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Solubility Enhancement of Telmisartan as Solid Dispersion by Different Methods

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Abstract

Background Telmisartanis an antihypertensive angiotensin II receptor antagonist drug commonly used to treat hypertension. It's a BCS Class II poorly soluble drug in the Biopharmaceutical Classification System (BCS). Objective To increase the solubility and rate of dissolution of Telmisartan utilizing a solid dispersion method. Methods Two methods were obtained to prepare solid dispersion ofTelmisartan: solvent evaporation and kneading method. Each method used different polymersusing soluplus, poloxamer (188,407), and polyethylene glycol (4000,6000) as hydrophiliccarriersin different ratiosof 1%, 2%, and 3%. Results It was observed that the solid dispersion showsan increase in solubility in comparison to its pure drug. The best formula was obtained withthe formula (Telmisartan, soluplus at a 1:3 ratio) Conclusion By preparingTelmisartanas asolid dispersion via the solvent evaporation method, its solubility, and dissolution have been improved. Using a 1:3 ratio of hydrophilic carriers (drug: carrier). Its enhanced wettability and decreased crystallinity result in enhanced drug solubility and dissolution.

Keyword

Poloxamer, Polyethylene glycol, solid dispersion, soluplus,Telmisartan

Solubility is a solute's capacity to dissolve in a solvent to form a homogenous solution. The saturation concentration represents the degree of a substance's solubility in a specific solvent, that is when adding more soluteto a solution does not increase its concentration (1,2). Dissolution is the process whereby a solute dissociates in a solvent to generate a molecularly homogeneous dispersion called a solution. Most new medications have poor water solubility and formulation difficulties in drug delivery systems. Enhancing the solubility and dissolution rate of these medications are crucial pre-formulation research steps in the creation of pharmaceutical products. class II andclass IV of the Biopharmaceutical Classification System (BCS) present solubility challenges, where dissolutionis the rate-limiting step for drug absorption (2,3). Numerous approaches, such as salt creation, complexation,micronation, solid dispersions, micelles, emulsions, and nanonizationthat used to improve the solubility of poorly soluble drugs.

Solid dispersion (SD) is gaining a great deal of importance for increasing thesolubility and dissolution of poorly soluble drugs (4,5,6).

Solid dispersion contains one or more active chemicals suspended in a solid inert carrier. Methods of preparation include melting, microwaving, dissolving in a solvent, and kneading.Soluplus, poloxamer, and polyethylene glycols with varying molecular weights are utilized as carriers in solid dispersion systems (7).

Telmisartan (TEL) is a popular antihypertensive angiotensin II receptor antagonist used to treat hypertension, renal disease,and congestive heart failure(8).

Telmisartan is rapidly absorbed after oral administration, and its bioavailability, which varies with dose, is around 42% (9,10).

Soluplus® is an amphiphilic polymeric solubilizing agent. It is soluble in water and exhibits a greater degree of solubility in numerous organic solvents (11).

Materials and Methods

Materials: Telmisartan from NANIING AOCHENG CHEMICAL China,Polyethylene glycol 4000 from Gainland Chemical Company UK, Poly ethylene glycol 6000 from HIMEDIA India, Poloxamer 188 from Alfa Aesar USA, Poloxamer 407 from Sigma-Aldrich Japan, Soluplus from BASF Germany.

Preparation methods of solid dispersion

Solvent Evaporation Method

Fifteen formulas (F1-F15) of TEL SDwere prepared by a solvent evaporation method, and mlsof the aqueous solution of carriers 1,2,3 g was added to mls of methanolic solution of TEL(1g). The resulting mixture was stirred for 1 hr. Evaporation of the solvent was done at a temperature of 45єC until dried. The dry bulk was crushed and sieved via sieve no.60 and stored for further study as shown in table 1(11).

Kneading method

Fifteen formulas (F1-F15) of TEL SD were prepared by the kneading method. One gram of TEL was mixed with carriers (1,2,3) g in a mortar for 5 min. A few drops of methanol were added drop by drop until the mixture became slurry, and this slurry mixture was kneaded for 20 minutes. The dried masswas pulverized and sieved via sieve no.60 and stored for further study (12).

Table 1: Composition of SD in Different Formulas Prepared by Solvent Evaporation, and Kneading Methods

Formula code	TEL (g)	Poloxamer 188 (g)	Poloxamer 407 (g)	PEG 4000 (G)	PEG 4000 (G)	Soluplus (g)
F1	1	1				
F2	1	2				
F3	1	3				
F4	1		1			
F5	1		2			
F6	1		3			
F7	1			1		
F8	1			2		
F9	1			3		
F10	1				1	
F11	1				2	
F12	1				3	
F13	1					1
F14	1					2
F15	1					3

Evaluation of SD

Determination of the percentage yield (PY%)

The yield % was computed for each SD formula utilizing Equation 1(1).

PY%= [the actual weight of SD / Theoretical weight of SD] x100 .... Eq (1)

Determination of drug content

According to saturated solubility results, the amount of SD formula equal to 10mg of TEL was dissolved in 10 ml methanol, and the volume was adjusted to 50 ml in a volumetric flask.

Onemlsample of the solution was diluted 10 times with methanol. UV spectrophotometry was used to measure the solution's drug content by detecting the absorbance at 296 nm.The amount of drugs in the SD was determined as a percentage equation 2(4,13,14).

Drug content%= [The actual weight of TEL / Theoretical weight of TEL]x100 .... Eq (2)

Determination of the saturated solubility

Anextraamount of pure TEL and SD was added to 10 ml of water, the samples were incubated for 48 hours at 37 °C in a water bath shaker, following that, a 0.45 µm syringe filter was used to filter it. By using a UV spectrophotometer at 296 nm, samples were analyzed to determine Telmisartan's dissolved amount. The calibration curve equation was used to determine the TEL concentration. Only the formula that showed the greatest solubility was used in subsequent research (1,15).

Select the best formula

Based on the solubility studies and other SD characteristics.

Results

Determination of percentage yield and drug content of SD

The SD that was prepared from the sol formula (drug: soluplus) displayed a high percentage yield between 88 -99 %.

All formulations were determined to have drug content that ranged from 98-100 %w/w, which is following USP criteria(16).

Table 2 displays the data for percentage yield and drug content.

Table 2: Percentage Yieldand Drug Contentof SD

Formula code	Solvent Evaporation Method A		kneading methodB	
	PY%	Drug content	PY%	Drug content
F1	99	100%	95	99%
F2	98	99%	95.3	98.8%
F3	98.2	98.8%	94	98.6%
F4	93	98.6%	92	98.2%
F5	92	98.2%	90	98%
F6	90	98%	90	99%
F7	98	100%	96	98.5%
F8	97	98.5%	96.5	98.2%
F9	97	98.2%	97	98%
F10	96	99%	93	98.5%
F11	95.5	99.5%	94.3	99%
F12	96	99%	93	99%
F13	99.8	99.8%	97	99.8%
F14	100	100.1%	98.5	99.5%
F15	100	100%	99	99.4%

Saturation solubility for TEL SD

Table 3 presents the outcomes of saturation solubility tests for TEL SD.

Table 3: Solubility of SD Formulas Prepared by Solvent Evaporation and KneadingMethods using Different Carriers in Distilled Water at 37C°

Saturation solubility mg/ml of different methods			
Formula code	Formula ratio (TEL: carriers)	SolventEvaporation Method A	kneading method B
Pure TEL		0.0002	
F1	1:1(TEL: POL188)	0.024±0.031	0.008±0.005
F2	1:2(TEL: POL188)	0.041±0.021	0.05±0.011
F3	1:3(TEL: POL188)	0.058±0.003	0.067±0.011
F4	1:1(TEL: POL407)	0.003±0.011	0.015±0.023
F5	1:2(TEL: POL407)	0.073±0.004	0.025±0.011
F6	1:3(TEL: POL407)	0.097±0.002	0.054±0.012
F7	1:1(TEL: PEG4000)	0.016±0.031	0.012±0.017
F8	1:2(TEL: PEG4000)	0.021±0.022	0.013±0.005
F9	1:3(TEL: PEG4000)	0.028±0.032	0.017±0.012
F10	1:1(TEL: PEG6000)	0.011±0.021	0.014±0.017
F11	1:2(TEL: PEG6000)	0.033±0.033	0.018±0.006
F12	1:3(TEL: PEG6000)	0.052±0.011	0.025±0.012
F13	1:1(TEL: Sol)	0.099±0.021	0.086±0.005
F14	1:2(TEL: Sol)	0.122±0.001	0.097±0.011
F15	1:3(TEL: Sol)	0.134±0.001	0.111±0.005

±SD(n=3)

Factors affect the solubility of SD.

Effect type of carrier

Significant improvement in the solubility of TEL was found, which may be due tothe hydrophilic nature of all the utilized carriers, in addition to the possible formation of a hydrogen bond between TEL and carriers, which contributed to the

improvement in TEL solubility. The solubility was shown:

soluplus>poloxamer188>
poloxamer407>PEG6000>PEG4000.

Soluplus has a high hydration activity in aqueous solutions and a wide surface area due to its composition of hydrophilic groups and good hydrophilic characteristics, which allowed for the largest solubility to be attained (17).

Poloxamer 188 and 407 have solubility enhanced more than PEG due to the surfactant properties of poloxamer(18,19).

Effect carrierratio

Solubility studies for SD by comparing the increased carrier concentration found 1:3 ratio for each carrier were higher solubility than the 1:1 and 1:2 ratios,more solubility results from a high hydration caused by a high concentration of hydrophilic carriers (20,21).

Effect method of preparation

The formulas prepared by the solvent evaporation method showed the highest solubility, seen FA3 more than FB3, FA6more than FB6, FA9 more than FB9, FA12 more than FB12, and FA150.134 whichthe highest solubility incomparison tothe kneading method in it FB15 was 0.108 due to formation of amorphous state and decrease the particle size that results from melting the carrier completely that increase the solubility of TEL by interaction with it, the solubility of the pure drug was 0.0002 mg/ml, indicating that solid dispersion enhances the solubility by 670, 540fold respectively as compared to the pure drug(22,23,24).

Selection of the best formula

The solubility results of SDshow that FA15(TEL: Sol) at a ratio 1:3prepared by solvent evaporation methodwas selected to bethe best formulawhich had the highest solubility.

Conclusion

TEL's solubility was enhanced by producing it as a solid dispersion via the solvent evaporation method with a 1:3 ratio of a hydrophilic carrier (drug: soluplus). Increased wettability and decreased crystallinity contribute to enhanced drug solubility and dissolution. FA15 was able to achieve maximum solubility with increased dissolution by employing soluplus as a hydrophilic carrier with a large surface area. FA15 was able to achieve maximum solubility with increased dissolution by employing soluplus as a hydrophilic carrier with a large surface area.

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