Telmisartan Spongelike Particles as Oral Capsule: Effect of Polymer Type and Concentration on the Formulation Properties.

Hussam H. Tizkam* , Alaa A. Abdul Rassol and Ahmed A. Hussain****
* Department o f Pharmaceutics, College of Pharmacy, University of Kerbala, Iraq.
** Department o f Pharmaceutics, College of Pharmacy, University of Baghdad, Iraq.
Corresponding author E-mail: Hussam.Taskam@uokerbala.edu.iq
Received ( ), Accepted ( )

Abstract
Telmisartan (TEL) is a selective angiotensin II receptor blocker used in the management of cardiovascular disorders. It is a class II drug according to Biopharmaceutics Classification System (BCS); with poor solubility and high permeability. Due to its hydrophobic nature, TEL shows low dissolution profile in gastrointestinal fluid resulting in poor absorption, and consequently poor bioavailability.
The aim of current study is to prepare TEL spongelike particles (SP) system that enhances the dissolution rate and solubility of TEL. The TEL SP formulas were prepared by quasi-emulsion solvent diffusion method using different types of polymer, e.g., Eudragit E100, Eudragit RS100, Eudragit S100, Eudragit RL100 or Eudragit L100. The effect of polymer type and concentration on the formulation of TEL SP were investigated.
Twenty TEL SP formulations were prepared. They were investigated and characterized for production yield, loading efficiency and *in vitro* drug release in 0.1N HCl pH 1.2).
The results showed that the best TEL SP formula was F2 which was prepared using Eudragit E100 as the SP-forming polymer at drug:polymer ratio of (5:1).
The TEL SP formula (F2) showed good production yield, loading efficiency, and fast dissolution rate in 0.1 N HCl (more than 80% in less than 30 min). The selected TEL SP formula (F2) was incorporated into hard gelatin capsules.
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.
Key wards: Telmisartan, spongelike, solubility, Eudragit.

تحضير وتقييم الاسفنجيات الدقيقة لعقار التلمسارتان على شكل كبسول فموي

حسام حامد تزكام*، علاء عبد الحسين عبد الرسول، احمد عباس حسين****
* فرع الصيدلانيات، كلية الصيدلة، جامعة كربلاء، العراق.
** فرع الصيدلانيات، كلية الصيدلة، جامعة بغداد، العراق.
البريد الالكتروني: Hussam.Taskam@uokerbala.edu.iq

الخلاصة
يعتبر عقار التلمسارتان من الادوية الفعالة في علاج امراض القلب والشراين. وهو يعتبر من الادوية ذات الانتقاء العالي في اغلاق مستقبلات الانجيوتنسين من النوع الثاني . يمتاز هذا العقار بذوبانية منخفضة، نفوذية عالية، وامتصاص وتوافر بايلوجي قليل.
تم اجراء هذه البحث لدراسة الاسفنجيات الدقيقة لعقار التلمسارتان من اجل زيادة ذوبانيته في الماء وزيادة امتصاصه. وقد استخدمت طريقة انتشار المذيب في شبه المستحلب باستعمال بوليمرات مختلفة مثل يودراجيت آر اس 100، يودراجيت اس 100، يودراجيت آر ال 100، يودراجيت ال 100، يودراجيت اي 100.
تم تصييغ 20 صيغة دوائية للتلمسارتان على شكل اسفنجيات دقيقة وقد تم دراسة العوامل المؤثرة على تصييغ الاسفنجيات الدقيقة لعقار التلمسارتان مثل نوع البوليمروتركيزه. وقد تم تقييم الصيغ الدوائية للتلمسارتان عن طريق دراسة عامل الانتاج، عامل الاحتباس بالاضافة الى دراسة سرعة الذوبانية في الوسط الحامضي عند دالة هيدروجينية مقدارها (1،2).

اضهرت النتائج ان افضل الصيغ هي الصيغة (F2) والتي تكونت من اليودراجيت اي 100 عند نسبة دواء:بوليمر مقداره (5:1).

واضهرت النتائج ان الصيغة (F2) كانت ذات مواصفات مقبولة من ناحية عامل الانتاج، عامل الاحتباس بالاضافة الى سرعة الذوبانية في الوسط الحامضي عند دالة هيدروجينية مقدارها (1،2).

في الختام، يمكن ان نستنتج ان طريقة الاسفنجيات الدقيقة هي طريقة ناجحة من اجل زيادة ذوبانية بعض الادوية مثل التلمسارتان.

الكلمات المفتاحية: تلمسارتان، الاسفنجيات الدقيقة، ذوبانية، يودراجيت.

1. Introduction

The spongelike particles (SP) drug delivery system is one of the new methods that used to enhance the water solubility of poorly soluble drugs. They are spongelike structures that are introduced recently in pharmaceutical field [(1)].

The SP are microparticulate system, comprising highly cross-linked polymeric porous microspheres having numerous voids in the particle that resembles a true sponge. They can be loaded with wide range of drugs within a collapsible structure that have large porous surface which can be administered in different dosage forms. It can be a rigid structure; hard as a piece of ceramic, or soft as a bathroom sponge depending on the polymer composition, degree of cross-linking and on the formulation parameters [(2)].

The SP are mesh-like structures that have a proven spherical nature with a very high solubilization capacity for poorly soluble drugs. It is increasingly becoming acceptable that SP drug delivery has the potential to increase solubility, enhance bioavailability, improve controlled release of drugs, and enable precise targeting of the drug to the site of action [(3)].

This carrier system has been utilized for topical, oral, parenteral, nasal and pulmonary drug delivery. However, SP are used mostly for topical delivery but recently they are used for oral administration. Although SP have many advantages, its oral delivery researches are relatively little, thus it is a rich unexplored area of research [(4)].

The SP systems are made of well-known, widely used polymers. The Eudragit polymers are widely used as film coating materials in oral pharmaceutical formulations. They are also used in topical formulations and are generally regarded as nontoxic and nonirritant materials. The chemical structure of various Eudragit polymers is illustrated in figure (1) [(5)].

Telmisartan (TEL) is angiotensin II receptor blocker used in the management of cardiovascular disorders. 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, such as vascular smooth muscle and the adrenal gland. TEL is highly selective towards AT1 receptors. The selectivity of the compound is demonstrated by an affinity approximately 10,000 times higher to the AT1 than to the AT2 receptors [(6, 7)].

It 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 chemical structure of TEL is illustrated in figure (2).

The aim of current study is to prepare TEL SP prepared by quasi-emulsion solvent diffusion method in order to enhance the dissolution rate and solubility of TEL.

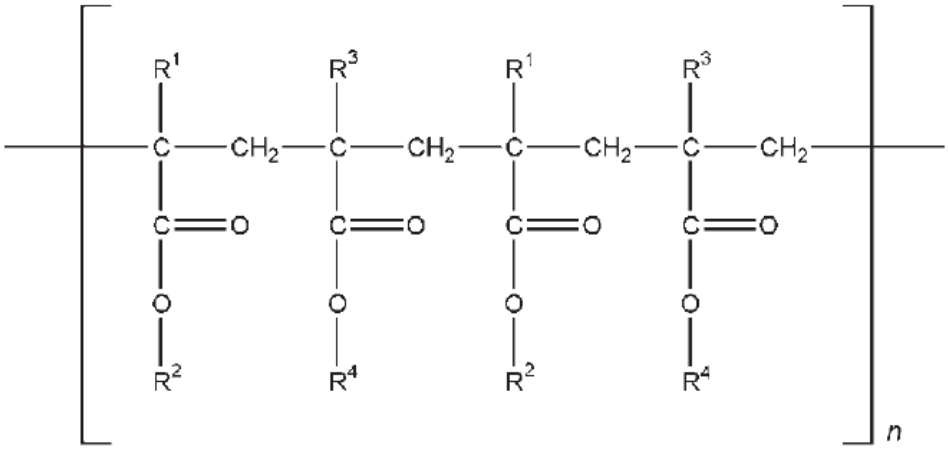


Figure (1): The chemical structure of Eudragit polymers.

For Eudragit E:	For Eudragit L and S:	For Eudragit RL and RS:
R_1, R_3 = CH_3	R_1, R_3 = CH_3	R_1 = H, CH_3
R_2 = $CH_2CH_2N(CH_3)_2$	R_2 = H	R_2 = CH_3, C_2H_5
R_4 = CH_3, C_4H_9	R_4 = CH_3	R_3 = CH_3
		R_4 = $CH_2CH_2N(CH_3)_3^+Cl^-$

The ratio of the free carboxyl groups to the ester groups is 1:1 in Eudragit L, RL and 1:2 in Eudragit S, RS.

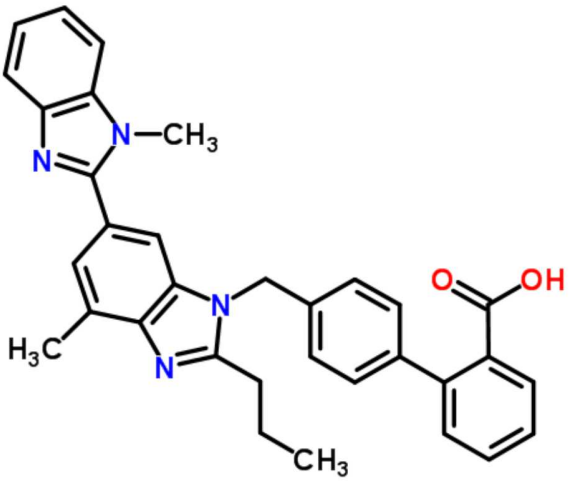


Figure (2): The chemical structure of TEL.

2. MATERIALS AND METHODS

Materials

The following materials were used in this study: Telmisartan (Hetero drugs limited, India). Eudragit S 100, Eudragit RS 100, Eudragit L 100, Eudragit RL 100, Eudragit E 100 (Evonik Rohm GmbH, Germany). Polyvinyl alcohol (Sigma Chemical co. USA). Dichloromethane (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 formulas were prepared by quasi-emulsion solvent diffusion method. The internal phase consisted of certain amount of different types of polymers, e.g., Eudragit E100, Eudragit RS100, Eudragit S100, Eudragit RL100 or Eudragit L100 dissolved in 5 ml of dichloromethane (DCM). Glycerol (1 ml) was used as plasticizer. Then, TEL was added gradually to the internal phase at different drug:polymer ratio and dissolved under sonication at 35 ^{0}C for 15 min. The resulting solution was then poured into 200 ml polyvinyl alcohol (PVA) aqueous solution which represents the external phase. The mixture was stirred at stirring rate of 1000 rpm for 1 hr. The SP were formed as a result of diffusion of the organic solvent out of the formulas. 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 [10, 11]. The composition of SP formulas is given in table (1).

Evaluation of TEL SP Formulations

Determination of Production Yield

The production yield (PY), expressed as percentage, of all SP formulas was determined by calculating the initial weight of the solid materials and the final weight of the obtained SP (equation 1) [12].

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

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 [13]. To minimize the error, LE experiment was carried out in triplicate ± S.D.

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

In-vitro Drug Release Study of TEL SP Formulations

In vitro dissolution study was performed for all TEL SP formulas using USP dissolution test apparatus-I (basket assembly). 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. Samples of dissolution fluid (5 ml) were withdrawn at predetermined time intervals and immediately replaced with 5 ml of fresh dissolution medium to maintain a sink condition. The samples were filtered through a whatman filter paper, suitably diluted and analyzed at λmax of TEL using a double-beam UV-visible spectrophotometer. The drug release experiments were conducted in triplicate ± SD to minimize the error [14, 15].

For the 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.

Table (1): Composition of TEL SP Formulas Prepared by Quasi-Emulsion Solvent Diffusion Method.

Formula No.	Drug : polymer ratio	TEL (gm)	Type of polymer
F1	2.5:1	0.5	Eudragit E100
F2	5:1	1	Eudragit E100
F3	7.5:1	1.5	Eudragit E100
F4	10:1	2	Eudragit E100
F5	2.5:1	0.5	Eudragit S100
F6	5:1	1	Eudragit S100
F7	7.5:1	1.5	Eudragit S100
F8	10:1	2	Eudragit S100
F9	2.5:1	0.5	Eudragit RS100
F10	5:1	1	Eudragit RS100
F11	7.5:1	1.5	Eudragit RS100
F12	10:1	2	Eudragit RS100
F13	2.5:1	0.5	Eudragit L100
F14	5:1	1	Eudragit L100
F15	7.5:1	1.5	Eudragit L100
F16	10:1	2	Eudragit L100
F17	2.5:1	0.5	Eudragit RL100
F18	5:1	1	Eudragit RL100
F19	7.5:1	1.5	Eudragit RL100
F20	10:1	2	Eudragit RL100

3. Results

Evaluation of TEL SP Formulations

Determination of Production Yield and Loading Efficiency

The PY and LE of all of the TEL SP formulas were measured as shown in table (2). The PY was between 68–96% for all the formulas whereas the LE varied between 45–88% for all formulas. Statistically, there was a significant difference between formulas ($p < 0.05$) regarding both the PY and the LE.

The PY and LE are important measures for microparticulate systems. They give an idea about the production and scale-up capabilities and the encapsulation power of that particular technique. Some of the microparticulate techniques, e.g. liposomes, suffer from low PY and LE whereas other techniques, such SP method, have good or even excellent PY and LE [16].

The Effect of Polymer Type on PY and LE

Since the SP is a polymeric microparticulate system, the type of polymer plays a crucial role on the SP attributes, namely, the PY and LE.

Different types of polymers, e.g., Eudragit E100, Eudragit RS100, Eudragit S100, Eudragit RL100 and Eudragit L100, were studied to reveal their effects on the PY and LE as shown in figure (3).

Although they were very good, the PY and LE of Eudragit E100 (formula F2, table 3) were the lowest among all other types of polymers used. This fact may be attributed to the low viscosity of the internal phase of Eudragit E100 as compared with other types, giving a chance for the drug to escape outside the droplets, thereby reducing the PY and LE [17]. This hypothesis was reinforced by the fact that the viscosity of Eudragit E100 is the lowest among all other types, as seen in table (4) [5].

Table (2): The PY and LE of all TEL SP Formulas.

Formulas	PY (%) *	LE (%) *
F1	68	45
F2	85	72
F3	86	76
F4	88	79
F5	70	48
F6	86	76
F7	88	80
F8	90	82
F9	70	50
F10	87	73
F11	89	80
F12	91	85
F13	72	53
F14	88	75
F15	90	78
F16	93	81
F17	70	50
F18	86	79
F19	92	83
F20	96	88

* PY: Production Yield, LE: Loading Efficiency.

However, this hypothesis is not so accurate; as the viscosities of Eudragit E100, Eudragit RL100 and Eudragit RS100 are close to each other. Besides, statistically there was no significant difference between the PY and LE of all polymers. As a result, the researchers believe that the PY and LE are intrinsic features for each particular polymer without correlation with viscosity.

To confirm the above fact, the chemical structure of Eudragit polymers had been explored [18]. It seems that there is no physicochemical relationship between TEL and all types of Eudragit polymers as it obvious from the chemical structure of them (see figure 1 and 2); therefore, there is no higher affinity for one type of Eudragit polymers than another for encapsulation of TEL. Again, the researchers believe that the PY and LE are intrinsic features for each particular Eudragit polymer.

The Effect of Polymer Concentration on the PY and LE of TEL SP

The effect of four drug:polymer ratios, namely 2.5:1, 5:1, 7.5:1, and 10:1 on the PY and LE of TEL SP were investigated for each particular polymer type. The results are given in table (5).

It was found that increasing the drug:polymer ratio increased the PY and LE. At higher drug:polymer ratio, the available polymer can encapsulate more amount of drug. The higher PY leads eventually to a greater LE, that means, a larger amount of drug can be encapsulated. It is assumed that a high PY leads mostly to high LE, and the reverse is true [19].

Although there was an increase in PY and LE with increasing drug:polymer ratio for each polymer type (figure 4), but statistically this increment was not significant when using a one-way ANOVA test at level of $p<0.05$. This fact may be attributed to the excellent PY and LE that were obtained for all Eudragit polymers, and one can conclude that all of them were showed maximum performance regarding the encapsulation of TEL.

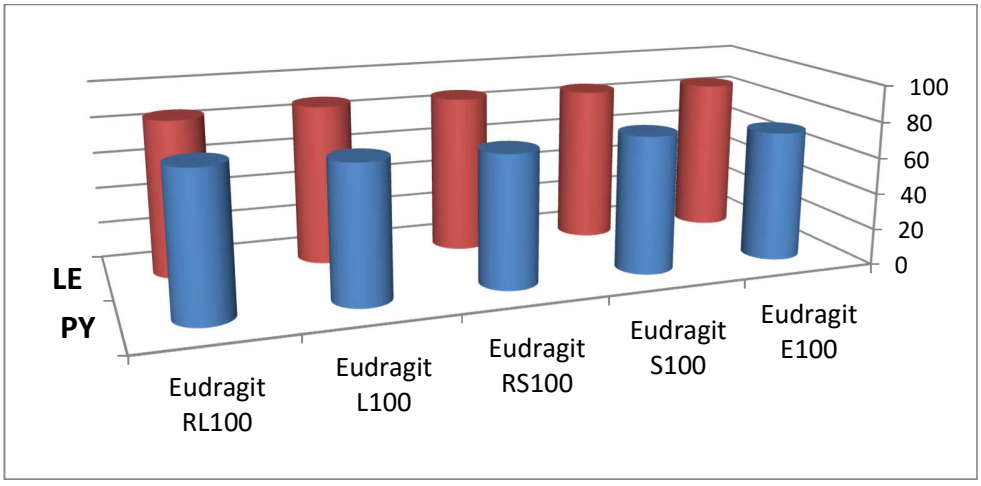


Figure (3): The effect of polymer type on the PY and LE of the prepared TEL SP.

Table (3): The Effect of Polymer Type on the PY and LE of the Prepared TEL SP.

Formula No.	Drug:polymer ratio	Internal phase					External phase		Stirring rate (rpm)	Stirring time (hr)	Drying Temp. (^{0}C)	PY (%) *	LE (%) *
		TEL (gm) *	Type of polymer	Polymer (gm)	DCM (ml) *	PVA (gm) *	Glycerol (ml)	Water (ml)					
F2	5:1	1	**Eudragit E100**	0.2	5	0.05	1	200	1000	1	40	**85**	**72**
F6	5:1	1	**Eudragit S100**	0.2	5	0.05	1	200	1000	1	40	**86**	**76**
F10	5:1	1	**Eudragit RS100**	0.2	5	0.05	1	200	1000	1	40	**87**	**73**
F14	5:1	1	**Eudragit L100**	0.2	5	0.05	1	200	1000	1	40	**88**	**75**
F18	5:1	1	**Eudragit RL100**	0.2	5	0.05	1	200	1000	1	40	**86**	**79**

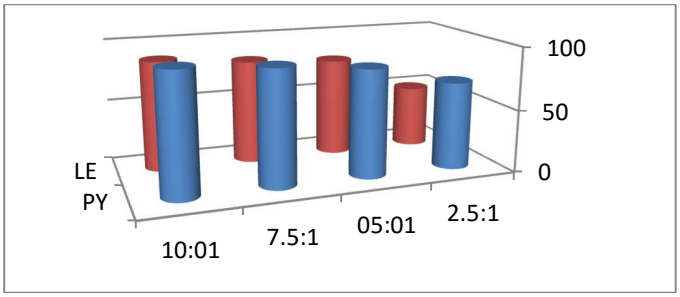
* TEL: telmisartan, DCM: dichloromethane, PVA: poly vinyl alcohol, PY: production yield, LE: loading efficiency.

Table (4): The Viscosity of Different Types of Eudragit Polymers.

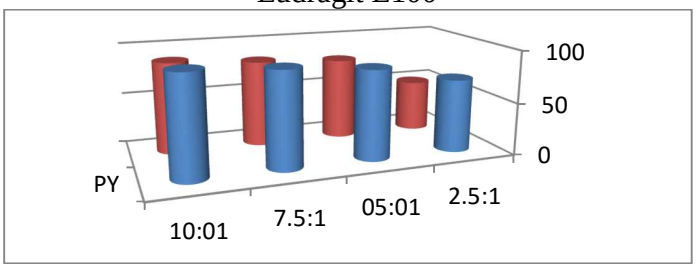
Polymer Type	Viscosity (Mpas)
Eudragit E100	3-12
Eudragit RL 100	1-15
Eudragit RS 100	1-15
Eudragit L100	50-200
Eudragit S100	50-200

Table (5): The Effect of Drug:polymer Ratio on the PY and LE of the Prepared TEL SP.

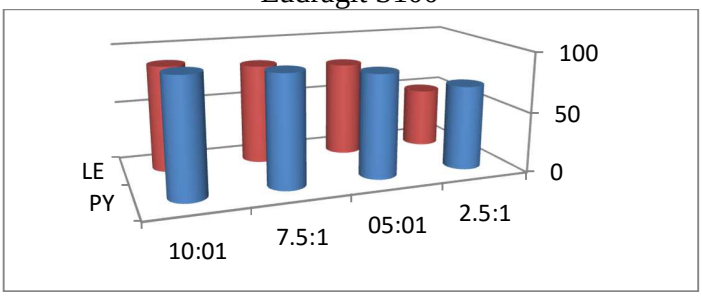
	Internal phase					External phase							
Formula No.	**Drug:polymer ratio**	**TEL (gm)**	**Type of polymer**	**Polymer (gm)**	**DCM (ml)**	**PVA (gm)**	**Glycerol (ml)**	**Water (ml)**	**Stirring rate (rpm)**	**Stirring time (hr)**	**Drying Temp. (^{0}C)**	**PY (%)**	**LE (%)**
F1	**2.5:1**	0.5	Eudragit E100	0.2	5	0.05	1	200	1000	1	40	**68**	**45**
F2	**5:1**	1	Eudragit E100	0.2	5	0.05	1	200	1000	1	40	**85**	**72**
F3	**7.5:1**	1.5	Eudragit E100	0.2	5	0.05	1	200	1000	1	40	**86**	**76**
F4	**10:1**	2	Eudragit E100	0.2	5	0.05	1	200	1000	1	40	**88**	**79**
F5	**2.5:1**	0.5	Eudragit S100	0.2	5	0.05	1	200	1000	1	40	**70**	**48**
F6	**5:1**	1	Eudragit S100	0.2	5	0.05	1	200	1000	1	40	**86**	**76**
F7	**7.5:1**	1.5	Eudragit S100	0.2	5	0.05	1	200	1000	1	40	**88**	**80**
F8	**10:1**	2	Eudragit S100	0.2	5	0.05	1	200	1000	1	40	**90**	**82**
F9	**2.5:1**	0.5	Eudragit RS100	0.2	5	0.05	1	200	1000	1	40	**70**	**50**
F10	**5:1**	1	Eudragit RS100	0.2	5	0.05	1	200	1000	1	40	**87**	**73**
F11	**7.5:1**	1.5	Eudragit RS100	0.2	5	0.05	1	200	1000	1	40	**89**	**80**
F12	**10:1**	2	Eudragit RS100	0.2	5	0.05	1	200	1000	1	40	**91**	**85**
F13	**2.5:1**	0.5	Eudragit L100	0.2	5	0.05	1	200	1000	1	40	**72**	**53**
F14	**5:1**	1	Eudragit L100	0.2	5	0.05	1	200	1000	1	40	**88**	**75**
F15	**7.5:1**	1.5	Eudragit L100	0.2	5	0.05	1	200	1000	1	40	**90**	**78**
F16	**10:1**	2	Eudragit L100	0.2	5	0.05	1	200	1000	1	40	**93**	**81**
F17	**2.5:1**	0.5	Eudragit RL100	0.2	5	0.05	1	200	1000	1	40	**70**	**50**
F18	**5:1**	1	Eudragit RL100	0.2	5	0.05	1	200	1000	1	40	**86**	**79**
F19	**7.5:1**	1.5	Eudragit RL100	0.2	5	0.05	1	200	1000	1	40	**92**	**83**
F20	**10:1**	2	Eudragit RL100	0.2	5	0.05	1	200	1000	1	40	**96**	**88**



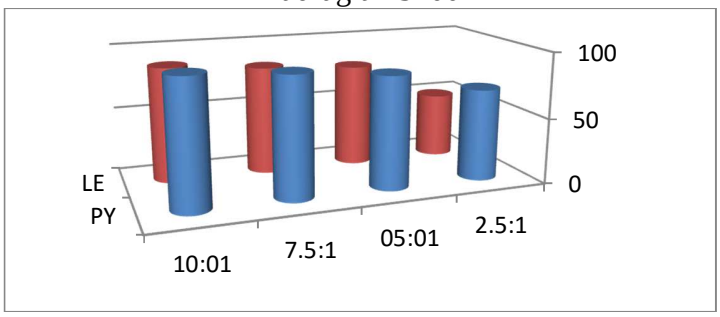
Eudragit E100



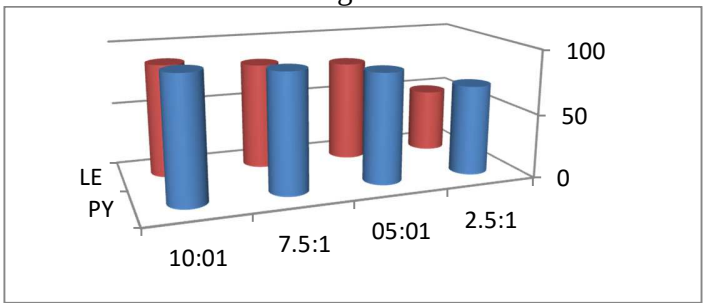
Eudragit S100



Eudragit RS100



Eudragit L100



Eudragit RL100

Figure (4): The PY and LE of various Eudragit polymers as a function of drug:polymer ratio.

In-vitro Drug Release Study of TEL SP Formulations

In vitro dissolution study in 0.1 N HCl (pH 1.2) was performed for all TEL SP formulas in addition to pure TEL and the brand tablet Micardis® 40 mg using USP dissolution test apparatus-I as shown in figure (5).

It was found that the best release profile among all the twenty formulations was that of the formula F2; therefore, it was selected as the best candidate for the future work.

The significantly improved surface area of the finely and molecularly dispersed TEL in the SP may be the principal factor responsible for their observed higher dissolution rates [(20)].

It is worth mentioning that the time for 75% release (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 [(13)]. The T 75% for all TEL SP formulas in 0.1 N HCl (pH 1.2) are listed in table (6). This table indicates that the TEL SP Formula (F2) showed faster release rate than both Micardis® and raw material. The T 75% of TEL SP capsule (formula F2) was 20 min in comparison to 30 min for Micardis® tablets. Regarding the pure TEL raw material, it did not approach 75% release at all.

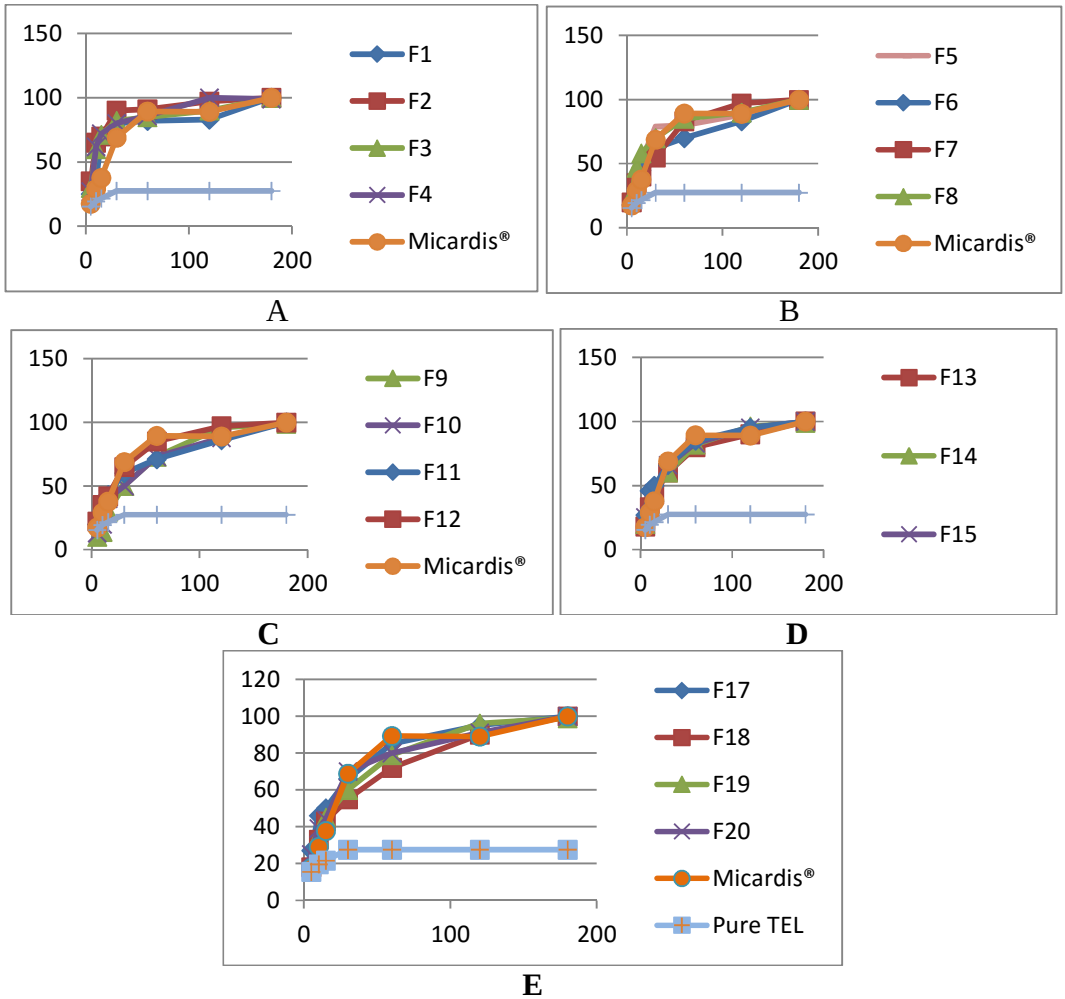


Figure (5): The release profile of TEL SP formulations, Micardis® and pure TEL raw material in 0.1 N HCl (pH 1.2) at 37± 0.5 ^{0}C. A: Eudragit E100, B: Eudragit S100, C: Eudragit RS100, D: Eudragit L100, E: Eudragit RL100.

Table (6): The Time for 75% Release for all TEL SP Formulas in 0.1 N HCl (pH 1.2)

Formulas	T 75% (min)
F1	23
F2	20
F3	21
F4	21
F5	25
F6	62
F7	40
F8	36
F9	62
F10	62
F11	62
F12	36
F13	52
F14	49
F15	45
F16	40
F17	65
F18	63
F19	55
F20	40
Micardis®	40
Pure TEL	Not accessible

Conclusion

The present work showed that the SP technique can be effectively used for preparation of oral capsule of practically insoluble drugs such as TEL. The TEL SP formulated with the Eudragit E100 at drug:polymer ratio of 5:1 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. It can also be concluded from this study that the release rate of the prepared formulas is directly related to the type and concentration of the polymer used.

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. C Omo˘Glu T., G¨On¨Ul N., Baykara T. (2002). The Effects of Pressure and Direct Compression on Tabletting of Microsponges. Int. J. Pharm. (242), 191–195.
2. 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.
3. Subramanian S, Singireddy A, Krishnamoorthy K, Rajappan M. (2012). Nanosponges: A Novel Class of Drug Delivery System-Review. J Pharm Pharm Sci. 15(1): 103-111.
4. 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.
5. Rowe R., Sheskey P., Quinn M. (2009). Handbook of Pharmaceutical Excipients. The Pharmaceutical Press. 6th Edition, 1-917.
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. Vatsal A., P. Chaudhari. (2012). Optimization and Evaluation of a Formulation Containing Low Soluble Antihypertensive Agent. Int J Curr Pharm Res. Vol 4, Issue 2, 37-41.
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. Saboji K., Manvi V., Gadad P., Patel D. (2011). Formulation and evaluation of ketoconazole microsponge gel by quasi emulsion solvent diffusion. Journal of cell and tissue research. 11(1): 2691-2696.

11. John D., Harinath M. (2008). Topical anti-Inflammatory gels of fluocinolone acetonide entrapped in Eudragit based microsponge delivery system. Res. J. Pharm. Tech. 1(4): 502-506.
12. Ganesan V., Kanth K. (2013) Preparation and In-vitro Evaluation of Microballoon Drug Delivery System of Telmisartan. IJPSDR. Vol 5, Issue 4 (141-145).
13. Ganesan V., Kanth K. (2013). Preparation and In-vitro Evaluation of Microballoon Drug Delivery System of Telmisartan. IJPSDR. Vol 5, Issue 4 (141-145).
14. USP 36- NF 31 (The United States pharmacopoeia), (2013). Electronic Edition.
15. 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.
16. Upadhyay R. (2011). Design & Evaluation of Aceclofenac Loaded Microsponge for topical Delivery. Kle. 1-10.
17. Subhash S., Vaghani S., Jivani P., Vasanti S., Satish S., Patel M. (2010). Preparation and characterization of 5- FU loaded microspheres of Eudragit and ethylcellulose. Acta Pharm Sciencia. 52: 391-9.
18. Subhash S., Vaghani S., Jivani P., Vasanti S., Satish S., Patel M. (2010). Preparation and characterization of 5- FU loaded microspheres of Eudragit and ethylcellulose. Acta Pharm Sciencia. 52: 391-9.
19. Jelvehgari M., Siahi R., Azarmi S., Gary P., Martin A. (2006). The microsponge delivery system of benzoyl peroxide: Preparation, characterization and release studies. International journal of pharmaceutical. 308:124-132.
20. Trotta F., Zanetti M., Cavalli R. (2012). Cyclodextrin-Based Nanosponges As Drug Carriers. Beilstein J. Org. Chem. 8, 2091–2099.