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SOLID DISPERSION OF TELMISARTAN USING POLOXAMER 407 OR PEG6000 AS HYDROPHILIC CARRIER

Hayder J. Sadique[1] and Mowafaq M. Ghareeb[2*]

[1,2]Department of Pharmaceutics, College of Pharmacy, Baghdad University, Iraq.

ABSTRACT

Telmisartan (TEL) is an antihypertensive agent that inhibits the angiotensin. TEL is a BCS class II compound. Therefore, bioavailability of TEL can be improved by increasing its solubility. Recently solid dispersion technique gain high interest by pharmaceutical researcher as an approach for solubility enhancement for poorly soluble dugs. Sixteen formulas of solid dispersion of TEL were prepared using two polymers separately PEG6000 and poloxamer 407 at 4 drug to polymer ratios (1:1, 1:3, 1:5, and 1:7) following two method of preparations (melting and solvent evaporation). The prepared solid dispersions were evaluated for production yield percent, drug content, solubility, FTIR, and DSC study analysis. The results indicate that all prepared formulas of solid dispersion show solubility enhancement at different degree but the maximum solubility enhancement was observed with poloxamer 407 at ratio of 1:1 prepared in melt method. The solubility of telmisartan solid dispersion is increased 27 times the pure one. In addition, the results indicate that as polymer to drug ratio increased, the solubility was increased regarding PEG6000 while the best ratio for poloxamer was 1:1. Moreover, comparison of methods shows that the melting method produce higher enhancement in solubility than solvent evaporation method for both polymers.The FTIR study reveals that there is no chemical interaction while DSC analysis shows disappearance of endothermic peak of drug indicates reducing crystallinity of drug. It can be concluded from the results of this study that solid dispersion of Telmisartan with poloxamer 407 is promising approach for solubility enhancement by simple method.

Keywords: Telmisartan, Solid dispersion, PEG6000, Poloxamer407.

INTRODUCTION

A larger part of compounds formulated at Particle Sciences have minimum or no aqueous solubility (68% less than 1µg/ml; 18% between 1-10 µg/ml; 14% more than 10µg/ml) [1], make it important to develop methods and strategies to enhance solubility and dissolution rate. In general, methods used to increase solubility and enhance dissolution of drugs can be derived from the equation of Noyes Whitney [2] in which there are two main approach to deal with improve the dissolution rate; first by micronizing the compound and change the surface properties; and secondby rising the apparent C_s by addition of solubility upgrading exciepent [2].

One of the interesting technique to enhance solubility and dissolution rate is the solid dispersion in which the enhancement in solubility is done by different mechanism including elimination of the impact of lattice energy via stabilization of drug in the more soluble amorphous state [3]; reduce the particle size which in turn increase the surface area available for dissolution [4]; increase the wettability of compound [5]; and higher level of porosity [6].

Telmisartan (TEL), an antihypertensive drug, was selected as a model drug. Therapy with this drug offers a good quality of life for hypertensive patients due to the minimal side effects [7]. TEL is manufactured and supplied in the free acid form which has very poor solubility, resulting in low bioavailability [8]. The chemical structure of TEL is shown in Figure 1.

It is a crystalline powder, relatively insoluble in water, and freely soluble in alkaline aqueous solutions[9]. TEL is an orally administered antihypertensive agent that inhibits the angiotensin II AT1 receptor subtype without affecting other receptor systems involved in cardiovascular regulation[8]. TEL is a BCS class II

Corresponding Author:-**Mowafaq Mohammed. Ghareeb** Email:-mopharmacy@yahoo.com

compound i.e. water-insoluble, lipophilic and highly permeable. Therefore, bioavailability of TEL can be improved by increasing its solubility. It is reported that the oral bioavailability of TEL is 42-58 % [10].

Such drugs after oral administration often show dissolution as the rate-limiting step for their *in vivo* absorption and the appearance of the pharmacological effect. Therefore, improvements in solubility and/or dissolution rate of poorly water-soluble drugs may lead to enhancement in their bioavailability[11, 12].

MATERIAL AND METHODS

MATERIAL

Telmisartan was supplied by Awamedica, Iraq.Poloxamer 407, PEG 6000, and absolute ethanol were supplied by Samara Drug Industries (SDI), Iraq. Double distilled water was used for all the experiments. All other materials utilized in the research were of pharmaceutical grade

METHODS

ESTIMATION OF TELMISARTAN

Calibration curve of telmisartan in ethanol was prepared as shown in figure (2) by dissolving 40 mg of pure drug in 100ml of absolute ethanol then one ml of resulted stock solution were diluted with 5,10,15,20, and 25 ml of ethanol using UV-visible spectrophotometer Model –Spuv-25-sco-Tech, Germany at 296 nm. The method obeyed Beers law with (r=0.9994).

PREPARATION OF SOLID DISPERSION

The solid dispersion of TEL was prepared following two methods:

Melt Method

This method includes melting the carrier on hot plate using aluminum pan, after addition of pure drug with continues stirring, then it cooled down. The product was collected milled and sieved through 200 micron sieve then stored in desicater for further study. This procedure is done for both polymers in the ratio of (1:1, 1:3, 1:5, and 1:7)as shown in table (1)[13-15].

Solvent Method

Solid dispersion by this method was prepared as shown in table (1) by complete dissolving the pure drug in ethanol then polymer was added to the solution until clear solution, and evaporates the solvent using hot air dryer, then the product was collected; milled and sieved through 20 micron sieve then stored in the desicater for further study. The procedure was done for both polymers in the ratio of (1:1, 1:3, 1:5, and 1:7) [16-18].

Production Yield

Percentage of practical yield is calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

PY (%) = practical mass (solid dispersion)/theoretical mass (drug +carrier) ×100

Drug Content

Ten milligram of prepared solid dispersion of all formulas were accurately weighted and dissolved in 10 ml of ethanol then filtered through 0.45 micron filter paper, the filtrate analyzed using UV-visible spectrophotometer at 296 nm. Then drug content was calculated using the constructed calibration curve.

Phase Solubility Study

Excess amount of solid dispersion in plane class test tube containing 10 ml of water allow shaking for 72hr at 25 ℃ in water bath. Then samples were filtered by 0.45 micron Millipore; then one ml of the filtrate was diluted with 4 ml of ethanol which then analyzed using UV-visible spectrophotometer at 296 nm and drug content was calculated.

Infrared Spectroscopy

Infrared spectra of pure drug and selected formula of solid dispersion were obtained using Shimadzu FTIR 8000, Japan, A KBrdict was prepared by compression the solid sample with solid potassium bromide (KBr) and the spectra were collected in the 400 cm^{-1} to 4000 cm^{-1} region.

Differential Scanning Calorimetry (DSC)

This test was done to investigate the thermal behavior of pure drug and solid dispersion formula using DSC 60 shimadzu, Japan. About 2 mg of samples were placed in a sealed aluminum pan. An empty aluminum pan was used as a reference. The heating rate of 10 °C/min in the temperature range from 25 to 300 °C was used.

RESULT AND DISCUSSION

Production Yield And Drug Content

The production yields of all prepared SDs formulas are shown in the following table 2. The results of yield are within acceptable limit, moreover the drug content also within limits according to the USP which state that drug content should be between (85% - 110%).

Phase Solubility Study

The solubility results of the 16 prepared formulas are shown in the following table 3.

The results indicate that all prepared formulas of solid dispersion show solubility enhancement at different degree but the maximum solubility enhancement was

observed with poloxamer 407 at ratio of 1:1 prepared in melt method. Since the solubility of pure telmisartan in water is 4µg/ml, thus the solubility of telmisartan solid dispersion is increased 27 times the pure one. In addition, the results indicate that as polymer to drug ratio increased, the solubility was increased regarding PEG6000 while the best ratio for poloxamer was 1:1. Moreover, comparison of methods shows that the melting method produce higher enhancement in solubility than solvent evaporation method for both polymers.

On the other hand, comparison the impact of the two polymers reveals that poloxamer shows better improvement in solubility than PEG6000 at different ratio and method of preparation. The solubility enhancement was observed to higher degree with poloxamer 407 than PEG 6000 and this is may be attributed to the higher solubilizing capacity, higher hydrophilic/lipophilic balance value (HLB= 18-23) of this copolymeric surfactant which makes it highly water soluble carrier and finally the micellarsolubilization of the drug especially when its concentration exceeds the critical micelle concentration (CMC) which was reported to range from 5 to 6.7 g/L[19, 20].

FTIR ANALYSIS

The FTIR spectra of pure drug and formula SD_9 show that there is no interaction between drug and poloxamer 407 as the main peak of telmisartan still present in the spectrum of selected formula (SD9) as shown in table 4. The presence of broad band peak in region near 3000 cm^{-1} indicates the formation of hydrogen bonding. As shown in figure 3and4.

Differential scanning calorimetry (DSC)

The DSC thermogram of selected formula (SD9) shows disappearance of sharp peak of Telmisartan corresponding to its melting point at 252 °C indicates the formation of amorphous form of drug which has more solubility than crystalline form as shown in figure 5 and 6.

1

Fig 1. Chemical structure of telmisartan

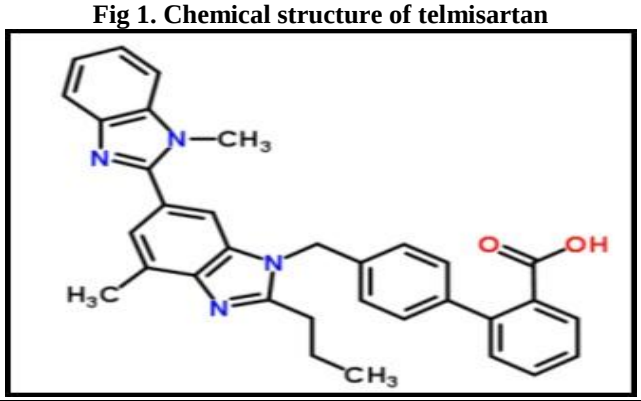

Fig 2. Calibration curve of Temisartan in ethanol

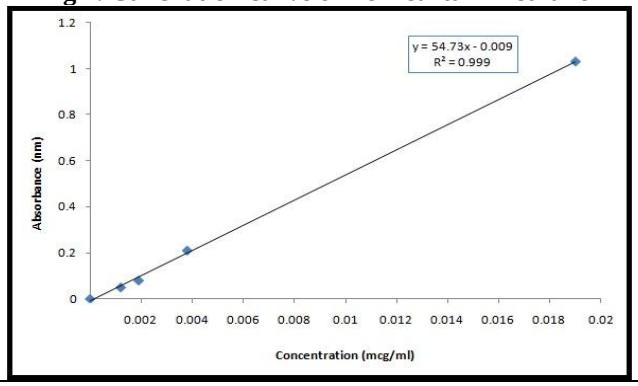

Fig 3. FTIR spectrum of Telmisartan

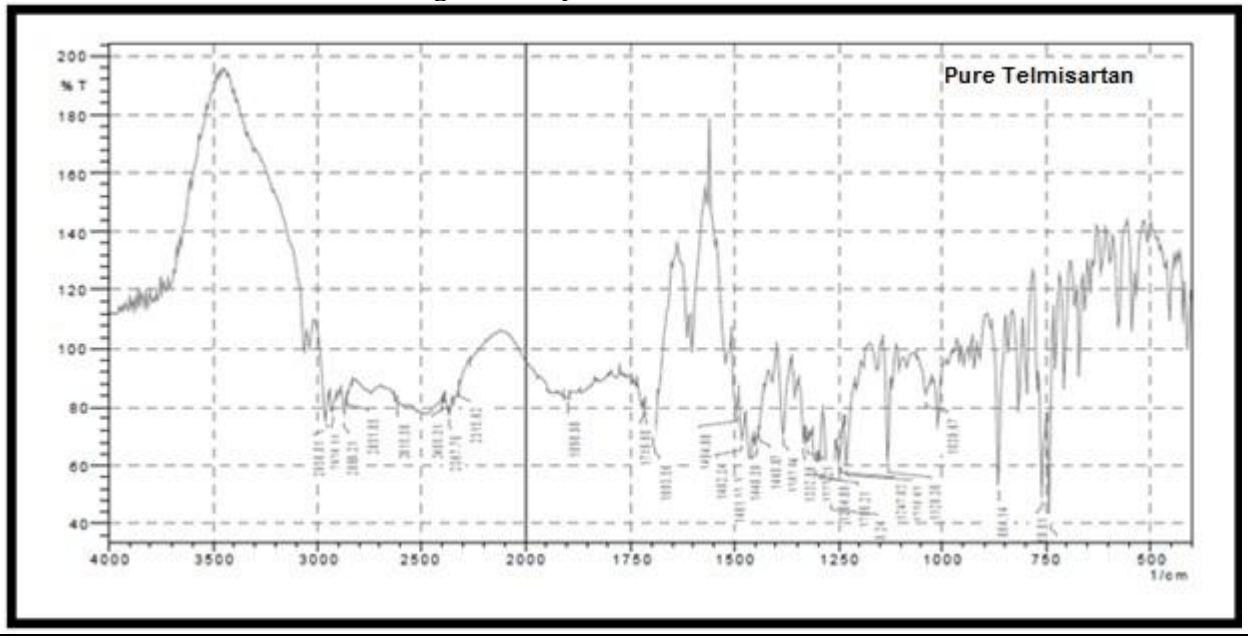

Fig 4. FTIR spectrum of Telmisartan and poloxamer 407 (SD_9)

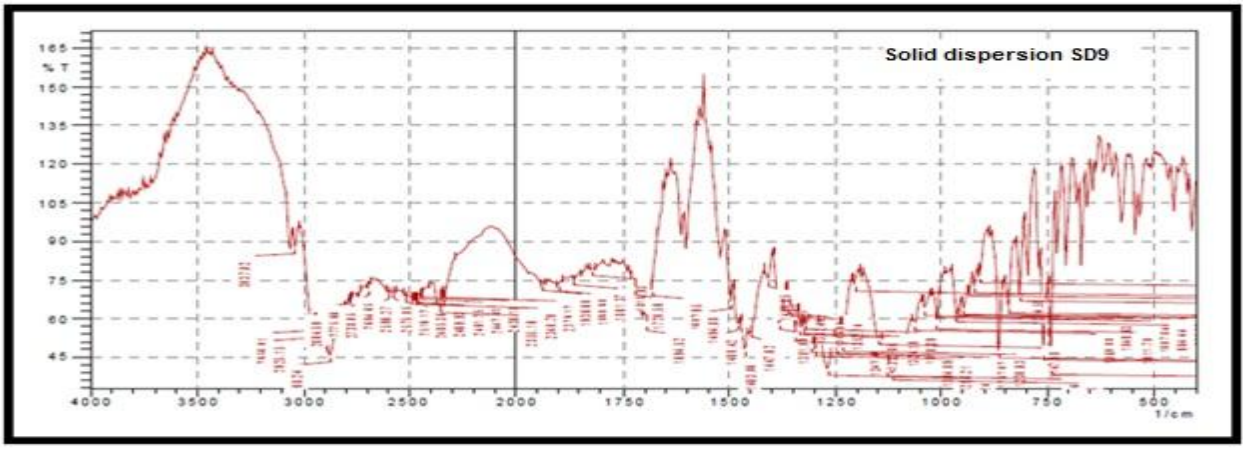

Fig 5. DSC of Telmisartan

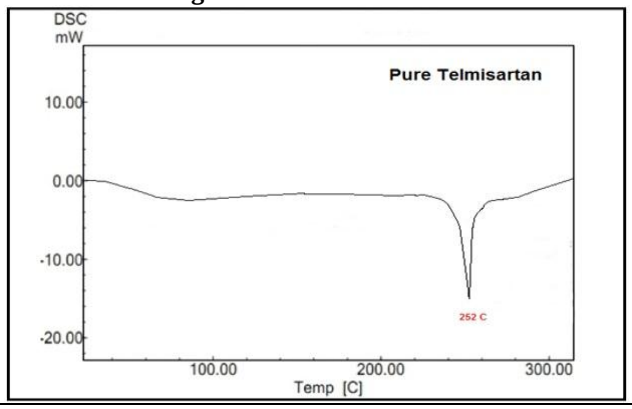

Fig 6. DSC of Telmisartan and poloxamer 407 (SD9)

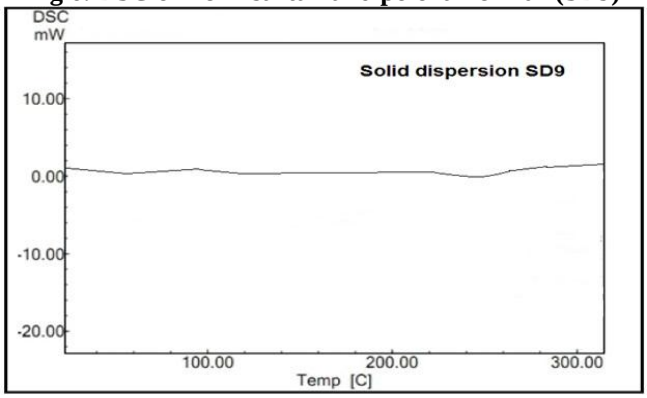

Table 1.composition of telmisartan solid dispersion formulas

Formulas code	Polymer type	Drug: polymerratio	Method of preparation
SD_1	PEG 6000	1:1	Melting
SD_2	PEG 6000	1:3	Melting
SD_3	PEG 6000	1:5	Melting
SD_4	PEG 6000	1:7	Melting
SD_5	PEG 6000	1:1	Solvent evaporation
SD_6	PEG 6000	1:3	Solvent evaporation
SD_7	PEG 6000	1:5	Solvent evaporation
SD_8	PEG 6000	1:7	Solvent evaporation
SD_9	Poloxamer 407	1:1	Melting
SD_{10}	Poloxamer 407	1:3	Melting
SD_{11}	Poloxamer 407	1:5	Melting
SD_{12}	Poloxamer 407	1:7	Melting
SD_{13}	Poloxamer 407	1:1	Solvent evaporation
SD_{14}	Poloxamer 407	1:3	Solvent evaporation
SD_{15}	Poloxamer 407	1:5	Solvent evaporation
SD_{16}	Poloxamer 407	1:7	Solvent evaporation

Table 2. Production yield and drug content of the prepared solid dispersion formulas

Formulas code	PY (%)	Drug content (%)
SD_1	95.0	94.0
SD_2	96.0	95.0
SD_3	97.0	94.5

SD_4	98.0	96.0
SD_5	92.0	90.0
SD_6	92.0	90.5
SD_7	95.0	92.0
SD_8	96.0	94.0
SD_9	97.0	96.0
SD_{10}	97.5	96.0
SD_{11}	98.0	96.5
SD_{12}	98.0	97.0
SD_{13}	93.0	91.0
SD_{14}	94.5	92.5
SD_{15}	96.0	94.7
SD_{16}	96.4	94.2

Table 3. Solubility data of the prepared solid dispersion of all formulas

Formulas code	Solubility in water µg/ml
SD_1	15
SD_2	27.5
SD_3	40
SD_4	41
SD_5	5
SD_6	7
SD_7	10
SD_8	35
SD_9	109
SD_{10}	25.5
SD_{11}	15.5
SD_{12}	11.5
SD_{13}	45.5
SD_{14}	34.5
SD_{15}	23
SD_{16}	13

Table 4. The characteristic main functional groups FTIR bands of Telmisartan in SD9

Functional group	Wave number cm^{-1}
Acidic OH	2920.37
Aliphatic C-CH_3	1381.08
Aromatic C=N	1691.43
C=0	1454.90

CONCLUSION

It can be concluded from the results of this study that solid dispersion of Telmisartan with poloxamer 407 at ratio of 1:1 is promising approach for solubility enhancement by simple method which may be attributed to the higher solubilizing capacity, higher hydrophilic/lipophilic balance value (HLB= 18-23) of this copolymeric surfactant which makes it highly water soluble carrier and finally the micellarsolubilization of the drug especially when its concentration exceeds the critical micelle concentration (CMC) which was reported to range from 5 to 6.7 g/L [19].

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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