
<tr>
<td>2</td>
<td>Mixed Tab</td>
<td>50.6±3.69, 78.5±3.26</td>
</tr>
<tr>
<td>3</td>
<td>Avicel pH 102</td>
<td>89.7±4.16, 113.9±3.5</td>
</tr>
<tr>
<td>4</td>
<td>Sodium starch glycolate</td>
<td>65.9±4.21, 79.5±3.5</td>
</tr>
<tr>
<td>5</td>
<td>Pregelatinised starch</td>
<td>59.5±3.64, 75.6±4.1</td>
</tr>
<tr>
<td>6</td>
<td>Potato starch</td>
<td>64.9±4.24, 75.6±4.1</td>
</tr>
<tr>
<td>7</td>
<td>Crospovidone</td>
<td>59.5±3.64, 75.6±4.1</td>
</tr>
<tr>
<td>8</td>
<td>Cab-o-sil</td>
<td>60.3±4.43, 75.6±4.1</td>
</tr>
</tbody>
</table>

Table 3: Composition for Tablets (450 mg)

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>Amount (mg) Tablet (SSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSD (1:10)</td>
<td>440</td>
</tr>
<tr>
<td>Avicel pH 102</td>
<td>2</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 4: Evaluation of tablets of Surface solid dispersion

<table>
<thead>
<tr>
<th>S No</th>
<th>Evaluation Tests</th>
<th>SSD tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Disintegration Time</td>
<td>1.2 minutes</td>
</tr>
<tr>
<td>2</td>
<td>Hardness</td>
<td>4.95±0.02 Kgfm²</td>
</tr>
<tr>
<td>3</td>
<td>Friability</td>
<td>0.576%</td>
</tr>
<tr>
<td>4</td>
<td>Solubility Variation</td>
<td>451±6±4.39</td>
</tr>
<tr>
<td>5</td>
<td>Content Uniformity</td>
<td>97.5±1.52</td>
</tr>
</tbody>
</table>

Each value represents mean ±sSD (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.
ENHANCEMENT OF DISSOLUTION OF TELMISARTAN

Sood Neha et al

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 SSD (B) and Cab-o-sil polymer (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 2θ (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 2θ (6.84°, 14.24°, 22.37°). The diffraction patterns of the SSD indicated changes in the crystalline nature of the drug. The relative 2θ 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.

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.

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

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

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.

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.
ENHANCEMENT OF DISSOLUTION OF TELMISARTAN

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.

ACKNOWLEDGEMENTS
The authors are grateful to M/S Ranbaxy Laboratories, Poanta sahib (India) for the gift sample of drug, Telmisartan.

REFERENCES
ENHANCEMENT OF DISSOLUTION OF TELMISARTAN


