Available online at www.elixirpublishers.com (Elixir International Journal)

Pharmacy

Elixir Pharmacy 90 (2016) 37921-37924

ISSN: 2229-712X

Formulation and Characterization of Telmisartan Solid Dispersions by using PEG-6000

Rakesh Singh* and D.A.Jain

Institute of Pharmaceutical Science and Research Centre, Bhagwant University Ajmer.

ARTICLE INFO

Article history:

Received: 14 March 2013;

Received in revised form:

20 January 2016;

Accepted: 26 January 2016;

Keywords

PEG-6000,

Solid dispersion,

Solubility,

Telmisartan.

ABSTRACT

This article investigates enhancement Solubility is an important physicochemical factor affecting absorption of drug and it's therapeutic of the dissolution profile of Telmisartan effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. Telmisartan is an angiotensin II receptor antagonist which is used in the prevention and treatment of Hypertension. One of the major problems with it is its low solubility in biological fluids, which results into poor bioavailability after oral administration (~42%) and late onset of action poorly soluble drug, Telmisartan. Solid dispersions were prepared using Polyethylene glycol-6000 (PEG-6000). Telmisartan solid dispersions were prepared in 1:1, ratios of the drug to polymer ratio & it's applied to different techniques of Solid dispersion (by weight) like using Physical mixing, Kneading method solvent evaporation method & fusion method. The formulations were characterized for solubility parameters; drug content studies drug release studies and drug-polymer interactions by using FTIR spectrum & X-RD. Formulation Containing 1:1 ratio of drug: PEG-6000 (Kneading method) show best release with cumulative release of 45.53% as compared to 98.37% for the pure drug. The interaction studies showed no interaction between the drug and polymer, it was concluded that PEG -6000 as carrier can be very well utilize to improve the solubility of poorly soluble drugs.

Introduction

The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The ability to deliver poorly soluble drugs will grow in significance in the coming years as NCEs are relied upon for a larger share of the revenue within the pharmaceutical market by innovator companies. Its will based on bioavailability of drugs

The bioavailability of poorly water soluble drug is often limited by its dissolution rate, which in turn is controlled by the surface area available for dissolution. Larger the surface area, higher will be the dissolution rate. Since the surface area increases with decreasing particle size, decrease in particle size, which can be accomplished by conventional methods like trituration, grinding, ball milling, fluid energy micronization, salt formation and precipitation. Although these conventional methods have commonly been used to increase dissolution rate of the drug, there are practical limitation with these techniques, the desired bioavailability enhancement may not be achieved. Therefore formulation approaches are being explored to enhance bioavailability of poorly water soluble drugs. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists.

The generic drug manufacturers will need to employ economically efficient methods of delivery as more low solubility drugs go off patent, in order to maintain a competitive edge and sufficiently compete as profit margins shrink in this price-sensitive.to industry.

These *in vivo* and *in vitro* characteristics and the difficulties in achieving predictable and reproducible *in vivo*/*in vitro* correlations are often sufficiently formidable to halt development on many newly synthesized compounds due to solubility issues. The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class II and IV drugs, compounds which feature poor solubility and high permeability, and poor solubility and poor permeability, respectively. Drug substances are considered highly soluble when the largest dose of a compound is soluble in <250mL water over a range of pH from 1.0 to 7.5; highly permeable compounds are classified as those compounds that demonstrate >90 percent absorption of the administered dose in contrast, compounds with solubility below 0.1mg/mL, and often-even compounds with solubility below 10 mg/mL present difficulties related to solubilisation during formulation.

Telmisartan is 2-(4-{[4-methyl-6-(1-methyl-1*H*-1,3-benzodiazol-2-yl)-2-propyl-1*H*-1,3-benzodiazol-1- yl]methyl} phenyl)benzoic acid. Telmisartan is antihypertensive agent. The major drawback of this drug is its low aqueous solubility that delays its absorption from the gastrointestinal tract. Prolonged use of the drug is associated with hypokalemia, hypotension, tachycardia and urinary tract infection

In the present work solid dispersions of Telmisartan was prepared by four different method of solid dispersion using water soluble polymers such as PEG- 6000. The prepared solid dispersions were evaluated for % practical yield, drug content, in-vitro dissolution. rate studies and interactions between drug and polymer using FT-IR and X-RD spectral studies.

Polyethylene glycol 6000 (PEG) is a polyether compound with many applications from industrial manufacturing to medicine. The structure of PEG is (note the repeated element in parentheses): **$HO\text{-}CH_2\text{-}(CH_2\text{-}O\text{-}CH_2\text{-})_n\text{-}CH_2\text{-}OH$**

PEG is also known as polyethylene oxide (PEO) or polyoxyethylene (POE), depending on its weight.

Tele:

E-mail addresses: rakesh01py40@yahoo.co.in

Polyethylene glycol, referred to as PEG, is used as an inactive ingredient in the pharmaceutical industry as a solvent, plasticizer, surfactant, ointments and suppository base, and tablet and capsule lubricant. PEG has low toxicity with systemic absorption less than 0.5%.

Experimental

Materials

Telmisartan was obtained as a gift sample Medley pharma Daman. Polyethylene glycol 6000 (PEG4000) Sodium Lauryl Sulphate (SLS) and HCL were purchased from SD-Fine Chem. Industries Mumbai. Double distilled water was used for all the experiment

Estimation of Telmisartan

An U.V. Spectrophotometric method based on the measurement of absorbance at 296 nm in a Phosphate buffer (pH 7.4) Containing Sodium lauryl sulphate (0.2 %) in 100 ml of volumetric flask to get a concentration of 10µg/ml. and it was used for the estimation of Telmisartan. The method was validated or linearity, accuracy, precision and interference. The method obeyed Beers law in the concentration range of 1-10 µg/ml (r^2=0.993). When a standard drug solution was repeatedly assayed (n=6), the relative error and coefficient of variation were found to be 0.80% and 1.0% respectively.

Preparation of Telmisartan solid dispersions by different method

Telmisartan solid dispersions were prepared by different method using carriers (PEG-6000) in proportions viz 1:1, (drug : carrier).

Complexes of TEL & & PEG-6000 were prepared in the molar ratio of 1:1(on the basis of phase solubility study) by different methods like Physical mixing, Kneading, Solvent evaporation, and Fusion method.).

Physical Mixture

Physical mixture was prepared by triturating & PEG-6000 together for 30 min in a clean and dry glass mortar until a homogeneous mixture was obtained. And then was forced through sieve no 100.

Kneading Method

TEL & PEG-6000 was mixed separately in glass mortar along with water to obtain a homogeneous paste. The drug (either in powder form or as solution with minimum quantity of methanol) was then slowly added to the paste and the mixture was triturated for 1 hr. during the process the water content was empirically adjusted to maintain the consistency of the paste. Methanol was added to assist dissolution of TEL during the process. The paste was dried at room temp., pulverized and forced through sieve no 100.

Fusion Method

TEL & PEG-6000 were thoroughly mixed and placed in a sealed container with a small amount of water. The contents are heated to about 100^0C and then removed and dried. The mass was then pulverized and forced through sieve no 100.

Solvent evaporation Method:

A solution of Telmisartan in methanol was gradually added to equi-molar concentration of TEL & PEG-6000 in water and agitated at 50^0C for 30 min and toward the end of addition turbidity developed in the mixture. At the end of this period the solution was filtered, and the moist solid was kept in oven 50^0C for removal of last trace of solvent. The mass was then pulverized and passed through sieve no 100.

Table 1. Composition of solid complexes by using Tel & PEG-6000

Type of formulation	TEL: : β-CD & PEG-6000 (molar ratio)	Solid dispersion Method	Media
TPPM	1:1	Physical Mixing	---------
TPKW	1:1	Kneading	Water
TPKM	1:1	Kneading	Methanol + Water
TPSE	1:1	Solvent Evaporation	Methanol + Water
TPFW	1:1	Fusion	Water

Result & Discussion

Method

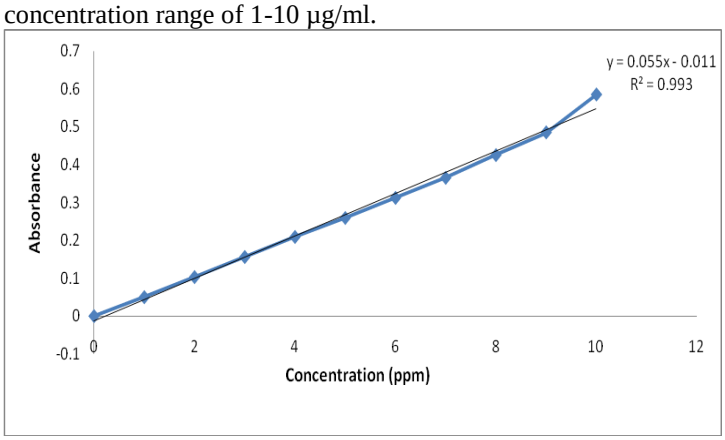
Preparation of Stock Solution

Standard stock solution of Telmisartan was prepared by dissolving 10 mg of drug in 100 ml of Phosphate buffer (pH 7.4) Containing Sodium lauryl sulphate (0.2%) in 100 ml of volumetric flask to get a concentration of 10 µg/ml.

Preparation of Working Standard Solutions and construction of standard graph:

To construct Beer's law plot for Telmisartan, the stock solution was further used to prepare working standard solutions of concentrations ranging from 1 to 10 µg/ml different aliquots of working standard solutions of Telmisartan was transferred separately into a series of 10 ml volumetric flasks and diluted to 10 ml using phosphate buffer .The absorbance were measured at λmax 296 nm against buffer as blank. The results are shown in graph

The standard graph for Telmisartan was plotted by taking concentration of drug on x-axis and absorbance on y-axis and is shown in graph. The drug has obeyed Beer's law in the concentration range of 1-10 µg/ml.



Graph 1. Standard curve for the estimation of Telmisartan in phosphate buffer pH 7.4

The linear relationship between the concentration of Telmisartan and the corresponding absorbance values was shown by- Y = 0.055 X + 0.011 Where, Y = absorbance, and X = concentration of Telmisartan (µg/ml) A positive correlation between the concentration of Telmisartan and the corresponding absorbance values was observed (correlation coefficient, (r^2 = 0.993). The amount of Telmisartan in either the PEG complex or the dissolution fluids was calculated using the linear relationship as given above from the graph.

Fourier Transforms Infrared (FTIR) spectroscopy.

FTIR Spectroscopy was performed on Lab India by scanning the sample in zink seleniume (Znse). Before taking the spectrum of the sample, a blank spectrum of air background was taken. Number of scans, 24; resolution, 4 cm−1; range, 500–4000 cm−1 The sample of Pure Drug, PEG-6000 were scanned.

The complexes of PEG-6000 with TEL prepared by different methods were scanned by FTIR ranges from 500-4000, There is no interaction between drug PEG-6000. (Figure 3).

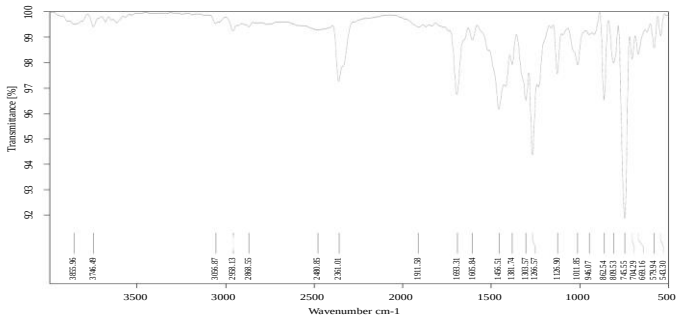


Fig 1. FTIR spectrum of Telmisartan

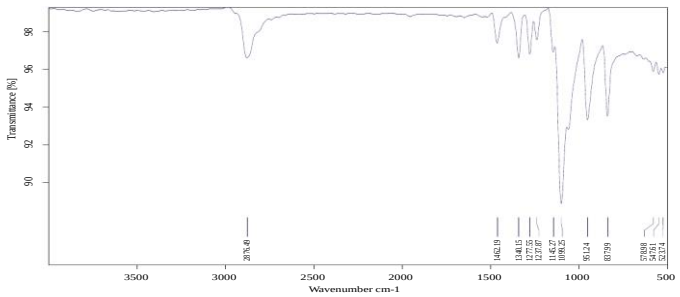


Fig 2. FTIR spectrum of PEG-6000

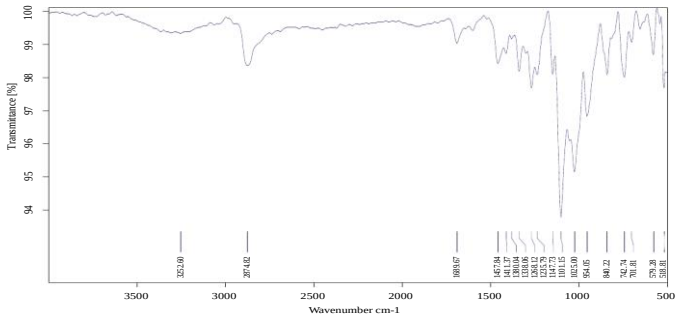


Fig 3. FTIR spectrum of TPPM (TEL & PEG-6000 complex prepare by physical mixing).

X-ray Diffractometry

The X-ray diffractometry (XRD) pattern of Telmisartan and its various complexes with PEG -6000 are shown in fig.4 X-ray powder diffraction patterns were recorded on X-ray diffractometer (Rigaku, Japan; Model X-PERT-PRO) with monochromatized Cu radiation, the voltage and current used were 45 kV and 40 mA respectively.

Physical mixtures of TEL PEG-6000 (1:1) molar ratio have shown slightly reduced crystallinity of TEL. Other samples of inclusion complexes prepared by different methods (Kneading, Solvent Evaporation, and Fusion method) all the formulation have shown disappearance or reduced crystalline intensities than the pure crystalline drug, exhibiting drug amorphization and entrapment of TEL in PEG-6000.

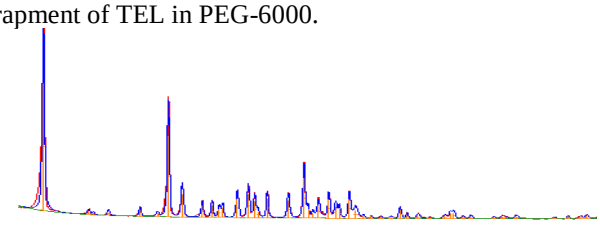


Fig 4. Telmisartan

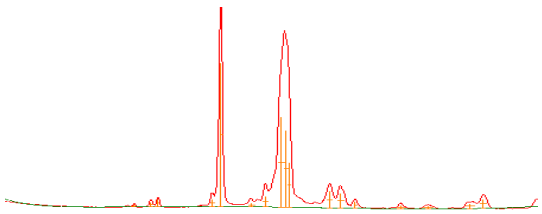


Fig 5. PEG-6000

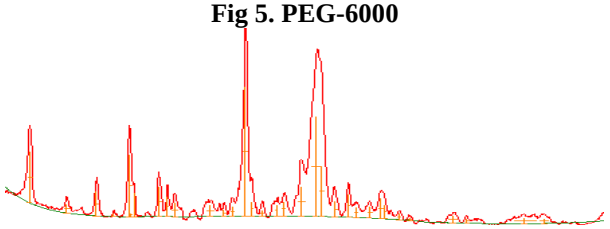


Fig 6. X-RD graph of Physical mixing

Drug Content:

Samples of each solid complex were assayed for drug content by dissolving 100 mg of the complex in 100 ml ethanol. The drug content was determined at 296 nm by UV-Spectrophotometer. The experiment was conducted in triplicate.

Saturation Solubility

To evaluate increase in solubility of Telmisartan after formation of inclusion complexes, saturation solubility measurements were carried out as follows: Known excess of different formulation of TEL was added to 25 ml of phosphate buffer (pH 7.4). Samples were shaken at room temperature for 24 hr. Samples were then filtered, suitably diluted and analyzed spectrophotometrically at 296 nm. The experiment was conducted in triplicate (n=3).

Preparation of complexes

All the complexes prepared were of excellent flow property (angle of repose was below 20^0C). For further assay or formulation purpose granulometric size fraction of <150 µm was used.

First of all, the actual drug content in each formulation was determined. The results are reported in Table 2. As can be seen, all the formulation showed a good agreement between theoretical and actual drug content. Which correspond to the content uniformity of TEL in its complex formulations?

Table 2. Percentage Drug content of various formulation

Formulation	Theoretical drug content	Practical drug content in 100mg (mean n=3)	% Drug content
TPPM	27.64	27.02	97.68
TPKW	27.64	26.93	97.10
TPKM	27.64	27.12	98.12
TPSE	27.64	27.08	97.93
TPFU	27.64	27.11	98.08

Table 3. Saturation solubility data of different formulation of Telmisartan & PEG-6000

Formulation	Saturation solubility(µg/ml)
Pure TEL	11.95 ± 0.84
TPPM	88.50 ± 2.10
TPKW	138.78 ± 2.32
TPKM	146.10 ± 2.35
TPSE	121.15 ± 2.63
TPFU	123.82 ± 2.43

Mean saturation solubility ± SD (n=3)

***In vitro* drug release study**

The dissolution studies were performed using Digital Tablet Dissolution Test apparatus - DISSO 2000 (Lab India, Mumbai, India), an 8-station dissolution rate test apparatus with a paddle stirrer. The tablets of different formulations equivalent to 20 mg TEL were placed in the dissolution vessel containing 900 ml phosphate buffer (pH 7.4) maintained at 37^0C ± 1 0C and stirred at 50 rpm. Samples of dissolution medium (5mL) were withdrawn and replaced with a fresh dissolution medium at different time intervals, suitably diluted, and assayed for Telmisartan by measuring absorbance at 296 nm. The dissolution experiments were conducted in triplicate (n=3). The dissolution efficiency after 10 min interval,

Graph 2. Comparative study of different formulation of Tel & PEG-6000

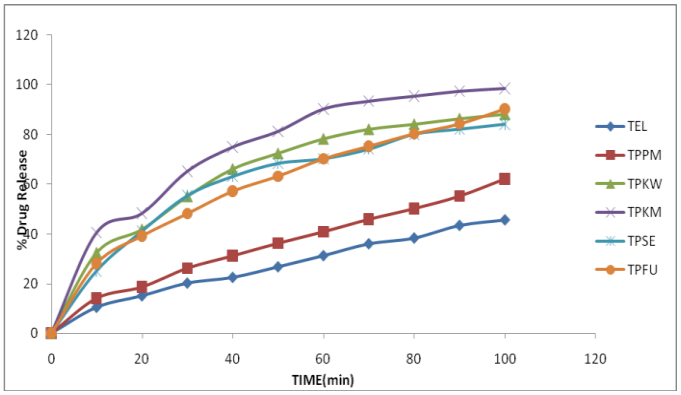


Table 4. Dissolution profile of different formulation of TEL & PEG-6000 in phosphate buffer 7.4

Time (min)	% Drug Release from the formulations (mean; n=3)					
	TEL	TPPM	TPKW	TPKM	TPSE	TPFU
0	0	0	0	0	0	0
10	10.53	14.12	32.45	40.48	25.17	28.1
20	15.16	18.63	41.84	48.18	41.12	39.12
30	20.28	26.2	55.1	65.12	55.41	48.1
40	22.58	31.15	66.13	74.82	63.13	57.1
50	26.84	36.23	72.42	81.13	68.41	63.12
60	31.34	40.82	78.24	90.1	70.24	70.1
70	36.12	45.84	82.11	93.23	74.12	75.13
80	38.43	50.16	84.14	95.25	80.12	80.15
90	43.52	55.18	86.35	97.25	82.18	84.13
100	45.75	62.1	88.16	98.37	84.18	90.15

Conclusion

Solubility studies showed a significant, linear increase in the aqueous solubility of the Telmisartan with increasing concentration of PEG so improvements in the saturation solubility of Telmisartan

An inclusion complex of Telmisartan with PEG was prepared successfully by the physical mixing, kneading, solvent evaporation and fusion methods in the molar ratio of 1:1. This was confirmed by FTIR and XRD studies.

These in all five methods employing kneading method using methanol-water as solvent employing exhibited the fastest and highest in vitro dissolution rate when compared to the tablet of pure Telmisartan, and during stability study there was very slight decrease in its dissolution profile.

These findings are extremely important from a commercial point of view as the prepared complexes removes drawback of a poor dissolution profile of Telmisartan.

Acknowledgment

The authors acknowledge for Bhagwant University & also thank to Medley pharma Daman as they provide gift sample for project work.

Reference

[1] Michael Hite, Stephen Turner, Cathy Federici, SCOLR Inc; Oral delivery of poorly soluble drug. *Pharmaceutical Manufacturing and Packing Sourcer Summer '03 issue, Samedan Ltd.*

[2] Fromming KH, Szejtli J. CDs in Pharmacy. Dordrecht, *The Netherlands: Kluwer Academic;* 1994.

[3] Mauro Serratoni , Michael Newton , Steven Booth , Ashley Clarke; Controlled drug release from pellets containing water-insoluble drugs dissolved in a self-emulsifying system; *European Journal of Pharmaceutics and Biopharmaceutics 65 (2007) 94–98.*

[4] Akash Jain, Yingqing Ran, and Samuel H. Yalkowsky. Effect of pH-SodiumLauryl Sulfate Combination on Solubilization of PG-300995 *AAPS Pharm Sci Tech 2004; 5 (3) Article 45)*

[5] Mauro Serratoni, Michael Newton, Steven Booth, Ashley Clarke; Controlled drug release from pellets containing water - insoluble drugs dissolved in a self-emulsifying system. European Journal of Pharmaceutics and Biopharmaceutics 65 (2007) 94–98

[6] Naveen Ahuja, Om Prakash Katare, Bhupinder Singh; Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers; *European Journal of Pharmaceutics and Biopharmaceutics 65 (2007) 26–38.*

[7] Higuchi T, Connors KA. Phase-solubility techniques. *Adva Anal Chem Instr. 1965; 4: 212-217.*

[8] Telmisartan - from Wikipedia, the free encyclopedia; Retrieved from "http:// en. wikipedia .org/wiki/Telmisartan".

[9] Mekalingam, Vobalaboina,Venketeswar, Enhancement of solubility & dissolution rate of poorly water soluble Drug using Cosolvency & solid dispersion Techniques, International Journal of pharmaceutical Sciences & nanotechnology Vol-1, issue-4,

[10] Verheyen S, Blaton N, Kinget R, Van den Mooter G. Mechanism of increased dissolution of diazepam and temazepam from polyethylene glycol 6000 solid dispersions. Int J Pharm. 2002 Dec 5;249 (1-2):45-58.

[11] Darío Leonardi, María Gabriela Barrera,et al. Development of prednisone: Polyethylene glycol 6000 fast-release tablets from solid dispersions: Solid-state characterization, dissolution behavior, and formulation parameters. AAPS PharmSciTech. 2007 October; 8(4): 221–228.

[12] Margarita Valero, Carmen Carrillo at el, Ternary naproxen: β-cyclodextrin: polyethylene glycol complex formation International Journal of Pharmaceutics 265 (2003) 141–149.