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ENHANCEMENT OF SOLUBILITY OF TELMISARTAN USING VARIOUS METHODS AND CARRIERS

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ABSTRACT

The aim of this study was to enhance the solubility of telmisartan for which solid dispersions with different carriers were prepared by hydrotropy, physical mixture and solvent evaporation method. The interaction studies of solid dispersions showed no interaction between the drug and the carrier. Hydrotropic solid dispersions prepared with urea showed enhancement in solubility by l7.42 folds and 99.14±0.69% release in 60 minutes in distilled water. The physical mixture of telmisartan and cross povidone showed enhancement in solubility by 9.71 folds and 68.38±1.47% release in 60 min in distilled water. The solvent evaporation method showed an increase in solubility by 12.28 folds and 99.76±1.95 % release in 60 minutes in distilled water and 99.78% release in 45 min in 0.1N HCL. The hydrotropic agent, urea was successful in improving the dissolution rate of telmisartan by hydrotropy method and crosspovidone improved the dissolution rate of telmisartan by solvent evaporation method.

KEYWORDS: Solid dispersion, solubility, carrier, hydrotropy.

INTRODUCTION

Bioavailability of poorly water-soluble hydrophobic drugs is limited by their solubility and dissolution rate. The development of solid dispersions is a practically viable method to enhance bioavailability of poorly water-soluble drugs.[1-3]

The aim of present study was to overcome the poor aqueous solubility of telmisartan, an anti-hypertensive drug, by using hydrotropic solid dispersion (HSD) technology, solvent

evaporation method and physical mixture method using suitable carriers. The carrier used in HSD method was urea. The carriers used for physical mixture and solvent evaporation method were sodium starch glycolate, crosspovidone, croscarmellose sodium, which help in enhancing the solubility of the drug. The prepared solid dispersions were subjected to physicochemical characterization and in-vitro studies.[4,5]

MATERIALS AND METHODS

Telmisartan was obtained as a gift sample from Aurobindo Pharma Ltd.. Urea was purchased from Accord labs. Crosscarmellose sodium, sodium starch glycolate, crosspovidone were purchased from S. D. fine chem. Ltd. India.

Preparation of Hydrotropic solid dispersion (HSD)

Hydrotropic solid dispersions were prepared using urea. 10 ml of distilled water maintained at 40^0C was placed in a 25 ml beaker. To this hydrotropic agent was added and dissolved. The drug telmisartan was added to this solution and stirred using magnetic stirrer. Stirring was continued till semi solid mass was formed. Then this semisolid mass was dried as thin layer on watch glass, and then scraped. The powder of solid dispersion was passed through sieve, stored in air tight container.

Preparation of Physical Mixtures (PM)

The physical mixtures (PM) of drug with different carriers were prepared by blending method. The physical mixtures were prepared at various drug to carrier ratios with all the carriers in the increasing order of carrier amounts. The carriers used were sodium starch glycolate, crospovidone, crosscarmellose sodium.

Preparation of solid dispersions by solvent evaporation method (SEM)

The solid dispersions were prepared using methanol as solvent. The solid dispersions were prepared with various drug to carrier ratios with all the carriers in the increasing order of carrier amounts. The carrier was dissolved in methanol in a china dish and the mixture was heated until the solvent evaporated. The resultant solid dispersion was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and stored.[6,7]

Table 1: Formulae for solid dispersions of telmisartan and carriers.

Formula code		Weight of the drug(mg)	Weight of the carrier(mg)
Hydrotropic solid dispersion (HSD)			
SDU_1		20	20
SDU_2		20	60
SDU_3		20	100
	D:C ratio	**Physical mixtures**	
PC_1	1:1	20	20
PC_2	1:3	20	60
PC_3	1:5	20	100
		Solvent evaporation method(SEM)	
SEM_1	1:1	20	20
SEM_2	1:3	20	60
SEM_3	1:5	20	100

SDU- HSD of telmisartan and urea, Physical mixtures-D-drug -telmisartan and C-carrier-crospovidone -PCP_1, PCP_2, PCP_3, sodium starch glycolate -$PSSG_1$, $PSSG_2$, $PSSG_3$, crosscarmellose sodium-CCS_1, CCS_2,CCS_3, solvent evaporation method-D-drug -Telmisartan C-carrier-Crospovidone- $SEMCP_1$,$SEMCP_2$, $SEMCP_3$, sodium starch glycolate -$SEMSSG_1$, $SEMSSG_2$, $SEMSSG_3$.

Solubility studies

An excess of pure telmisartan, physical mixtures and solid dispersions were added to screw capped bottles containing distilled water. Bottles were shaken mechanically at 26°C for 24 hours and aliquots are withdrawn filtered and assayed for drug content at 283 nm spectrophotometrically.

Dissolution study of solid dispersions

Dissolution studies were performed with solid dispersions prepared and also with pure drug. USP typeII apparatus was used. The bath temperature was maintained at 37 ± 0.5°C. Distilled water was used as median and the RPM was set to 50. 5ml of aliquot was withdrawn for every 5 minutes.

RESULTS AND DISCUSSIONS

Interaction studies by FTIR of solid dispersions

FTIR studies have shown that there is no interaction between the drug and the carriers.

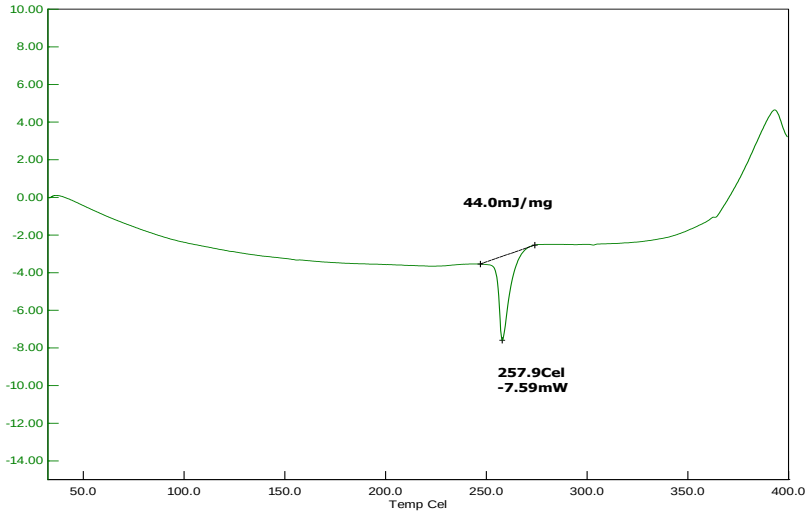

Figure 1: DSC graph of $SEMCP_3$.

$SEMCP_3$ -solid dispersion prepared by solvent evaporation method containing carrier crosspovidone.

DSC of the pure drug telmisartan showed a sharp peak at 269^0C. DSC of solid dispersions showed peak characteristic of the drug with no additional peak and so the drug and carrier showed no interaction.

Table 2: Solubility studies of hydrotropic solid dispersions.

Formulation	Solubility(mg/ml)	Improvement in solubility (folds)
SDU_1	0.030±0.02	8.57
SDU_2	0.048±0.01	13.71
SDU_3	0.061±0.03	17.42

The solubility of telmisartan in water was reported as 0.0035mg/ml, telmisartan can be considered as a practically insoluble drug.Urea has greater wetting properties hence shows greater solubility.

Table 3: Solubility studies of solid dispersions prepared by physical mixture and solvent evaporation method.

Formulation	1:1	1:3	1:5	Improvement in folds
Physical mixtues (mg/ml)				
Crosspovidone	0.022±0.01	0.031±0.01	0.034±0.01	9.71
Sodium starch glycolate	0.013±0.02	0.015±0.03	0.018±0.02	5.14
Solvent evaporation method (mg/ml)				

Crosspovidone	0.025±0.01	0.034±0.01	0.043±0.01	12.28
Sodium starch glycolate	0.014±0.02	0.018±0.03	0.026±0.02	7.42

Solubility of pure drug is 0.0035mg/ml (1fold)

The increase in the solubility rate is in the order sodium starch glycolate<crosspovidone. The reason attributed for this could be because of higher wetting properties of crosspovidone and increased surface area available for dissolution compared to other carriers.[8]

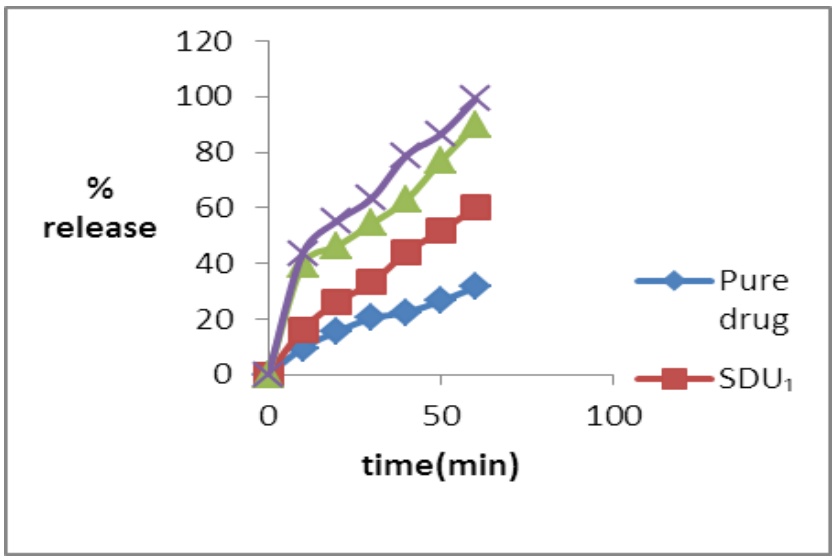

Figure 2: In vitro release profiles of hydrotropic solid dispersions with carrier urea.

It was observed that % drug release from solid dispersion of telmisartan with urea showed substantial increase when compared to pure drug. The 1:5 ratio of drug: urea showed 99.14±0.69% release in 60 minutes in distilled water when compared to pure drug (0.0035 mg/ml; 31.43±0.50). Urea because of its grater wetting properties shows greater release compared to pure drug.

The physical mixture of telmisartan and crosspovidone PM_3 in 1:5 ratio showed % drug release of 68.38±1.47% release in 60 min in distilled water when compared to pure drug (0.0035 mg/ml; 31.43±0.50).This may be due to increased wettability of the drug by hydrophilic carrier crosspovidone and more drug getting available for dissolution due to good disintegrating properties crosspovidone.[9]

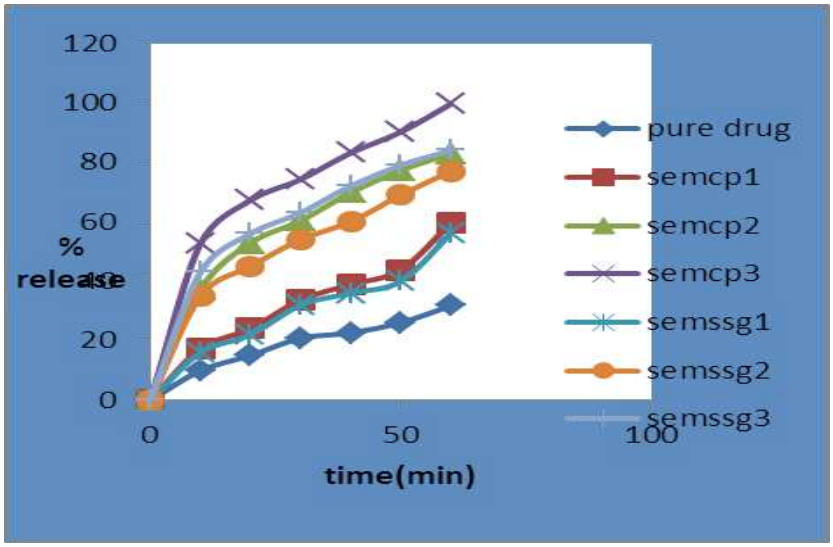

Figure 3: Comparative dissolution profiles of SEM solid dispersions of Telmisartan in distilled water.

Solid dispersion of telmisartan with crosspovidone by solvent evaporation method (1:5 ratio) showed 99.76±1.95 % release in 60 minutes in distilled water and 99.78% in 45 min in 0.1N HCL when compared to pure drug (31.43±0.50%). This may be due to increased wettability of the drug by hydrophilic carrier crosspovidone and more drug getting available for dissolution due to good disintegrating properties of crosspovidone. Crosspovidone has greater wettability, greater porosity and because of its good disintegrating nature it will dissolve rapidly, releasing very fine crystals of the drug. The larger surface area of the resultant suspension should result in an enhanced dissolution rate and thereby improved bioavailability.[10]

CONCLUSION

In conclusion, it can be stated that the objective of the study has been achieved. Hydrotropic solid dispersion technique and solvent evaporation dispersion technique were successful in improving the solubility and dissolution rate of poorly soluble drug telmisartan. Hydrotropic solid dispersions prepared with urea (1:5) showed enhanced solubility of 0.061±0.031mg/ml (increased by l7.42folds), 99.14±0.69% release in 60 minutes in distilled water when compared to pure drug (0.0035 mg/ml; 31.43±0.50). Hydrotropic agent urea was successful in improving the dissolution rate of telmisartan by hydrotropy method. Solid dispersion of telmisartan with crosspovidone by solvent evaporation method (1:5 ratio) showed enhanced solubility of 0.043±0.01 (increased by 12.28 folds), 99.76±1.95% release in 60 minutes in distilled water and 99.78% in 45 min in 0.1N HCL when compared to pure drug (0.0035

mg/ml; 31.43±0.50). Hydrophilic, insoluble, porous carrier crosspovidone was successful in improving the dissolution rate of telmisartan by solvent evaporation method.

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