Formulation of telmisartan microsponge tablets and In-Vitro evaluation of dissolution profile

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ABSTRACT

Objective: The aim of this study is to formulate microsponge of telmisartan as a tablet dosage form and evaluate the release profile in comparing with Micardis® the marketed telmisartan..

Methods: Temisartan microsponge was prepared by quasi-emulsion solvent diffusion method by using polymers either Eudragite E or eudragite L in organic solution as internal phase and aqueous solution of polyvinyl povidone as external phase. Five formulations of microsponge temisartan tablet were prepared including formulation 3 which contains pure telmisartan by direct compression method. All formulations were evaluated for flowability characteristic and release profile in comparison with marketed tablet Micardis®.

Results: Telmisartan microsponge was successfully formulated without any interaction or in compatibility with Eudragite polymer. The flow properties of the microsponge powder were with acceptable limit. The wetting and disintegration time of F1, F2, F4 and F5 in microsponge system were decrease in comparison to the F3 which used plain telmisartan and Micardis® a conventional tablet. The superdisintegrants crospovidone 5% which represented in formula F4 and F5 gave the rapid disintegration time compared to the other formulas. The dissolution profile of the temisartan for all formulation and comparing to the Micardis tablet indicated the improvement of the dissolution rate by using microsponge system.

Conclusion: It was indicated that telmisartan microsponge was successfully formulated and their tablet formulations proved to show better release profile in all aspects as compared to marketed (Micardis®) tablet. Using of different super disintegrates have significant effect on wetting and disintegration time of telmisartan tablet.

ملخص البحث

إن الهدف من هذه الدراسة هو صياغة microsponge من تلميسارتان كشكل من أشكال الجرعة الدوائية وهي الاقراص وتقييم التحرر المائي له و مقارنتها مع®Micardis الاقراص التقليدية المتوفرة في السوق..

لقد تم التحضير بواسطة شبه مستحلب وهي طريقة نشر المذيبات باستخدام البوليمرات إما Eudragite E أو eudragite L في المحلول العضوية كوسط داخلي ومحلول مائي من البولي فينيل البوفيدون كوسط خارجي. تم إعداد خمسة تركيبات تلميسارتان بما في ذلك الصيغة(3) التي تحتوي على تلميسارتان النقي باستخدام طريقة الضغط المباشر. تم تقييم جميع التركيبات لسيولتها مميزة والتحرر المائي في مقارنة مع قرص .®Micardis

النتائج :تلميسارتان microsponge صيغت بنجاح دون أي تفاعل أو عدم توافق مع Eudragite البوليمر. وكانت خصائص تدفق مسحوق microsponge مع الحد المقبول. لقد اظهر وقت ترطيب وتفكك F1 ، F2، F4و F5في نظام microsponge انخفاضا بالمقارنة مع F3 التي تستخدم telmisartan عادي و ®Micardisقرص التقليدي. superdisintegrates crospovidone قد استخدمت في صيغة F4 و F 5 فأعطت وقت التفكك اسرع كمقارنة مع الصيغ الأخرى. التحلل المائي للتلميسارتان لجميع الصيغ ومقارنتها إلى قرص Micardis اظهرت تحسن سرعة الذوبان باستخدام نظام.microsponge

وكاستنتاج لقد اثبت أن microsponge تلميسارتان صيغت بنجاح وصيغ الاقراص أثبتت أفضل التحرر المائي عنه في جميع وانب بالمقارنة مع(®Micardis) . باستخدام مختلف تفكك السوبر كان لها تأثير كبير على ترطيب والتفكك وقت قرص تلميسارتان

INTRODUCTION

Temisartan is used for treatment of hypertension by blocking angiotensin II receptor. Following oral administration, the maximum plasma telmisartan concentration reached after approximately 1 hr and maximum plasma concentration increases disproportionately with dose(1). Its oral administration and the plasma half-life is about 24 hours (1). The pharmacokinetics of orally administered telmisartan is nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses (2). The drug is practically insoluble in water and shows pH dependent solubility. Telmisartan is insoluble in the pH range 3-9 and sparingly soluble in strong acids(2). For this reason oral absorption and bioavailability of the drug is dose dependent and is about 42 % following a 40 mg dose and 85 % following a 160 mg dose (2). Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity.

Microsponges are highly crosslinked, patented, porous, polymeric microspheres that acquire the flexibility to entrap a wide variety of active ingredients that are mostly used for prolonged topical administration and recently for oral administration. In oral drug delivery the microsponge system increase the rate of solubilization of poorly water soluble drugs by entrapping them in the small pores. As the pores are very small the drug is in effect reduced to microscopic particles and the

significant increase in the surface area thus greatly increase the rate of solubilisation (3, 4). Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, elegance, flexibility in formulation, reduce side effects and modify drug release profiles (3, 4).

MATERIALS AND METHODS

Materials

The materials used in this study are shown in table (1).

Table (1): Materials and their suppliers used in this study

	Materials	Supplier
1	Eudragit E100	Evonik Degussa Ltd, India Pvt. Ltd, Mumbai
2	Eudragit 100	Evonik Degussa Ltd, India Pvt. Ltd, Mumbai
2	Croscarmellose Sodium (CCS),	Samarra Drug Industries (SDI), Iraq
4	Telmisartan.	
5	Crospovidone (CP)	3B Pharmaceutical(Wuhan) International Co. Ltd. China
6	Mannitol	Himedia Laboratories PVT. Ltd. Mumbai, India.
7	Mg stearate	Riedel-De-Haen AG seelze, Germany

Instruments

Table 2 shows the instruments used in this study.

Instruments	Manufacturer
Electronic balance	**Denver Instrument, Germany**
Tablet machine	**TDP, China**
Ovens	**Gallenhamp (Compenstat) oven BS, England and Memmert Oven, W. Germany**
Hardness tester	**Stokes, Monsanto Co. Ltd., USA**
pH-meter	**Hanna Instrument, Italy**
Dissolution apparatus	**Minhua pharmaceutical machinery co.,ltd. RC-6D. China**
Disintegration apparatus	**Minhua pharmaceutical machinery co.,ltd. BJ-3. China**
Spectrophotometer	**Sco tech, spuv-26, Germany**
FTIR Spectrophotometer	**IR Prestige-21, Shimadzu, Japan**
DSC	**DSC-60. Shimadzu, Japan**

Table (2): Instruments and their manufacturers used in this study

Methods

Telmisartan calibration curve

A solution of 100 µg/ ml of telmisartan in 0.1 HCL (pH 1.2) was prepared as stock solution. From this stock solution, a dilute (0.03 mg/ml) solution was prepared and scanned by UV spectrophotometer at the range of 200-400 nm, in order to determine the wave length of maximum absorbance (λ max) of telmisartan.

A series dilution of 5, 4, 3, 2, 1 and 0.5 µg/ ml were prepared from the stock solution and analyzed spectrophotometrically at the determined λ max. The absorbance obtained were recorded and plotted against concentrations to obtain a calibration curve.

Formulation of telmisartan microsponge

The telmisartan microsponge formulations were prepared by quasi-emulsion solvent diffusion method (5). Firstly, the external phase (aqueous phase) containing 200 mg of PVA dissolved in 500

ml of distilled water was prepared with heating and continuous stirring and then the resulted solution was left to cool.

The internal phase (organic phase) containing 200 mg of (Eudragit E100 or Eudragit L 100) dissolved in 5ml of methanol was prepared. One milliliter of glycerol was added as plasticizer, then 1000 mg of pure temisartan powder was added to the organic phase (it should be freshly prepare). Meanwhile, the internal phase was added to external phase with continuous stirring at 1000 rpm for 1 hr. After that, filtration we preformed to collect the formed MS. Then the sample (on filter paper) was put in oven at 40 ċ for drying. This procedure was repeated three times.

Entrapment efficiency and production yield

Accurately weighed quantities of microsponges were kept in 0.1 N HCL buffer solution for sufficient time to liberate entrapped drug. Theoretical quantity of drug was calculated as a ratio of added drug amount to total amount of drug and additives. The entrapment efficiency can be calculated by equation (1) and the actual drug content in microsponge formulation can be calculated by equation (2)

Entrapment Efficiency (%) = M_{act} / M_{the} x 100 ……. (1)

Loading efficiency (%) = (M_{act} / M_{ms}) x 100 ……..(2)

Where M_{act} is the actual amount of telmisartan in weighed quantity of microsponges, M_{ms} is the weighed quantity of microsponges, and M_{the} is the theoretical amount of telmisartan in microsponges.

Evaluation of telmisartan microsponge formulation

Differential scanning calorimetry (DSC) provides information about the physical properties of the drugs and demonstrate a possible interaction between drug and other compounds in the microsponge. Fourier transform infrared spectroscopy (FTIR) of pure temisartan and physical mixture of temisartan and Eudragite E and L were recorded and compared with the spectrum available in official book.

Formulation of telmisartan microsponge tablet

Five formulations were prepared as shown in table 3. All formulation were prepared using direct compression technique. Each formula was formulated by mixing all the ingredients (except the

lubricant) for 15 minutes after which the lubricant was added and blended for another 1 minute. The final mixture was compressed using a 10-mm single- punch tablet machine**.**

Table 3: different formlations of telmisartan tablets

Amount of contents mg	**F1**	**F2**	**F3**	**F4**	**F5**
Eudragit L 100	53.3	-		53.3	-
Eudragit E 100	-	53.3	-	-	53.3
Telmisartan pure	-	-	40	-	-
C.C.S 5%	17.5	17.5	17.5	17.5	17.5
C.P 5%	-	-	-	17.5	17.5
Avecil 102	80	80	80	80	80
Manitol	195.7	195.7	209	178	178
Meg. S	3.5	3.5	3.5	3.5	3.5

Flowability study of the prepared powder

The tan of angle of repose (**θ**) was calculated after measuring the height (**H**) and fixed base diameter (D) of the cone of the powder utilizing equation (3) by employing Funnel method (6).

Tan (Ø) = H/ 0.5 X **D** **…… (3)**

The Carr's index was achieved by using equation 4. Where ($V_\circ$) represent the initial volume of powder poured into a volumetric cylinder and (V_f) represent the volume of the tapped powder in the cylinder. The compressibility index was calculated using equation 4:

Compressibility Index = $\frac{V\circ - Vf}{V\circ} \times 100$ …… (4)

Evaluation of the prepared tablets

Wetting time

A tablet was placed on the filter paper in the petri dish and the time required for the complete wetting of the tablet was recorded as a wetting time. The mean of three determinations was used ± SD

Hardness

The hardness test of three tablets from each formulation batch were randomly evaluated and the average reading ± SD was recorded, using Monsanto hardness tester in which the hardness was expressed as a force in kg/cm^2 required to crush the tablet (5).

In vitro disintegration test

The disintegration tests were done for all formulation as well as conventional tablet (Mecardis) by using the USP disintegration apparatus. The time in seconds required for complete passing of all fragment of the tablet is recorded as disintegration time of the tablet(6)

In vitro dissolution studies

In vitro dissolution studies were performed all formulations and conventional tablets by using type II (paddle) dissolution apparatus at 100 rpm, and 900 ml of HCL buffer pH (1.2) as a dissolution medium at 37°C ± 0.5°C (7). An aliquot of five ml of the dissolution medium was withdrawn at specific time intervals, and replaced with 5 ml of the buffer and the absorbance of filtered solutions was determined using UV-spectrophotometer and drug content was determined from a standard calibration curve.

RESULTS AND DISCUSSIONS

Telmisartan calibration curve

The UV spectrum of standard solution of telmisartan in 0.1 N HCL pH (1.2) showed a sharp peach of λ max 291 nm (8). The standard curve of telmisartan and their relating concentrations and absorbances were plotted. The method was found to be linear in the range of 5-0.5 µg/mL with a regression coefficient closed 0.999 as shown in figure 1. The slope of equation was found to be steady in all the developed methods.

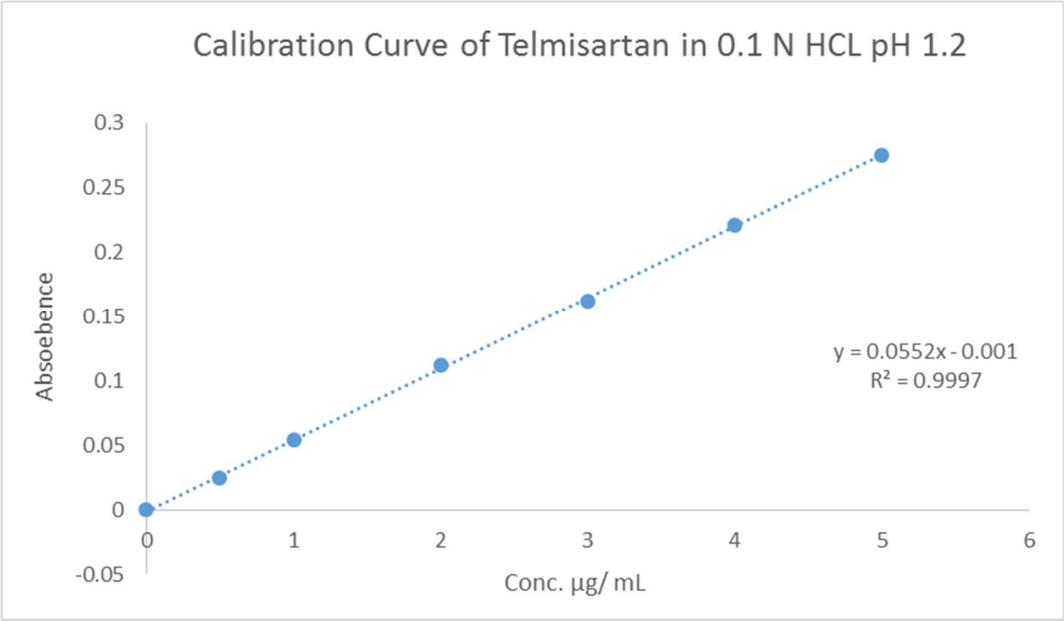


Figure 1 : Calibration curve of Telmisartan in 0.1 N HCL buffer solution at pH 1.2

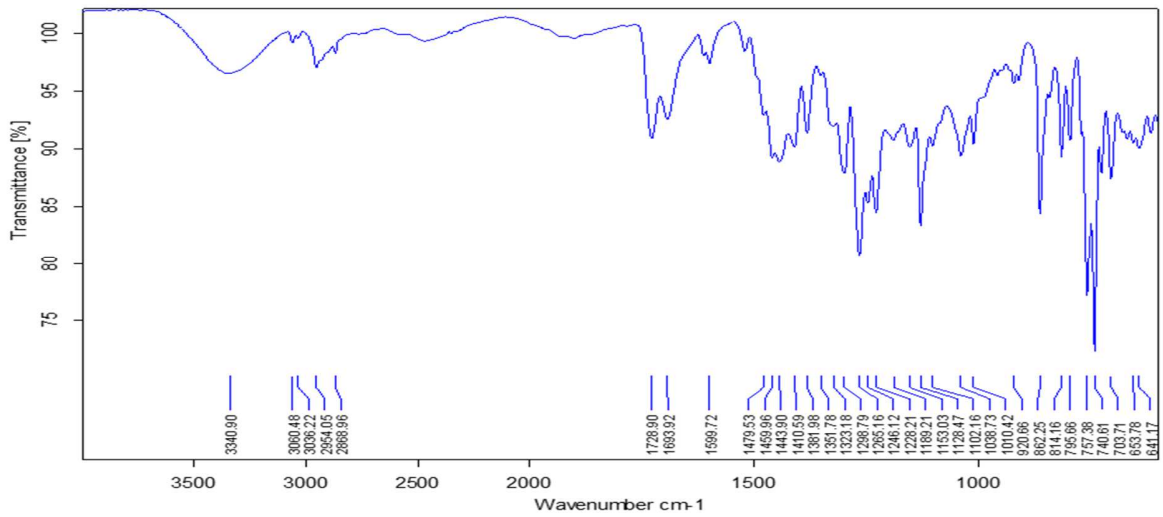
Evaluation of temisartan microsponge formulation

The quasi-emulsion solvent diffusion method used for the preparation of the microsponges was simple, reproducible, and rapid. Entrapment yield and loading efficiency of telmisartan microsponge formulation shows entrapment yield in the range of 82.35% for eudrogite E and 86.21% for eudrogite L and loading efficiency in the range of 75.25 to 76.39 % respectively.

The chemical stability or interaction of drug with Eudragite was evaluated by FTIR spectroscopy using KBr disc. The data in figure 2 indicates that there was no chemical interaction between the drug and Eudragite as all characteristic IR peaks related to pure drug, which were also appear in the IR spectrum of the formulas(9).

The DSC studies were achieved to prove that no interaction between the drug with Eudragite in microsponge. The DSC thermogram of temisartan (figure 3) showed sharp peak at 267 which is corresponding to the melting point of drug in crystalline form. This result indicated that the drug has crystalline nature with high purity(10).

A



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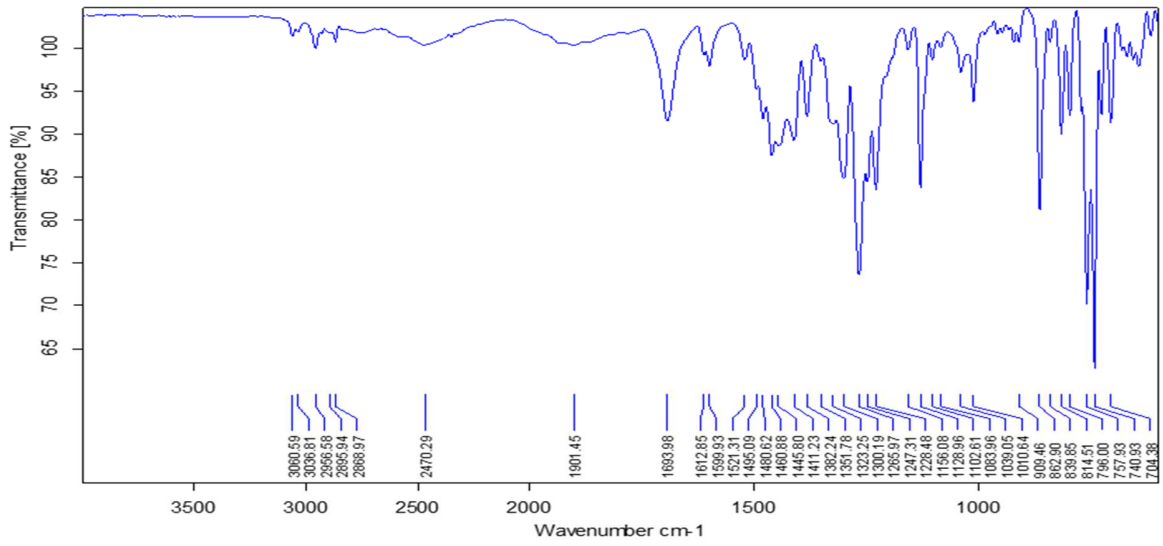
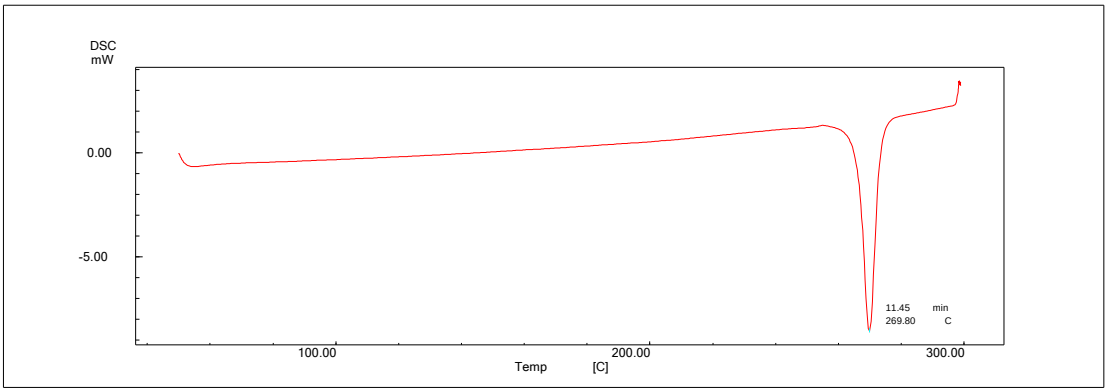
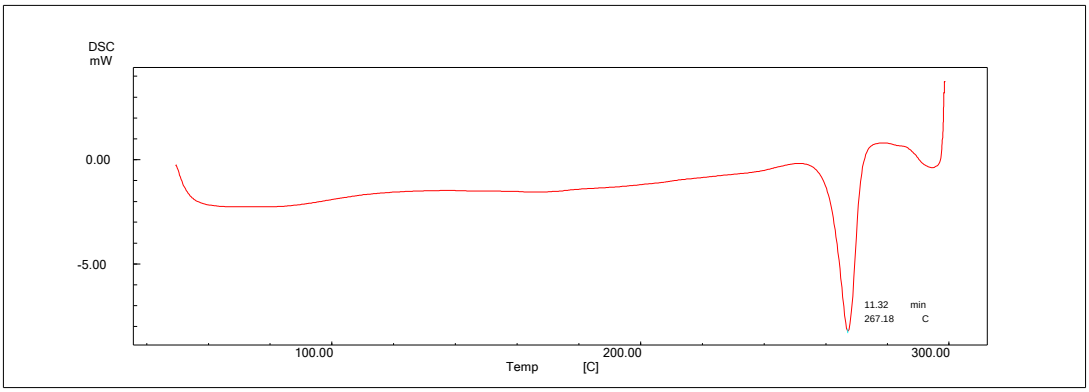


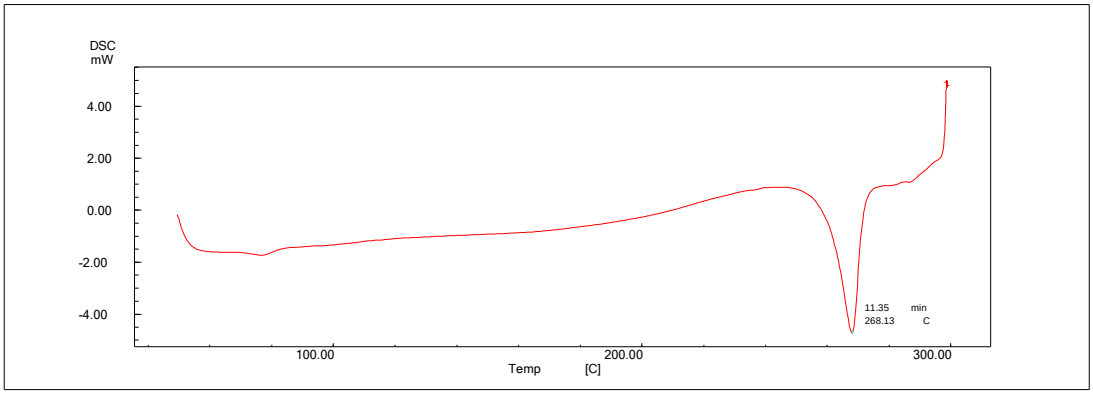
Figure (2) FTIR spectrum of telmisartan pure (A) and in microsponge (B)



(A) Pure telmisartan



(B) Microsponge



(C)Telmisartan. + Eudragite. (Physical Mix)

Figure 3 : DSC thermogram of telmisartan in pure (A), microsponge (B) and mixture (C)

Effect of microsponge formulation and superdisntigrants on the flowability of the prepared powders

Formulas of F (1-5) as illustrated in table 4 showed the effect of microsponge formulation with Eudregite E and L in the presence of different superdisintegrant types (CCS and CP) on the flowability of the prepared powders excluding F3 which represents the plain drug. The results of physical properties of the prepared powder had acceptable flow characters according to the Angle of repose value and Carr's index and there was no difference between the microsponge formulations with the F3. This result indicated that the microsponge formulation kept the powder flowability characteristics(4).

Table (4): Angles of repose, carr's index and flow properties of the prepared powders.

Formula no	Angle of repose	Carr's index	Flow character
F_1	30	21	Good and passable
F_2	29.1	18.2	Good and fair
F_3	25.2	18.8	Good and fair
F_4	27.3	23	Good and Passable
F_5	28	19.1	Good and Fair

Effect of microsponge formulation and superdisintegrents on the disintegration and wetting time of tablets.

Figure 4 shows the wetting and disintegration behaviour of the telmisartan microsponge tablets in water. It was observed that the formulation of microsponge system has significant reduce in wetting and disintegration time in regarding to the pure one F3 while in the presence of super disintegrants CP in F4 and F5 the wetting and disintegration time were less than in F1 and F2 where the superdisntigrent was CCS. Micardis, a conventional tablet, which showed a delay in the wetting and disintegration time.

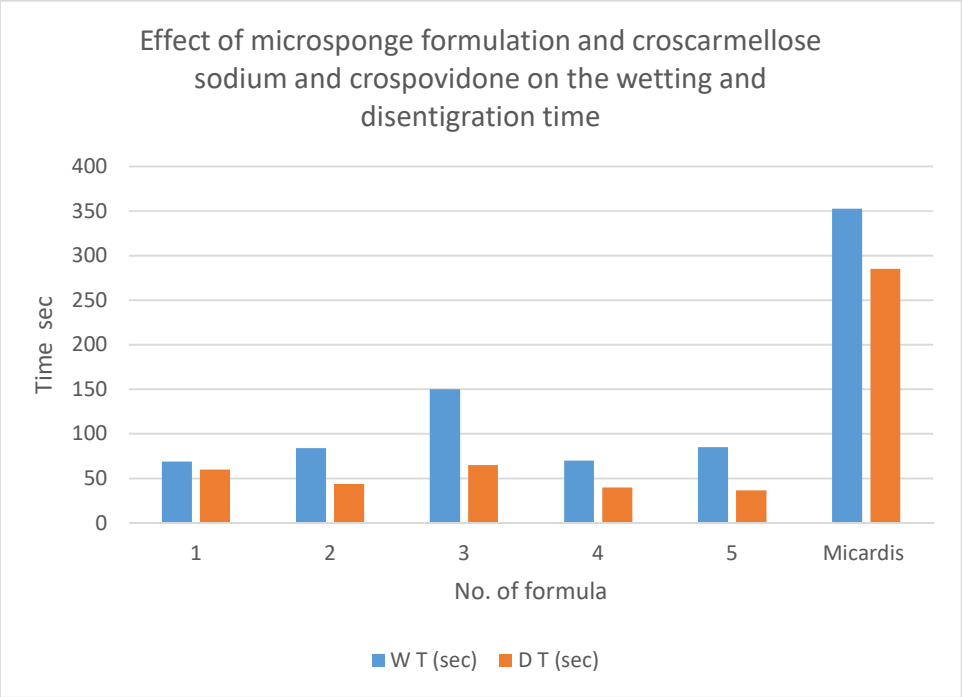


Figure 4 : wetting and disintegration time of temisartan microsponge and Micardis® tables

These results indicated that the microsponge system and superdisintegrent plays a major role in the dissolution and disintegration of the tablets.Superdisintegrants provide rapid disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of superdisintegrants, the wetted surface of the carrier increases, this promotes the wettability of the system, thus enhancing the disintegration and dissolution(11).

In vitro dissolution of telmisartan study

The release profile obtained for microsponge formulation in comparison with pure temisatan and Micarcidis ® tablets is presented in figure 5. It was observe that the release of temisartan was improved with microsponge formulation in respect to the pure one in F3. There was also improvement in the release time in respect to the Micardis a conventional tablet. These results rationalize the importance of the microsponge formulation due to increase of the surface area of the drug which will increase of dissolution rate(12, 13).

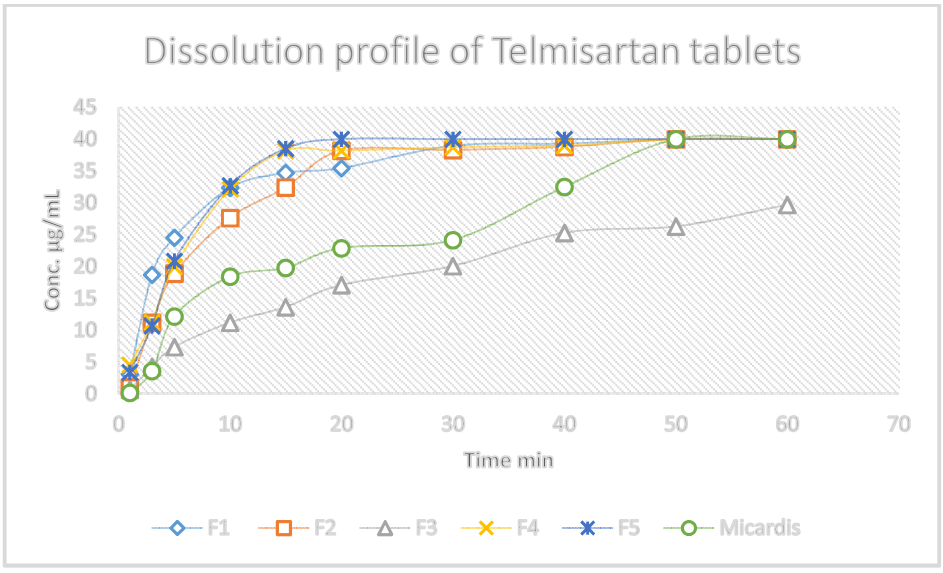


Figure (5): The dissolution profile of the microsponge, the plain telmisartan and (Micardis ®) tablets in HCL buffer at 37ºC ± 0.5 ºC and 100 rpm.

Conclusion

Temisartan microsponge formulation tablets were successfully formulated with an acceptable limit of flow characters. The microsponge system has a significant effect on the wettability and disintegration time of tablets. A conclusion can be drown from this results that the type of supedisintigrant with microsponge system has a synergism effect on the wetting and disintegration time. As comparison study of dissolution rate was significantly affected by microsponge formuation system to plain or Micardis® the marketed one.

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