ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Telmisartan Spongelike Particles as Oral Capsule II: Factors Affecting Formulation

Hussam H. Tizkam[1*], Alaa A. Abdul Rassol[2], Ahmed A. Hussain[2]

1. *Faculty of Pharmacy, AlSafwa University College, Iraq.*
2. *College of Pharmacy, University of Baghdad, Iraq.*

***Corresponding Author: Hussam H. Tizkam**

Abstract

Telmisartan (TEL) is selective angiotensin II receptor blocker sued in the management of cardiovascular disorders. It is a class II drug according to Biopharmaceutics Classification System (BCS). The aim of current study is to prepare TEL sponge like particles (SP) as a drug delivery system and investigate the different variables that may affect the formulation in order to enhance the solubility and dissolution rate thereof. The TEL SP formulations were prepared by quasi-emulsion solvent diffusion method using Eudragit E100 as SP forming polymer at drug: polymer ratio of (5:1). The effect of solvent type of internal phase, internal phase volume, stirring rate, stirring time, plasticizer concentration, surfactant concentration, external phase volume, and drying temperature on the formulation of TEL SP were investigated. Twenty five TEL SP formulations were prepared and filled into hard gelatin capsule. They were investigated and characterized for production yield, loading efficiency and *in vitro* drug release in 0.1N HCl (pH 1.2). Results showed that the best TEL SP formula was F15 which was prepared using 5ml of dichloromethane (DCM) as an internal phase solvent, 0.05 g of polyvinyl alcohol (PVA) as a surfactant, 1 g of sodium chloride as a porogen, 1 ml of glycerol as a plasticizer, 200 ml of water as an external phase solvent, 1000 rpm for 1 hr as the stirring rate and time, and 40 ^{0}C as a drying temperature. The F15 showed good production yield (82%), loading efficiency (73%), and fast dissolution rate in 0.1 N HCl (more than 80% drug release in less than 15 min). The *in vitro* release study showed that F15 had significantly better release characteristic ($p < 0.5$) when compared to both the pure TEL and the reference commercial tablet Micardis®. Finally, one can conclude that the SP technology can be a promising alternative way for the formulation of poorly water soluble drugs, such as TEL, into immediate release formulation.

Keywords: *Telmisartan, Sponge like, solubility, Eudragit E100.*

Introduction

The spongelike particles (SP) are a micro particulate system comprising highly cross-linked polymeric porous microspheres having numerous voids in the particle that resembles a true sponge [1].The SP can improve the wetting and solubility of molecules with poor solubility in water. The drugs can be molecularly dispersed within the SP structure and then released as molecules, avoiding the dissolution step. Consequently, the apparent solubility of the drug can be increased. Many formulation and bioavailability problems can be solved by enhancing the solubility and dissolution rate of a substance, and SP can greatly enhance the drug solubility [2]. By virtue of their biocompatibility and versatility, SP have many potential applications in the pharmaceutical field. Recently, it is proposed that SP are a promising innovative system for drug delivery. They can be used as excipients in preparing tablets, capsules, pellets, granules, suspensions, solid dispersions, or topical dosage forms or as new nanotechnological, multifunctional carriers [3].The quasi-emulsion solvent diffusion method is a simple and reproducible method that used for the preparation of SP. In this method, the key factor in the formation of the SP is the rapid diffusion of the organic solvent, e.g., ethanol or dichloromethane, into the aqueous medium. This rapid diffusion reduces the solubility of the SP forming polymer, e.g., Eudragit, in the droplets since

it is insoluble in water. The continuous mixing of the organic solvent and water at the interface of the droplets induces precipitation of the polymer, thereby forming a shell enclosing the solvent and the dissolved active ingredient. The finely dispersed small droplets of the polymeric solution of the drug were solidified in the aqueous phase via continuous diffusion of the organic solvent. That is why the quasi-emulsion *solvent diffusion* method is so called [4, 5].

Telmisartan (TEL) is angiotensin II receptor blocking agent used in the management of cardiovascular diseases. TEL blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues [6, 7]. TEL is classified as class II according to BCS system (drugs with low solubility and high permeability). It is practically insoluble in water (0.007 mg/ml).

The solubility of TEL in aqueous solutions is strongly pH dependent, with maximum solubility observed at high and low pH. In the range of pH 3-9 it is only poorly soluble [8, 9]. The previous work was the effect of polymer type and concentration on the formulation properties. It was conducted using different types of Eudragit polymers e.g., Eudragit E100, Eudragit RS100, Eudragit S100, Eudragit RL100 or Eudragit L100 [10]. The aim of current study is to prepare TEL SP as a drug delivery system and investigate the different variables that may affect the formulation in order to enhance the solubility and dissolution rate thereof.

Materials and Methods

Materials

The following materials were used in this study: Telmisartan (Hetero drugs limited, India). Eudragit E 100 (Evonik Rohm GmbH, Germany). Polyvinyl alcohol (Sigma Chemical co., USA).Dichloromethane and sodium chloride (Gainland chemical company, U.K.). Hydrochloric acid (Riedel-De-Haen AG seelze, Germany). Glycerol (BDH, England). Micardis 40 mg tablets (Boehringer Ingelheim, Germany). All reagents used were of analytical grade.

Methods

Preparation of TEL SP

The TEL SP formulations were prepared by quasi-emulsion solvent diffusion method. The internal phase consisted of 0.2 g of Eudragit E100 (E100) dissolved in 5 ml dichloromethane (DCM) . Glycerol (1 ml) was used as plasticizer. A predetermined weight (1 g) of TEL was added gradually to the internal phase at 5:1 drug: polymer ratio and dissolved under sonication at 35 ^{0}C for 15 min.

The resulting solution was then poured into 200 ml aqueous solution containing 50 mg of polyvinyl alcohol (PVA) which represents the external phase. The mixture was stirred at stirring rate of 1000 rpm for 1 hr. The SP was formed as a result of diffusion of the organic solvent out of the formula. The formed SP were filtered by ordinary filter paper and dried at temperature of 40 ^{0}C for 12 hr and stored for further investigations [11, 12].

Evaluation of TEL SP Formulations

Determination of Production Yield

The production yield (PY), expressed as percentage, of all TEL SP formulations was determined by calculating the initial weight of the solid materials and the final weight of the obtained SP (equation 1) [13].

$$PY\ (\%) = \frac{\text{Practical weight of SP}}{\text{Theoretical weight (polymer + drug)}} \times 100 \quad \ldots\ldots\ldots (1)$$

Determination of Loading Efficiency

A sample of TEL SP equivalent to 40 mg was dissolved in 100 ml of DCM. The solution was diluted suitably with DCM and spectrophotometric absorbance was measured at λmax of TEL. The drug content was calculated from the calibration curve and expressed as a percent loading efficiency (LE) as explained in equation 2 [14]. To minimize the error, LE experiment was carried out in triplicate ± S.D.

$$LE\ (\%) = \frac{\text{Actual weight of TEL in SP}}{\text{Theoretical weight of TEL}} \times 100 \quad \ldots\ldots\ldots\ldots (2)$$

Factors Affecting the Formulation of TEL SP

It is worth mention that when studying certain factor to reveal its effect on TEL SP attributes e.g., PY and LE, all other factors were kept constant. The factors that may affect on the formulation of TEL SP by quasi emulsion solvent diffusion method that were studied are:

The Effect of Solvent Type of Internal Phase

The formulations F1, F2 and F3 were prepared to select the most suitable solvent for the internal phase by using different type of organic solvents. Five milliliters of ethanol, DCM and acetone were used in the preparation of formulas F1, F2 and F3, respectively.

Effect of Internal Phase Volume

In order to determine the best volume of the organic solvent, four different volumes (5, 10, 15, 20 ml) of DCM were taken to study the effect of internal phase volume on the formulation of TEL SP. In the preparation of F2 formula, 5 ml of DCM was used while 10 ml was used in F4, 15 ml was used in F5 whereas 20 ml was used in F6.

Effect of Stirring Rate

To find out the most appropriate stirring rate on the formulation of TEL SP, different stirring rates (1000, 3000, 6000, 9000 and 12000 rpm) were employed. The formula F7 was prepared by using 3000 rpm stirring rate instead of 1000 rpm that was used in F2, while 6000 rpm was used in F8 and 9000 rpm in formula F9 whereas 12000 rpm was used in F10.

Effect of Stirring Time

The effect of time of stirring on the formulation of TEL SP was studied. A stirring time of 0.5, 1, 2 and 4 hr were used in the formulations F11, F2, F12 and F13, respectively.

Effect of Porogen

Porogens are materials that promote the formation of pores or channels inside the SP. The effect of addition of porogen on the formulation of TEL SP was studied using sodium chloride as a pore forming agent, i.e., porogen. Three different concentrations of sodium chloride (0.5, 1 and 1.5 g) were added to formulas F14, F15 and F16, respectively.

Effect of Plasticizer Concentration

The effect of plasticizer concentration on the formulation of TEL SP was studied using glycerol as a plasticizer. The TEL SP Formulations F2, F17 and F18 were composed of 1, 2.5 and 5 ml of glycerol, respectively.

Effect of Surfactant Concentration

To reveal the effect of surfactant concentration on the TEL SP, four formulas were formulated using different concentrations of PVA. The formulas F2, F19, F20 and F21 were composed of 0.05, 0.10, 0.15 and 0.20 g of PVA, respectively.

Effect of External Phase Volume

The effect of water volume, as external phase, on the formulation of TEL SP was studied. The formulas F2, F22 and F23 were formulated using 200, 300 and 400 ml of water, respectively.

Effect of Drying Temperature

The effect of different drying temperatures on TEL SP was investigated. The formula F2 was dried at 40 ^{0}C and the formula F24 was dried at 60 ^{0}C while the formula F25 was dried at 80 ^{0}C.

In-vitro Drug Release Study of TEL SP Formulations

In vitro dissolution study was performed for all TEL SP formulations using USP dissolution test apparatus-I with basket assembly (Copley scientific, UK). The dissolution was performed in 900 ml of 0.1 N HCl (pH 1.2), maintained at 37 ± 0.5°C and 75 rpm. A sample of TEL SP equivalent to 40 mg of pure TEL was filled in empty gelatin capsule in each test.

The samples were filtered through a whatman filter paper, suitably diluted and analyzed at λmax of TEL using a double-beam UV-visible spectrophotometer (Carry100 UV, Varian, Australia). The drug release experiments were conducted in triplicate ± SD to minimize the error [15, 16].For comparison purpose; the dissolution study was performed for the above mentioned TEL SP formulations in addition to 40 mg pure TEL powder filled in empty capsule and the brand tablet Micardis® 40 mg.

Selection of the Best Formula

The release profile of all TEL SP formulations was studied in addition to other properties, e.g., PY and LE, and compared with each other and with that of the brand tablet. Then, the best formula was selected on these bases.

Results and Discussion

Evaluation of TEL SP Formulations

Determination of Production Yield and Loading Efficiency

The PY and LE of all of the TEL SP formulations were measured as shown in table (1). The PY was between 55–85% for all the formulations whereas the LE varied between 35–74%. Statistically, there was a significant difference between formulations ($p<0.05$) regarding both the PY and the LE.

Table 1: The PY and LE of all TEL SP Formulations

Formula	PY (%)	LE (%)	Formula	PY (%)	LE (%)	Formula	PY (%)	LE (%)
F1	55	47	F10	64	67	F19	76	69
F2	85	72	F11	55	45	F20	70	64
F3	78	68	F12	79	62	F21	67	59
F4	77	63	F13	76	58	F22	83	73
F5	68	55	F14	83	73	F23	85	70
F6	63	35	F15	82	73	F24	85	71
F7	82	71	F16	79	72	F25	84	74
F8	77	71	F17	83	71			
F9	71	68	F18	84	73			

Factors Affecting the Formulation of TEL SP

The Effect of Solvent Type of Internal Phase

It was found that the best solvent of the internal phase that gave the highest PY and LE was DCM followed by acetone and then ethanol (table 1). This finding may be attributed to the boiling points of these solvents. The boiling points of DCM, acetone and ethanol are 40, 56 and 78.4 ^{0}C, respectively. Therefore, DCM would evaporate more rapidly. It is found that the higher solvent evaporation rate led to a higher solvent kinetic energy, which accordingly increased the rate of diffusion of the solvent from the inner organic phase to the outer aqueous phase.

This diffusion step is the critical parameter determining the PY and LE [17, 18]. In this study, DCM was selected as the best solvent because of two reasons. Firstly, DCM was the best regarding the PY and LE. It was found that there was a significant difference ($P<0.05$) between these three solvents in terms of PY and LY. Secondly, TEL is more soluble in DCM than the other two solvents [17, 18]. TEL is insoluble in water. Hence, water was selected as an external phase with PVA as surfactant to facilitate the formation of emulsions. Both the drug and the polymer (Eudragit E100) are insoluble in water and are solidified when contact with water.

Effect of Internal Phase Volume

It was found that increasing the volume of internal phase leads to decreasing the PY and LE of the prepared TEL SP (table 1). This may be due to the decrease in viscosity of the internal phase [19]. The reduction of PY that caused by decreasing the viscosity of the internal phase may be probably due to the lower concentration of the drug and polymer in the higher volume of the internal phase. The high internal phase volume decrease the probability of coalescence of the droplets in the emulsion, therefore decrease the chance of SP formation.

Regarding the LE, it is affected directly by the PY and any factor that decreases the PY, e.g., viscosity of the internal phase, may eventually decrease the LE. Besides, the low viscosity of the internal phase may facilitate the escape of drug out of the SP. Accordingly, it was adopted that the best volume of internal phase was 5 ml of DCM and it kept constant in the subsequent formulations.

This fact was in agreement with other literature [20].

Effect of Stirring Rate

It was observed that at higher stirring rates more vigorous turbulence was created within the external phase, then the polymer adhered to the paddle and glassware which led to reduction of the PY (table 1) [21].It was noted that as the stirring speed was increased, the mean particle size of SP was decreased. The mean particle size of formulations F2, F7, F8, F9 and F10 was 50, 44, 40, 35, and 33, respectively. This fact may be due to that increasing the stirring speed produces droplets of smaller size which may be attributed to the higher mechanical shear that applied during the higher stirring rates resulting in a rapid splitting of the formed droplets, allowing less chance of coalescing into bigger droplets [22]. However, the SP prepared with 1000 rpm had higher and more acceptable PY and LE and therefore, 1000 rpm was selected as the optimum stirring speed.

Effect of Stirring Time

It was found that a stirring time of 0.5 hr that used in the fabrication of the formula F11 is not useful for the formation of SP with reasonable PY and LE since there is no enough time for the SP to solidify (table 1). On the other hand, stirring time of 2 and 4 hr that applied in the formulations F12 and F13, respectively is not optimum as it is obvious from the low PY and LE. This may be due to that the longer stirring time allows the SP to adhere to the paddle or the glassware. In addition, at longer time of stirring there is more chance for the drug to leach out of the SP. Accordingly, it was adopted that the optimum stirring time is 1 hr.

Effect of Porogen

It was observed that the addition of porogen had lowered the PY of TEL SP as compared with the formula F2. This may be explained by knowing that the porogen, sodium chloride, was dissolved in water after the addition of the internal phase to the external phase (table 1). The porogen is freely soluble in water; hence it dissolves in the external phase leaving more channels and pores behind in the SP. The dissolved porogen lowers the solid content of the prepared TEL SP and therefore, decreases the PY. Regarding the LE, it is less affected by the addition of porogen, as it is obvious in table (1), since the LE is related directly to the encapsulation capacity of the polymer which is kept constant. However, the addition of porogen was found to have beneficial effect on the release characteristic of the prepared TEL SP, as will discussed latter.

Effect of Plasticizer Concentration

It was found that increasing the amount of plasticizer had no appreciable effect on the PY and LE of TEL SP (table 1). This may be due to the little effect of glycerol on the viscosity of the external phase. Therefore, even after the addition of 5 ml of glycerol in formula F18 there was no significant increase in the viscosity of the external aqueous phase which in turn, necessary for increasing the PY and LE, as discussed previously (see *Effect of Internal Phase Volume*). Therefore, 1 ml of glycerol was adopted for the subsequent formulations.

Effect of Surfactant Concentration

Table (1) reveals that increasing the amount of PVA from 0.05 g to 0.20 g was accompanied by a reduction of both PY and LE. The decrease in the PY and LE of the prepared TEL SP may be attributed to solubilization effect performed by PVA since the latter is an efficient solubilizing agent that increases the solubility of both the drug and the polymer resulting in less solid content in the prepared SP, and by doing so, decreasing the PY and LE [23]. Accordingly, the 0.05 g of PVA was regarded as the optimum amount of surfactant for the formulation of TEL SP and kept constant for the subsequent formulations.

The Effect of External Phase Volume

Theoretically, it may be thought for the first time that since the quasi emulsion solvent diffusion method depends entirely on the diffusion phenomenon, so increasing the volume of water may enhance the diffusion of DCM into the external phase thereby improve the attributes of the SP. However, it was observed that increasing the volume of water from 200 to 400 ml had no useful impact on PY and LE of TEL SP (table 1). This may be due to the fact that water at all these three concentrations represents an excess amount relative to the low internal phase volume and therefore, imparts no additional benefit for the SP. Based on the

above findings, the external phase volume was kept constant at 200 ml for the next TEL SP formulations.

Effect of Drying Temperature

It may expect that the drying kinetic may have a profound effect on the solvent evaporation from the SP which in turn affects on the pore formation and channeling process; properties that are reflected positively on the formulation attributes of the prepared TEL SP. However, the mentioned cascade was not achieved practically and this may be due to the low residual amount of the solvent in the prepared TEL SP. The PY, LE and the release characteristics (discussed latter) of the prepared TEL SP were not affected significantly ($P > 0.05$) by changing the drying temperature from 40 to 80 ^{0}C (table 1).

Finally, according to the obtained results, the optimum TEL SP formula that selected for the subsequent evaluation was formula F15. This formula was prepared using 5ml of DCM, 0.05 g of PVA, 1 g of sodium chloride, 1 ml of glycerol, 200 ml of water, 1000 rpm for 1 hr, and dried at 40 ^{0}C. The formula F15 was selected depending upon the optimization of the formulation characteristics such as PY, LE and the release profile as will seen later.

In-vitro Drug Release Study of TEL SP Formulations

The time for 75% release (T 75%) for all TEL SP formulations in 0.1 N HCl (pH 1.2) are listed in table (2). It was found that the best release profile among all the twenty five formulations in 0.1 N HCl was that of the formula F15; that's why it was selected as the optimum formula. The optimum release profile of the formula F15 may be attributed to the presence of porogen. This may be explained by knowing that the porogen, sodium chloride, was dissolved in water after the addition of the internal phase to the external phase.

The porogen is freely soluble in water; hence it dissolves in the external phase leaving more channels and pores behind it in the SP [24]. This finding is consistent with the fact that factors such as SP pore size, the loading of drug, and polymer composition govern the rate of drug release from the SP in topical and oral delivery [25]. The release profile of the TEL SP capsule of the optimum formula (F15) was also more favorable than that of Micardis® tablet and the pure TEL raw material as shown in table (3).

Table 2: The Time for 75% Release for all TEL SP Formulas in 0.1 N HCl (pH 1.2)

Formula	T 75% (min)	Formula	T 75% (min)	Formula	T 75% (min)	Formula	T 75% (min)
F1	30	F8	14	F15	10	F22	30
F2	20	F9	15	F16	12	F23	30
F3	27	F10	13	F17	23	F24	31
F4	14	F11	20	F18	29	F25	30
F5	14	F12	23	F19	29	Micardis	40
F6	13	F13	26	F20	33	Pure TEL	not accessible
F7	14	F14	13	F21	35		

Table 3: The Release Profile of the optimum TEL SP Formula (F15), Micardis® and Pure TEL*

Time (min)	% Release of F15	% Release of Micardis®	% Release pure TEL
5	36.55± 1.1	17.46±0.3 †	15.46±0.1 †
10	73.6±0.9	29.03±0.8 †	19.51±0.4 †
15	84.16±2.0	37.63±0.7 †	21.57±0.6 †
30	91.82±1.8	68.89±1.3 †	27.57±0.3 †
60	91±0.5	89.38±1.0	27.50±0.3 †
120	91.82±0.2	89±0.6	27.50±0.2 †
180	100±0.7	100±0.5	27.57±0.1 †

* Results are expressed as mean ± S.D (n=3).
† Significant difference ($P<0.05$).

Statistically, there was highly significant difference ($P<0.05$) between the release profile of the TEL SP capsule (F15) and pure TEL. In addition, a significant difference was found also between TEL SP capsule (F15) and Micardis® tablet as it is clear in figure (1). Figure (2) indicates that the TEL SP capsule (F15) showed faster release rate than Micardis® tablet. The T 75% of the TEL SP capsule was 3-fold faster than that of Micardis®. Regarding TEL raw material, it does not exceed 27.5% of the release profile even after 180 min. It is worth mentioning that the T 75% is an important parameter in

the quality control of dosage forms. According to USP, the solid oral dosage form should comply with the T 75% requirements in order to pass successfully the dissolution test [26].

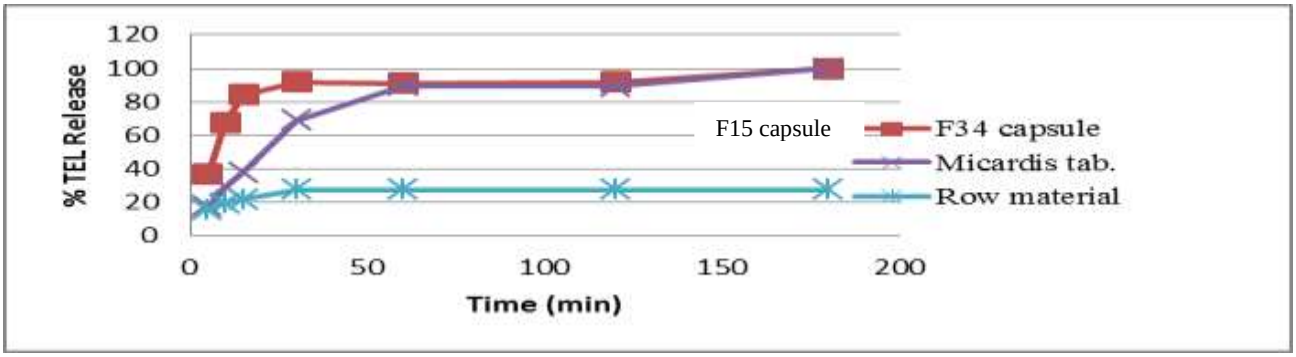

Figure 1: The release profile of TEL from TEL SP capsule (F15), Micardis® tablet and raw material in 0.1 N HCl at 37± 0.5 ºC

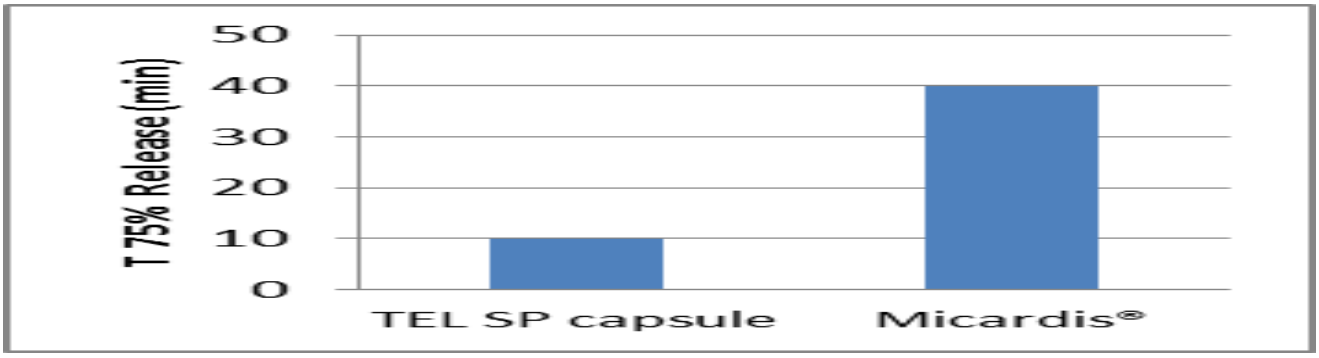

Figure 2: The time of 75% release of TEL from TEL SP capsule (F15) and Micardis® tablet in 0.1 N HCl at 37±0.5 ºC

To accurately confirm the preference of the prepared TEL SP capsule (F15) release profile compared to that of Micardis® tablet and TEL raw material, mathematical expressions had been used. To compare the dissolution profiles of two formulations (test and reference), the difference factor (F_1) and similarity factor (F_2), suggested by the FDA, are useful. Generally, F_1 values up to 15 (i.e. from 0 to 15) and F_2 values greater than 50 (i.e. from 50 to 100) ensure sameness (or equivalence) of the two curves [27].The calculated F_1 and F_2 values for the prepared TEL SP capsule (F15) when using Micardis® tablet as a reference were 84% and 9.7%, respectively. Whereas the F_1 and F_2 values when using TEM raw material as a reference were 99.99% and 0.43%, respectively. The above values indicate clearly the highly significant differences among these three formulations and there is a high degree of non-equivalence and non-similarity among them. These facts are best clarified in Figures (3) and (4). It is worth mentioning that the T 75% release profile of TEL from TEL SP capsule (F15) in 0.1 N HCl was better than that reported in literatures by other researchers (figure 5). For example, it was better than TEL nanosuspension [28], TEL solid dispersion [29], TEL orodispersible tablet [30], TEL microspheres prepared by emulsion evaporation technique [31] and TEL prepared by self microemulsifying drug delivery system [32].

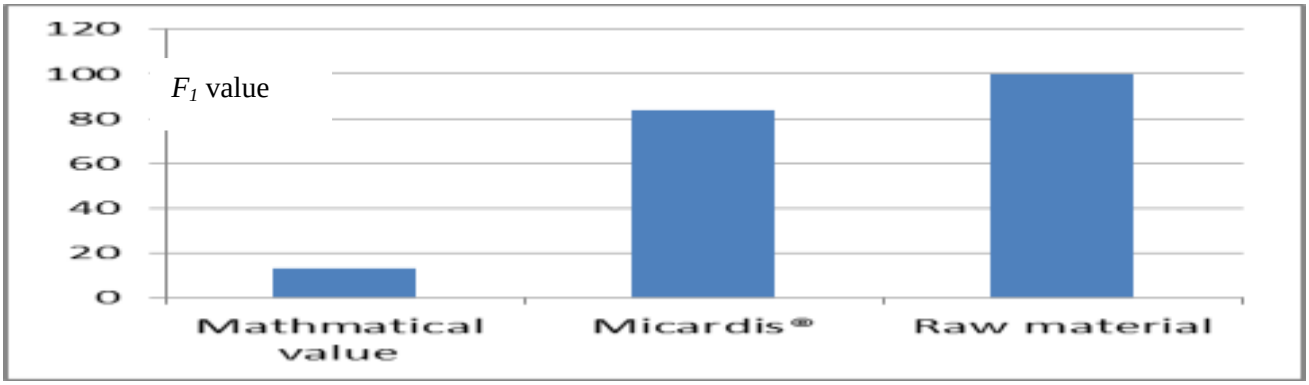

Figure 3: The calculated F_1 value of Micardis® tablet and TEL raw material. The mathematical value represents a number of up to 15

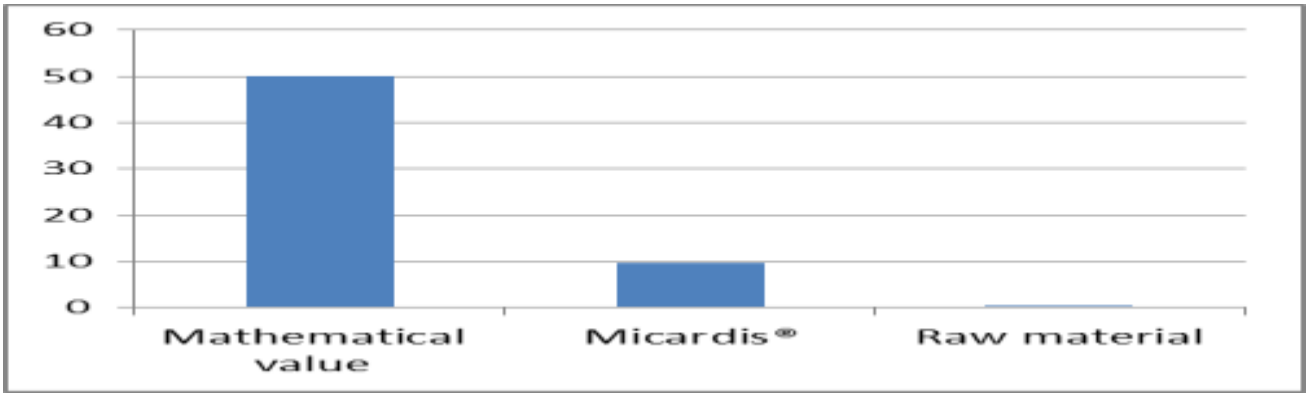

Figure 4: The calculated F_2 value of Micardis® tablet and TEL raw material. The mathematical value represents a number of not less than 50

Remaining one issue to discuss; that is, the odd solubility behavior of TEL. It is a carboxylic acid derivative with a free carboxyl group. According to Handerson-Hasselbatch equation (equation 3), an acidic drug with a pKa value of 3.83 is proposed to be completely ionized and soluble at pH values of 6-8. However, this is not the case in reality. TEL is insoluble in the pH range of 3-9 [33].

$$pH = pKa + \log\frac{[ionized]}{[unionized]} \quad \text{..... (3)}$$

The researchers believe that this unusual solubility profile can be attributed to the intramolecular hydrogen bonding. By exploring the chemical structure of TEL (figure 6), one can find that the terminal carboxyl group can form intramolecular hydrogen bond with the aromatic nitrogen in the imidazole ring. Therefore, it is the hydrogen bonding that actively "mask" the free carboxyl group of TEL. Accordingly, the TEL molecule is busy with intramolecular hydrogen bonding which in turn, decrease hydrophilicity and increase lipophilicity [34, 35].

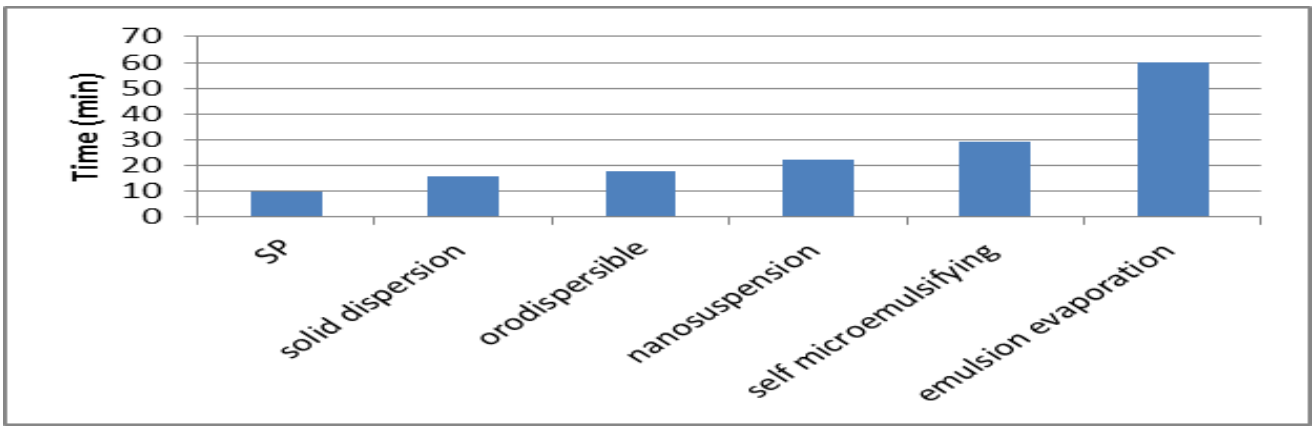

Figure 5: The T 75% release of TEL from various formulations [29-32]

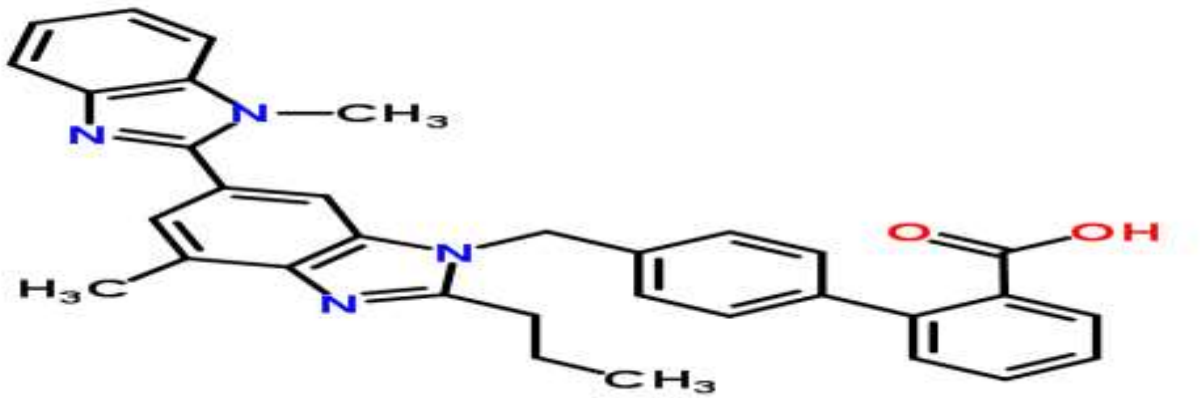

Figure 6: The chemical structure of TEL [34, 35]

Conclusion

The present study showed that the SP technique can be successfully used for formulation of oral capsule of practically insoluble drugs such as TEL. The TEL SP formulated with the sodium chloride, as a porogen, is the best formulation among all the batches of the prepared TEL SP capsules in terms of good release profile and enhancing the dissolution rate of TEL. The enhanced rate of drug dissolution from TEL SP is probably due to an increase in surface area of drug particles available for dissolution media; thus, this technique may improve bioavailability of poorly water-soluble drugs.

Acknowledgements

Authors are thankful to Feras Melhem from Evonik industries regional office for his kind efforts in supplying the materials of this research.

References

1. Tansel C, Omo˘Glu T, Gonui N, Baykara T (2003) Preparation and *In Vitro* Evaluation of Modified Release Ketoprofen Microsponges. I. J. Farmaco., 58, 101-106.
2. Prasad M, Ajay M, Babu B, Prathyusha P, Audinarayana N, Reddy K (2011) Micro sponge Drug Delivery System: A Review. Journal of Pharmacy Research, 4(5):1381-1384.
3. D'souza I, Masvekar R, Pattekari P, Pudi R (2004) Microspongic Delivery of Fluconazole for topical Application. Indo-Japanese Int. Conference on Adv. Pharm. Res. Tech., 76-83.
4. Orlu M, Cevher E, Araman A (2006) Design and Evaluation of Colon Specific Drug Delivery System Containing Flurbiprofen Microsponges. International Journal of Pharmaceutics, (318): 103-117.
5. Rae I, Biscans B (1999) Preparation of microspheres of ketoprofen with acrylic polymers by a quasi-emulsion solvent diffusion method. Powder Technol., 101: 120-133.
6. Csajka C, Buclin T, Brunner HR, et. Al (1997) Pharmacokinetic-Pharmacodynamic Profile of Angiotensin II Receptor Antagonists. Clin Pharmacokinet.. 32: 1-29.
7. Wexler R, Greenlee J, Irvin D (1996) Nonpeptide Angiotensin II Receptor Antagonists: The Next Generation in Antihypertensive Therapy. J Med Chem., 39:625-656.
8. John M, Beale J, John H Willson (2011) Gisvold's Textbook of Organic Chemistry and Pharmaceutical Chemistry, 12th edition, 982-983.
9. Kausalya J, Suresh K, Padmapriya S, Rupenagunta A, Senthilnathan B (2011) Solubility and Dissolution Enhancement Profile of Telmisartan Using Various Techniques. Int. J. Pharmtech. Res, 3(3): 1737-1248.
10. Tizkam H, Abdul Rassol A, Hussain A (2015) Telmisartan Spongelike Particles as Oral Capsule: Effect of Polymer Type and Concentration on the Formulation Properties. Kerbala journal of pharmacy and pharmaceutical science, (10)1-14.
11. Devane J (1998) Oral Drug Delivery Technology: Addressing The Solubility/Permeability Paradigm. Pharm. Technol., 68-74.
12. Singh R, Jain D (2013) Development, Characterization & Stabilization of Poorly Water Soluble Drugs Utilizing Solid Dispersion Techniques By Using Cyclodextrin. Journal of Drug Delivery & Therapeutics, 3(2): 74-79.
13. Bhagwat D., D'souza J (2012) Formulation and Evaluation of Solid Self Micro Emulsifying Drug Delivery System Using Aerosil 200 as Solid Carrier. International Current Pharmaceutical Journal, 1(12): 414-419.
14. Daisy S (2009) Solubility Enhancement-Eminent Role In Poorly Soluble Drugs. Research Journal of Pharmacy and Technology, (2):220-224.
15. Greenhalgh D, Williams C, Timmins P (1999) Solubility Parameters as Predictors of Miscibility in Solid Dispersions. Int. J. Pharm., (88): 1182-1190.
16. Sharma D (2009) Solubility Enhancement-Eminent Role in Poorly Soluble Drugs. Research Journal of Pharmacy and Technology, (2):220-224.

17. Moffat A, Osselton M, Widdop B (2011) Clarke's analysis of drugs and poisons. Volume 11, 4th Edition. The pharmaceutical press.

18. Mainardes R, Evangelista R (2005) PLGA nanoparticles containing praziquantel: Effect of formulation variables on size distribution. Int. J. Pharm., 290: 137-44.

19. Kawashima Y, Niwa T, Takeuchi H, Hino T, Ito Y (1992) Control of prolonged drug release and compression properties of ibuprofen micro sponges with acrylic polymer, Eudragit RS, by changing their intraparticle porosity. Chem. Pharm. Bull., 40: 196-201.

20. Mishra M, Shikhri M, Sharma R, Goojar M (2011) Optimization, formulation development and characterization of Eudragit RS 100 loaded micro sponges and subsequent colonic delivery. IJDDHR, 1(1): 8-13.

21. Ravi R, Kumar S (2013) Stand ration of process parameters involved erythromycin microsponges by quassi emulsion solvent diffusion method. IJPDT. 2013; 3 (1): 28-34.

22. Yang S, Cui D, You G, Fan L, Wang L, Yue P, Yang H (2003) Preparation of sustained-release nitrendipine microspheres with Eudragit RS and aerosil using quasi-emulsion solvent diffusion method. Int. J. Pharm., 259: 103-113.

23. Embil K, Nacht S (1996) The Microsponge Delivery System (MDS): A Topical Delivery System with Reduced Irritancy Incorporating Multiple Triggering Mechanisms for the Release of Actives. I. Microencapsulation, 13 (5): 575-588.

24. Richard W (1987) Method for delivering an active ingredient by controlled time release utilizing a novel delivery vehicle which can be prepared by a process utilizing the active ingredient as a porogen. United States Patent, 4690825.

25. Christensen S, Hargens W, Nacht S, Gans H (1977) Viscoelastic properties of intact human skin instrumentations, hydration effects and contribution of the stratum corneum. J. Invest Dermatol., 69: 282-286.

26. USP (2013) 36- NF 31 (The United States pharmacopoeia), Electronic Edition.

27. Lopes C, Lobo J, Pinto J, Costa P (2007) Compressed Matrix Core Tablet as a Quick/Slow Dual-Component Delivery System Containing Ibuprofen. AAPS Pharm. Sci. Tech., 8(3): 1-8.

28. Bajaj A, Rao M, Pardeshi A, Sali D (2012) Nanocrystallization by Evaporative Antisolvent Technique for Solubility and Bioavailability Enhancement of Telmisartan. AAPS Pharm Sci Tech., 13 (4): 1331-1340.

29. Chivate N, Chivate A, Shinde S, Saboji J (2013) Improvement of Bioavailability and Solubility of Telmisartan by Solid Dispersion Technique using Various Carriers. Int. J. Pharm. Sci. Rev. Res., (07): 36-41.

30. Sujitha M, Mariappan G, Rathnanand M (2012) Preparation and evaluation of orally disintegrating tablets of Telmisartan with pH independent release. Int. J. Pharm. Tech. Res, 4(3): 1152-1154.

31. Kendre P, Chaudhari P (2012) Formulation and Evaluation of Telmisartan Microspheres by Solvent Evaporation Technique. Indo American Journal of Pharmaceutical Research, 1(41): 651-658.

32. Hyma P, Chandra A, Abbulu K (2014) Formulation and Characterization of Telmisartan Self Micro emulsifying Drug Delivery System. Int. J. Pharm. Pharm. Sci., 6 (1): 120-125.

33. Sinko P (2011) Martin's Physical Pharmacy and Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences. Lippincott Williams & Wilkins. 6th Edition, 163-166.

34. Dinnebier R, Sieger P, Nar H, Shankland K, David W (2000) Structural Characterization of Three Crystalline Modifications of Telmisartan by Single Crystal and High-Resolution X-ray Powder Diffraction. Journal of Pharmaceutical Sciences, 89 (11): 1465-1479.

35. Alatas F, Ratih H, Soewandhi S (2015) Enhancement of Solubility and Dissolution Rate of Telmisartan by Telmisartan-Oxalic Acid Co-Crystal Formation. Int. J. Pharm. Pharm. Sci., 7 (3): 423-426.

