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Original Research Article

Formulation of Telmisartan Solid Dispersion using Poloxamer 188 and PVP

Hasanain Shakir Mahmood[1]
[1]University of Kerbala/ College of Pharmacy/ Departmant of Pharmaceutics, Kerbala, Iraq

***Corresponding author**
Hasanain Shakir Mahmood
Email: hasanain@live.com

Abstract: Solubility considered as the main challenge in preparing an oral dosage form of drugs had poor aqueous solubility. Solid dispersion (SD) is a solid dosage form which composed of poorly soluble drug dispersed though out a hydrophilic polymeric matrix, which could be crystalline or amorphous. Solid dispersion preparation may consist of one or more than one poorly soluble drug in an inactive solid polymeric matrix. Telmisartan (TLM) is an antihypertensive agent that belongs to Angiotensin Receptor Blockers (ARBs). This study shows the effect of using poloxamer 188 and polyvinyl pyrrolidone (PVP) in formulating TLM as solid dispersion and its solubility and dissolution properties. 10 formulas of TLM SD prepared using "solvent evaporation method". Results showed that the solubility of TLM SD improved for all formulas and increased as polymer ratio increased. The release profile of TLM was improved for SD than that of pure drug. Formulas F5 (TLM: PVP 1:4) and F8 (TLM: poloxamer 188 1:1) had the better release profile. This could reflect positively on the onset of drug action. Therefore, one may expect that the antihypertensive effect may be faster for TLM SD than pure TLM since its solubility, dissolution and hence absorption, will be initiated in the stomach.
Keywords: poloxamer 188 PVP, Solid dispersion, Solubility, Telmisartan.

INTRODUCTION:

Solubility considered as the main challenge in preparing an oral dosage form of drugs had poor aqueous solubility. The solubility directly effects on dissolution and thus effects on bioavailability and drug action. Solid dispersion is used to increase the solubility and hence the formulation of hydrophobic drugs [1, 2].

Solid dispersion (SD) is a solid dosage form which composed of poorly soluble drug dispersed though out a hydrophilic polymeric matrix, which could be crystalline or amorphous. Solid dispersion preparation may consist of one or more than one poorly soluble drug in an inactive solid polymeric matrix. It prepared by melting, melting solvent or solvent method. The drug prepared as solid dispersion could be either crystalline or amorphous (clusters). Solid dispersion may include many types such as amorphous precipitation in crystalline carrier, glass solution and suspension, solid solution and solid eutectic mixture. Solid dispersion preparation would lead to reduce the dose of the drug needed to achieve the desired effect. This occurs due to both increased dissolution rate and increased extent and rate of drug absorption. On the other hand, Solid dispersion related to instability like the change in crystallinity state of a drug and thus reduces the dissolution rate with time. The deteriorating effect of temperature and humidity is greater on solid dispersion than on physical mixture [1, 3-8].

Many advantages of a preparing solid dispersion of drugs would be achieved. A reduction in particle size is one advantage which would lead to increase surface area, increase wettability, dissolution rate, solubility and bioavailability. Another advantage is the degree of porosity related to solid dispersion which increases the drug release rate [9]. Telmisartan (TLM) is an antihypertensive agent that belongs to Angiotensin Receptor Blockers (ARBs). It is used for hypertension treatment, also prescribed to reduce the incidence of heart attack, stroke, or mortality from cardiovascular diseases in patients who are unable to take angiotensin converting enzyme (ACE) inhibitors.

According to the biopharmaceutical classification system (BCS), telmisartan belongs to class II drugs which have Low solubility and high permeability. Therefore, it is formulated as solid dispersion. This study shows the effect of using poloxamer 188 and polyvinyl pyrrolidone (PVP) in formulating TLM as solid dispersion and its solubility and dissolution properties [10].

Aim of the Project:

The purpose of preparation telmisartan as solid dispersion is to improve the absorption and bioavailability by increasing solubility.

MATERIALS AND METHOD:

Telmisartan purchased from Hetero drugs limited (India). All ingredients and reagents used were purchased from the local market and of analytical grade.

Determination of TLM melting point:

The melting point of TLM powder was measured according to USP using melting point apparatus. A capillary tube was closed from one end and filled with powdered drug. The temperature increased gradually until the powder converted to liquid state. The temperature at which the powder converted to liquid measured as the melting point [11].

Determination of TLM λmax:

A solution of 12 µg/ml TLM was scanned in UV-Visible spectrophotometer at 200-400 nm range and the maximum absorbance recorded as the λmax.

Calibration curve of TLM:

A serial dilution of TLM at concentrations of (4, 8, 12, 16, 20 and 24 µg/ml) in phosphate buffer pH 6.8 were prepared and scanned at λmax using UV-Visible spectrophotometer to construct a calibration curve of TLM.

Saturation Solubility:

An excess amount of TLM powder and TLM SD added to 10 ml of water in a test tube and leaved in a shaker water bath at room for 24 hours. The solution obtained were filtered with 0.45 µm filter and scanned at λmax using UV-Visible spectrophotometer [12].

Preparation of Telmisartan Solid Dispersion:

10 formulas of TLM SD were prepared by "solvent evaporation method". A series of drug: polymer ratio used, ranged from 4:1 to 1:4 (table 1). The drug and polymer dissolved in 20 ml dichloromethane, poured in a petri dish and placed in an oven at 40°C. The SD collected and stored for further studies.

Table 1: The composition of formulas

Formula code	TLM (mg)	PVP (mg)	Poloxamer 188 (mg)
F1	200	50	
F2	200	100	
F3	200	200	
F4	200	400	
F5	200	800	
F6	200		50
F7	200		100
F8	200		200
F9	200		400
F10	200		800

Determination of Production Yield (PY):

The weight of raw material (drug and polymer) used in each formula measured and compared to the weight of SD obtained for that formula. The PY measured for each of the 10 formulas prepared using the bellow equation:

$$PY = \frac{\text{Practical weight}}{\text{Theoretical weight (polymer + drug)}} X\ 100\ \%$$

Entrapment efficiency (EE) of TLM SD:

The TLM content in the SD was determined spectrophotometrically. A 10 mg TLM SD dissolved in 10 ml methanol and diluted with phosphate buffer pH 6.8 to suitable concentration. The amount of TLM in solution calculated using the calibration curve. The entrapment efficiency obtained using the equation below [13].

$$EE = \frac{\text{Actual wt. of TLM}}{\text{Theoretical wt. of TLM}} X\ 100\ \%$$

Dissolution study of TLM SD:

The dissolution profile of pure TLM and prepared TLM SD studied using USP apparatus II. Phosphate buffer (pH 6.8) used as dissolution medium to simulate intestinal fluid. The stirring rate was 75 rpm. An equivalent of 40 mg of pure TLM and TLM SD were placed in 900 ml dissolution medium and maintained at 37±3 °C. A 5 ml sample taken at (5, 10, 15, 20, 30, 45 and 60 min) intervals and filtered through a 0.45 µm filter paper. A 5 ml of fresh medium added after each withdrawing to maintain the dissolution

volume. Then the samples analyzed spectrophotometrically at λmax [14].

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR spectra of both pure TLM and TLM SD were measured to insure that there is no chemical interaction occurs during formulation.

RESULTS AND DISCUSSION:

Determination Telmisartan melting point:

The temperature 262°C was recorded as the melting point of pure TLM. This result agreed with references and reflected the purity of the powder used in the study [15].

Determination of λ max:

The spectrophotometric spectrum of TLM (Fig.1) showed a maximum absorbance at 297nm, which is close to that reported by references [16].

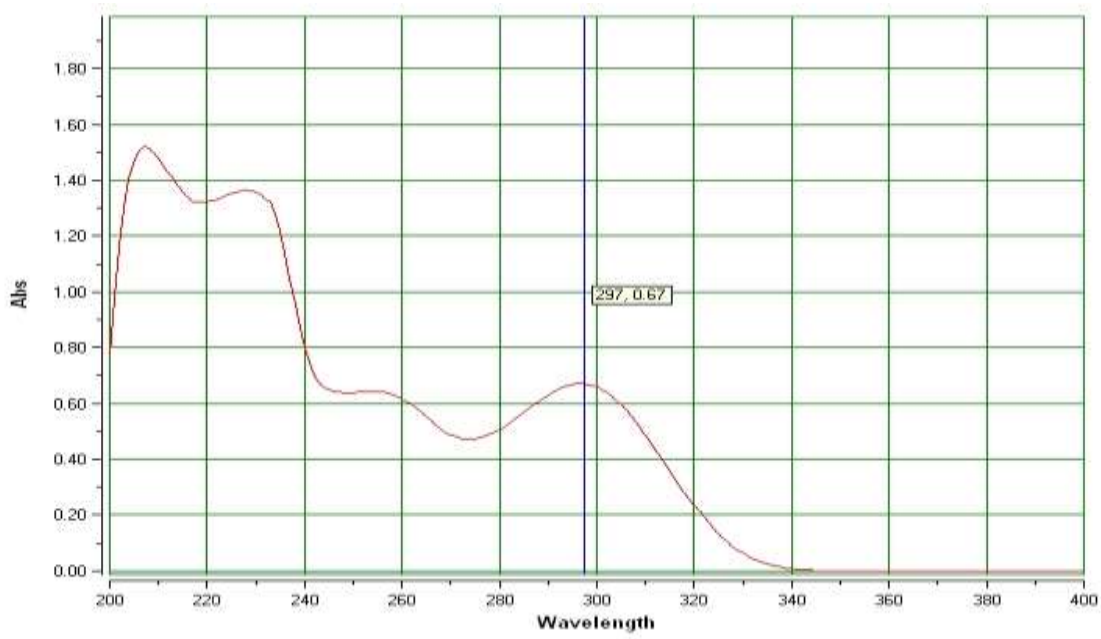

Fig 1: spectrophotometric spectrum of TLM

Calibration Curve of TLM:

The figure below (figure 2) shows the calibration curve of TLM in phosphate buffer 6.8 .The calibration curve found to follow Beer's law as a straight line obtained by plotting absorbance versus concentration.

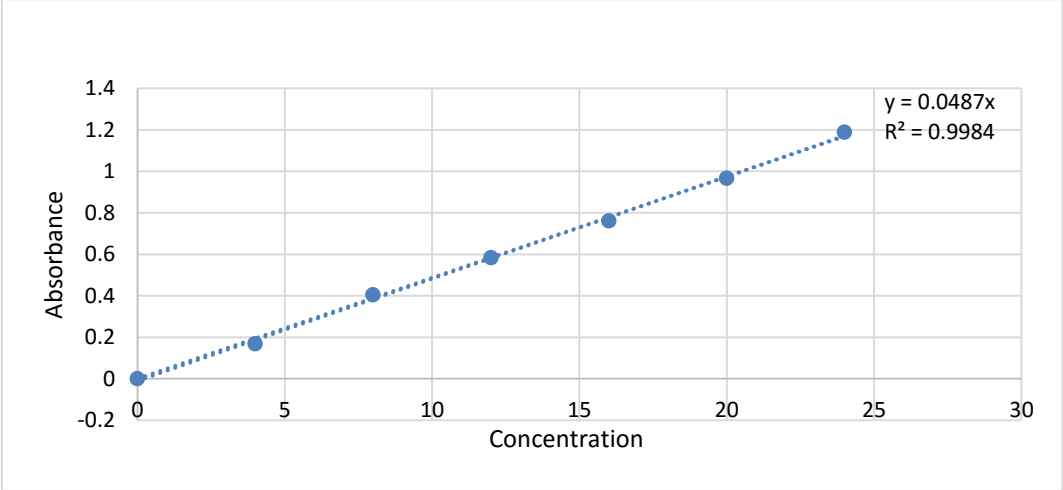

Fig 2: The Calibration Curve of TLM in Phosphate Buffer 6.8

Solubility Studies:

The results of saturation solubility study are shown in the table (2). The results reveal that pure TLM has very low water solubility. This fact is expected since TLM is classified as class II according biopharmaceutical classification (low solubility, high permeability). Similarly, TLM SD solubility was expected to increase since the drug is molecularly dispersed within the SD structure. Results shows that the solubility increased as the polymer ratio in the formula increased for all formulas. At the same time, it's noticed that PVP improved the solubility better than poloxamer 188 [17].

Table 2: Saturated Solubility of TLM SD and pure TLM

No. of Formula	Solubility(µg/ml)
Pure Drug	0.44
F1	4.51
F2	4.63
F3	4.86
F4	5.40
F5	6.28
F6	0.54
F7	0.63
F8	1.95
F9	1.72
F10	2.76

Production Yeild & Entrapment Efficiency:

The results of PY and EE are given in the table (3). The percentage of PY ranged from 98% for formula 2 to 44.6% for the formula 4. While EE shows a range of 90.4% for the formula 8 to 30.8% for formula 10. It is worth mentioning that not all of the TLM SD formulas gave acceptable PY and EE [18].

Table 3: The production yield & entrapment efficiency of TLM SD

No. of Formula	Production yield (%)	Entrapment efficiency (%)
1	72.8	80.1
2	98	70.2
3	68.5	78.4
4	44.6	60.9
5	87.6	87.9
6	96.6	84.8
7	75.6	64.5
8	82.5	90.4
9	95.9	47.2
10	62.2	30.8

Fourier Transform Infrared Spectroscopy (FTIR) of Telmisartan:

FTIR spectra of pure TLM, Poloxamer 188, PVP and TLM SD showed in figures (3-7). All the characteristic peaks of TLM are present in TLM SD. This result may confirm that there was no chemical interaction between TLM and polymers used [19].

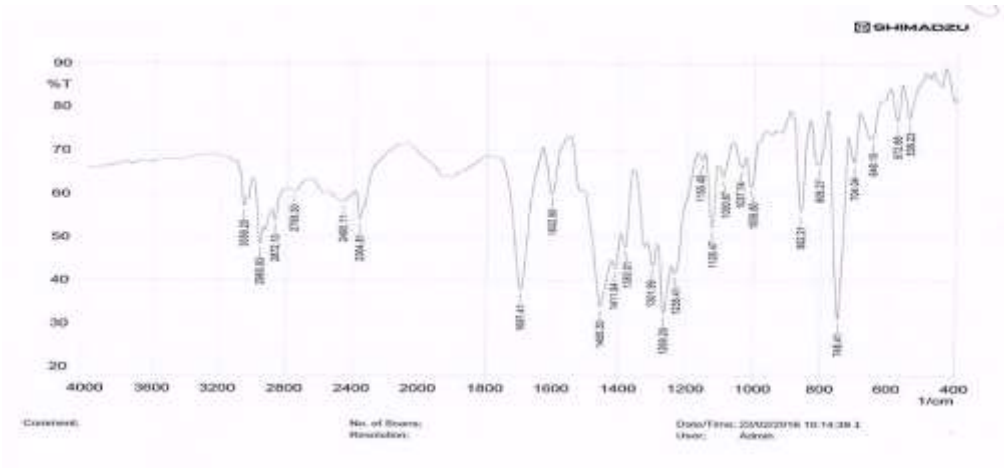

Fig 3: IR Spectrum of Telmisartan

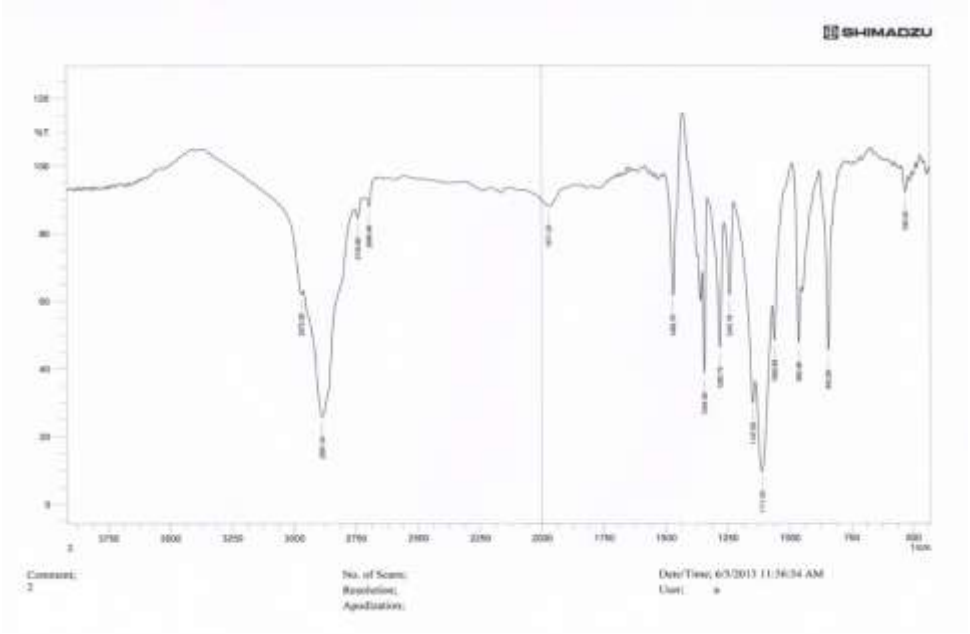

Fig 4: IR Spectrum of Poloxamer 188

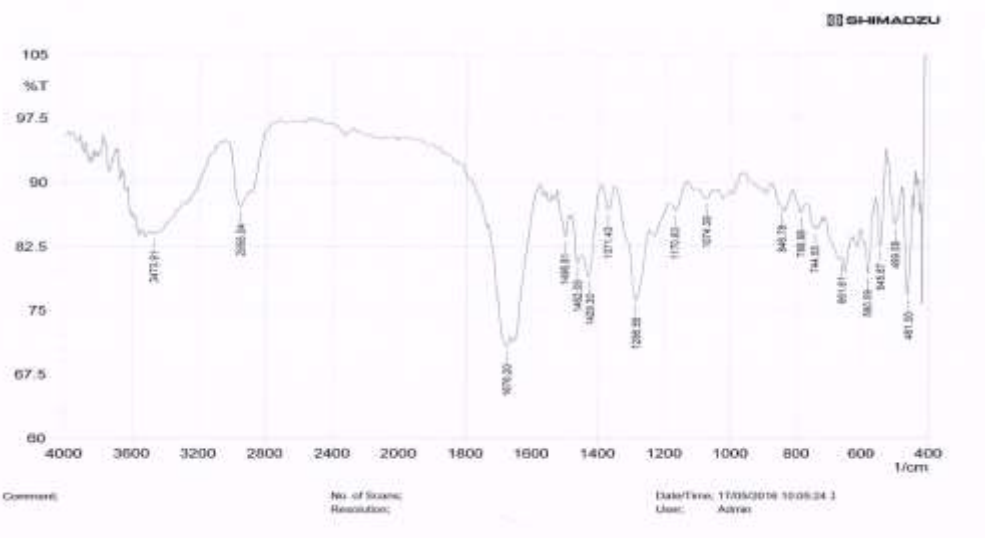

Fig 5: IR Spectrum of PVP

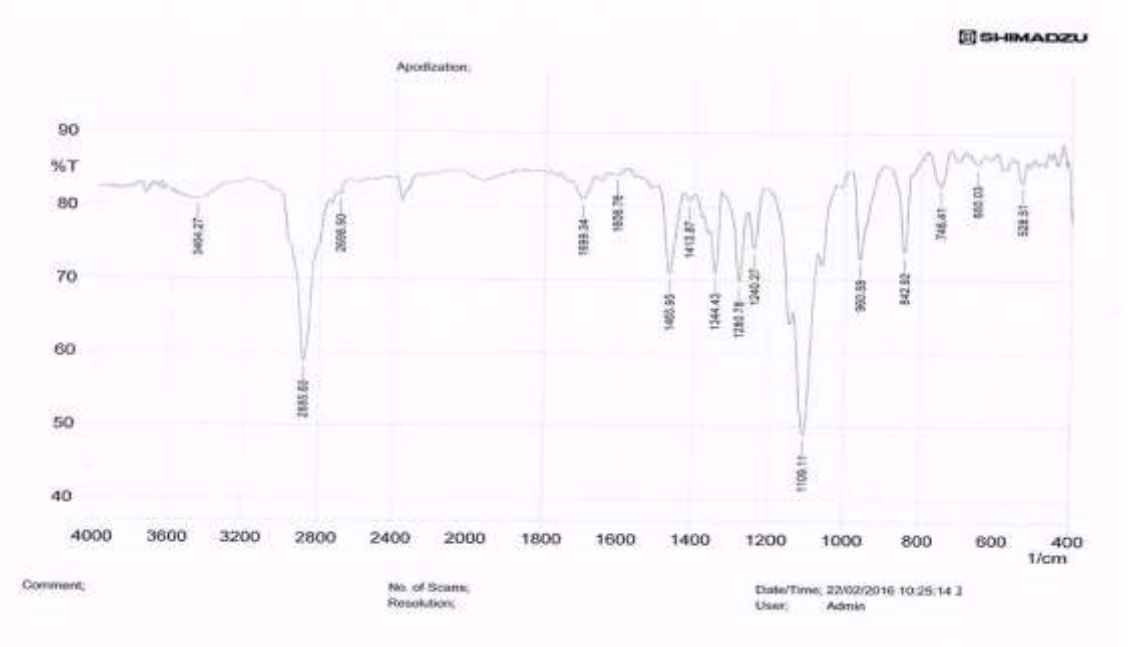

Fig 6: IR Spectrum of TLM SD using Poloxamer 188.

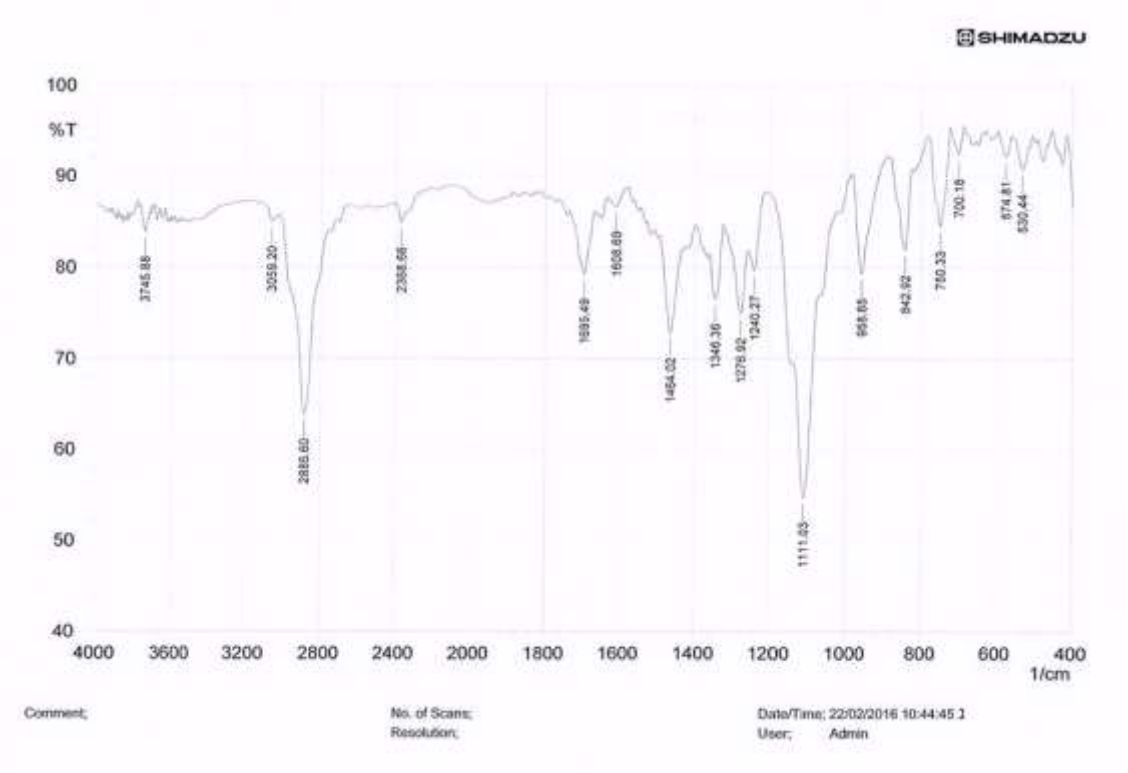

Fig 7: IR Spectrum of Telmisartan SD using PVP

Dissolution Studies of Telmisartan In-vitro:

The dissolution study showed that the release profile of TLM was improved for SD than that of pure drug. The figure (8) represent the dissolution profile of formulas prepared using PVP as polymer. It's clear that all formulas had faster dissolution than pure TLM with a fastest dissolution recorded for the formula (5) which had a maximum polymer ration (drug: polymer ratio is 1:4). Similarly, the figure (9) shows the release profile of TLM SD formulas prepared using poloxamer 188 as

polymer. In this figure, the formula (8) with drug: polymer ratio was 1:1 represent the quickest dissolution profile. Figure (10) compare between the dissolution profile of pure TLM, F5 and F8. F5 with the highest PVP content was the fastest in compare to F8 as it released about 98% of drug after 10 minutes (min) compared to F8 which released about 98% after 15 min. Both formulas (F5 and F8) had a release profile much better than pure TLM. This could reflect positively on the onset of drug action. Therefore, one may expect that the antihypertensive effect may be faster for TLM SD than pure TLM since its solubility, dissolution and hence absorption, will be initiated in the stomach [20, 21].

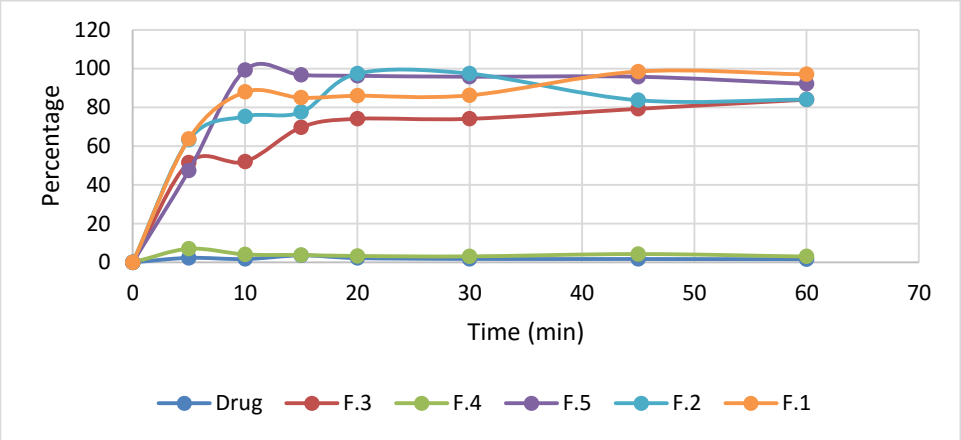

Fig 8: The release profile of TLM and the prepared SD formula (PVP) in phosphate buffer 6.8

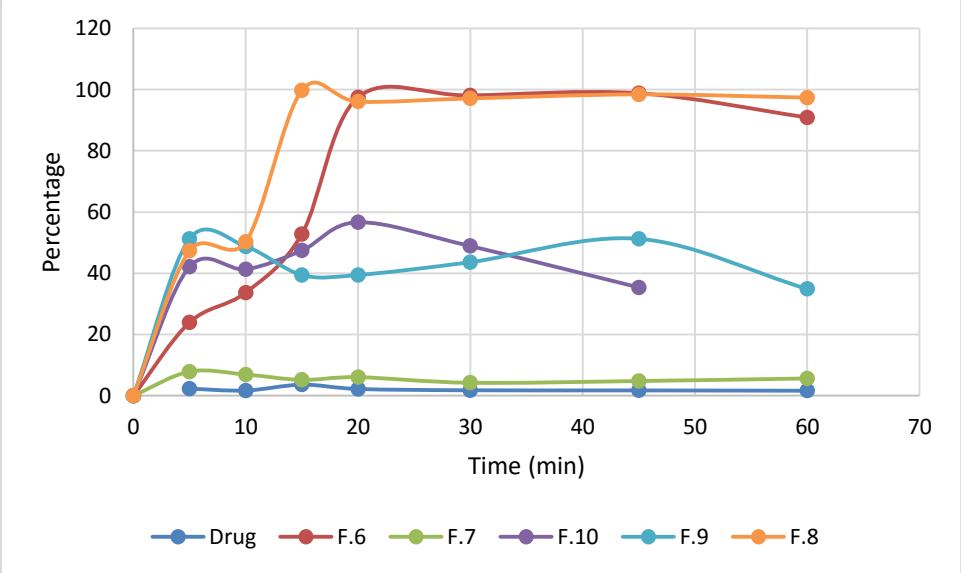

Fig 9: The release profile of TLM and the prepared SD formula (Poloxamer 188) in phosphate buffer 6.8

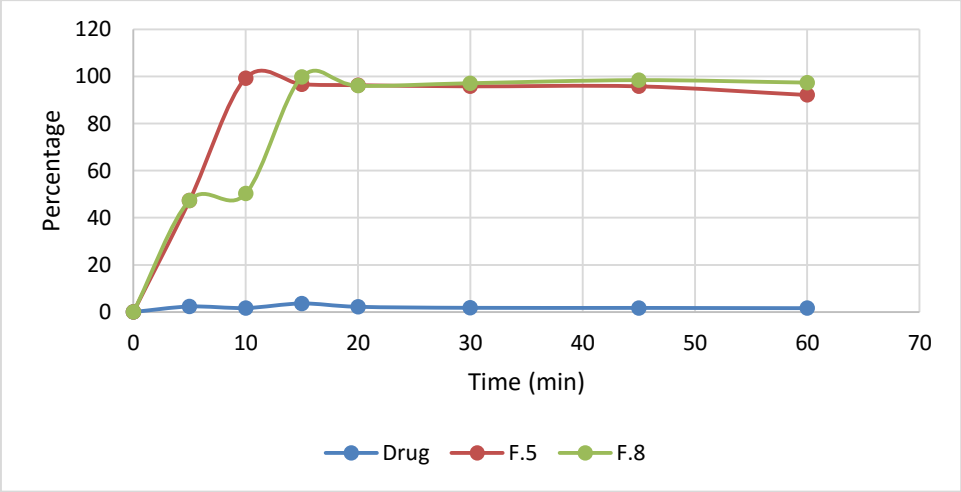

Fig 10: The release profile of TLM and the best formulas of both polymers in phosphate buffer 6.8

As shown in the above figures, the release profiles of all the prepared SD formulas were better than that of the pure drug. Formula 3 of PVP and formula 10 of poloxamer 188 were the best formulas of TLM SD and they showed the highest dissolution profile [20].

CONCLUSION:

An increase in water solubility and an enhancement of drug dissolution profile were successfully achieved by preparing TLM as SD using both Poloxamer 188 and PVP. Poloxamer 188 found to be suitable to formulate TLM as SD in a ratio of 1:1 (drug: polymer). While PVP found to be suitable to prepare TLM as SD in a ratio of 1:4 (drug: polymer).

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