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Original Article

# Formulation and evaluation of controlled-release of telmisartan microspheres: *In vitro/in vivo* study

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ARTICLE INFO

*Article history:*
Received 15 October 2013
Received in revised form
2 May 2014
Accepted 12 May 2014
Available online 8 August 2014

*Keywords:*
Microsphere
Release kinetics
Solvent evaporation
Telmisartan

ABSTRACT

The aim of this work was to design a controlled-release drug-delivery system for the angiotensin-II receptor antagonist drug telmisartan. Telmisartan was encapsulated with different EUDRAGIT polymers by an emulsion solvent evaporation technique and the physicochemical properties of the formulations were characterized. Using a solvent evaporation method, white spherical microspheres with particle sizes of 629.9–792.1 μm were produced. The *in vitro* drug release was studied in three different pH media (pH 1.2 for 2 hours, pH 6.8 for 4 hours, and pH 7.4 for 18 hours). The formulations were then evaluated for their pharmacokinetic parameters. The entrapment efficiency of these microspheres was between 58.6% and 90.56%. The obtained microspheres showed good flow properties, which were evaluated in terms of angle of repose (15.29–26.32), bulk and tapped densities (0.37–0.53 and 0.43–0.64, respectively), Carr indices and Hausner ratio (12.94–19.14% and 1.14–1.23, respectively). No drug release was observed in the simulated gastric medium up to 2 hours; however, a change in pH from 1.2 to 6.8 increased the drug release. At pH 7.4, formulations with EUDRAGIT RS 100 showed a steady drug release. The microsphere formulation TMRS-3 (i.e., microspheres containing 2-mg telmisartan) gave the highest $C_{max}$ value (6.8641 μg/mL) at 6 hours, which was three times higher than $C_{max}$ for telmisartan oral suspension (TOS). Correspondingly, the area under the curve for TMRS-3 was 8.5 times higher than TOS. Particle size and drug release depended on the nature and content of polymer used. The drug release mechanism of the TMRS-3 formulation can be explained using the Higuchi model. The controlled release of drug from TMRS-3 also provides for higher plasma drug content and improved bioavailability.



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http://dx.doi.org/10.1016/j.jfda.2014.05.001

## 1. Introduction

The maintenance of drug content at the site of action is the primary concern with any formulation design. Some conventional dosage forms can provide poor management of plasma drug concentrations. Drug-level fluctuations due to frequent administration and variations in their absorption and/or metabolism can result in toxic effects or render the drugs ineffective [1,2]. These problems can be resolved by designing new drug-delivery systems that can provide steady-state plasma concentrations of the drug(s) administered. Recently, extensive efforts have been dedicated to developing controlled-release drug-delivery systems. Another advantage of controlled-release drug delivery is enhancement of commercial value of the product by increasing its patent life. These dosage forms are designed to release the drug constantly over an extended period [1].

Controlled drug delivery by encapsulating the drug inside polymeric carriers has made great progress in last two decades as it can enhance the drug release and decrease adverse effects [3–6] by drug localization at the site of action and by controlling the drug release [7]. Moreover, entrapment inside the polymers can also shield the sensitive drugs (e.g., peptides/proteins) from chemical and enzymatic decomposition. Microspheres developed using biodegradable polymers are widely used to achieve controlled release of drugs [8,9]. The chief advantage of using biodegradable polymers is that after performing their tasks they break down in a biologically friendly manner.

Several microencapsulation techniques have been developed for this purpose; however, the appropriateness of such techniques depends on the nature of the drug/polymer. The most suitable microencapsulation techniques are emulsion solvent evaporation, phase separation, interfacial polymerization, and spray drying. Of these methods, emulsion solvent evaporation is the method of choice for microencapsulation of water-insoluble drugs using a water-insoluble polymer [4,10,11].

Telmisartan is a nonpeptide angiotensin-II receptor (type AT1) antagonist. It blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin-II by selectively blocking its binding to the AT1 receptor in adrenal gland and smooth muscles of vasculature. Following oral administration, peak concentrations ($C_{max}$) of telmisartan are achieved in the 1$^{st}$ hour. The bioavailability of orally administered telmisartan is nonlinear (20–160 mg) [12,13].

The rationale behind this study was to prepare the microspheres of telmisartan encapsulated in EUDRAGIT polymers to control the release of this highly base-soluble drug. EUDRAGIT RS 100 and EUDRAGIT RL 100 are water-insoluble, pH-independent polymers, whereas EUDRAGIT S 100 is a pH-dependent polymer [14]. In addition, the drug-release kinetics for the formulations developed were also evaluated.

## 2. Materials and methods

Telmisartan was obtained for IPCA (Ratlam, Madhya Pradesh, India). The polymers EUDRAGIT RS 100, EUDRAGIT RL 100, and EUDRAGIT S 100 were obtained from Evonik Degussa India Pvt. Ltd. (Saki Naka, Mumbai, India). Sodium lauryl sulfate (SLS), disodium hydrogen phosphate, potassium dihydrogen phosphate, and polyvinyl alcohol (PVA) were obtained from CDH (New Delhi, India). Analytical grade chloroform, sodium hydroxide, methanol, hydrochloric acid, and sodium chloride were procured from Merck Ltd. (Mumbai, India)

### 2.1. Preparation of microspheres (emulsion solvent evaporation method)

Suitable amounts of polymer were added to a chloroform solution of the drug. The aqueous phase was prepared by dispersing 0.2% PVA (polyvinyl alcohol) in water. The drug–polymer solution was added to the aqueous phase with constant mixing. The mixture was stirred with a propeller at 500 rpm for 3 hours at 25°C for complete removal of chloroform. The mixture was filtered to collect the microspheres, which were then washed with deionized water (Fig. 1). These microspheres were dried at room temperature for 24 hours [14–18]. The compositions of the different formulations are shown in Table 1 and the steps involved in their production are illustrated in Fig. 1.

### 2.2. Characterization

#### 2.2.1. Drug entrapment efficiency, drug loading, and drug yield

Microspheres (25 mg) were dissolved in 25 mL methanol and the resulting solution was filtered. The filtrate was diluted and analyzed for drug content [19,20] using the following equations:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Actual loading}}{\text{Theoretical loading}} \times 100 \quad (1)$$

$$\text{Drug loading (\%)} = \frac{\text{Weight of drug in microspheres}}{\text{Weight of microsphere}} \times 100 \quad (2)$$

$$\text{Yield (\%)} = \frac{\text{Weight of microsphere}}{\text{Total expected weight of drug and polymer}} \times 100 \quad (3)$$

Drug loading, percentage yield, and the drug encapsulation efficiency for all batches are presented in Table 1.

#### 2.2.2. Micromeritic studies of microspheres

Micromeritic studies of microspheres were performed as described earlier [21].

2.2.2.1. *Angle of repose*. The fixed funnel method was used for estimating the angle of repose for different formulations [11], ($n = 3$).

$$\theta = \tan^{-1}(h/r) \quad (4)$$

where $\theta$ is angle of repose, $r$ is the radius, and $h$ is the height.

2.2.2.2. *Bulk density and tapped density*. Microspheres (5 g) were added into a 5-mL graduated cylinder and the final

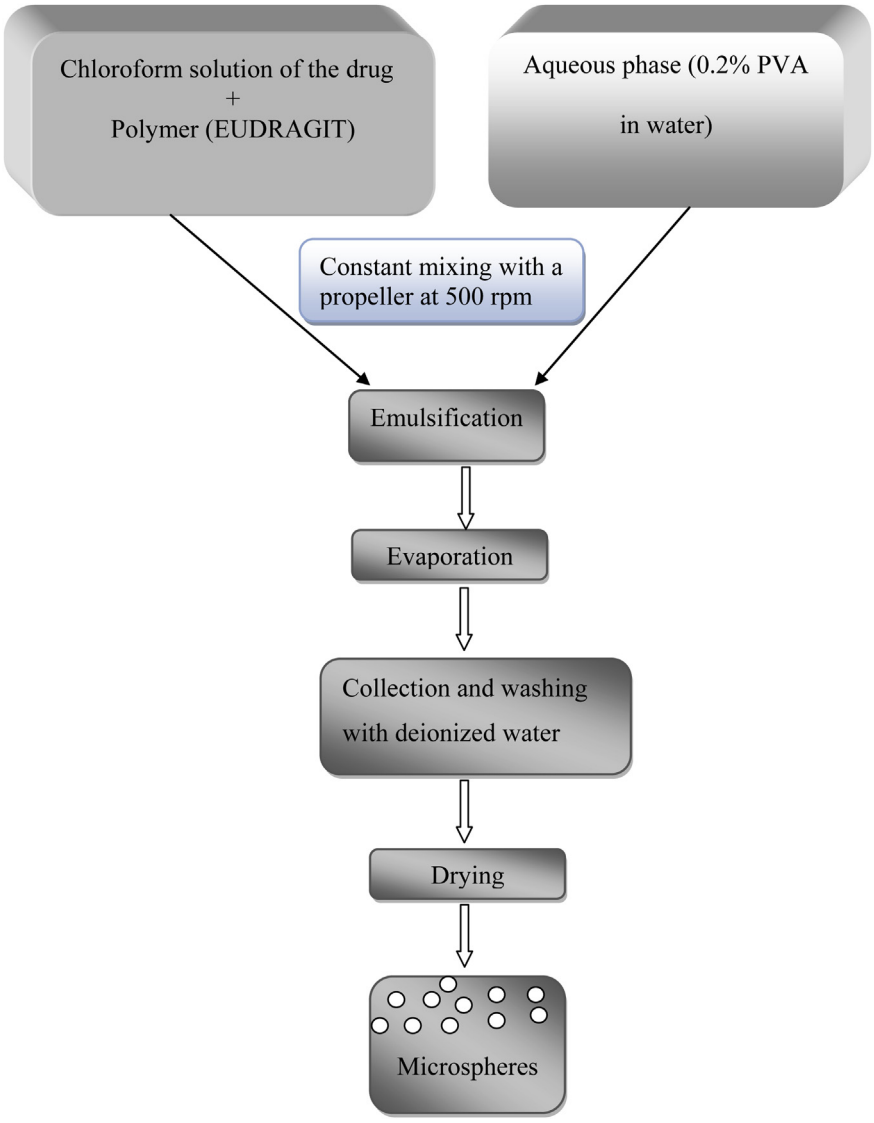


**Fig. 1 – Production of microspheres by the emulsion solvent evaporation technique.**

**Table 1 – Percentage yield, percentage loading, and encapsulation efficiency of telmisartan microspheres.**

| S. no. | Formulation code | Drug:polymer ratio | Theoretical loading (%) | Actual drug loading (%) | Encapsulation efficiency (%) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | TMS-1 | 1:1 | 50.00 | 29.3 ± 1.37 | 58.6 ± 0.42 | 76.3 |
| 2 | TMS-2 | 1:2 | 33.33 | 21.50 ± 1.1 | 64.50 ± 1.3 | 74.8 |
| 3 | TMS-3 | 1:3 | 25.00 | 18.49 ± 1.2 | 73.96 ± 1.5 | 80.3 |
| 4 | TMRL-1 | 1:1 | 50.00 | 29.48 ± 0.83 | 58.96 ± 1.61 | 68.7 |
| 5 | TMRL-2 | 1:2 | 33.33 | 20.37 ± 1.22 | 61.11 ± 0.33 | 84.9 |
| 6 | TMRL-3 | 1:3 | 25.00 | 17.64 ± 1.3 | 70.56 ± 0.81 | 77.5 |
| 7 | TMRS-1 | 1:1 | 50.00 | 33.26 ± 1.82 | 66.52 ± 1.03 | 81.4 |
| 8 | TMRS-2 | 1:2 | 33.33 | 25.43 ± 1.52 | 76.29 ± 0.53 | 87.3 |
| 9 | TMRS-3 | 1:3 | 25.00 | 22.64 ± 0.96 | 90.56 ± 0.26 | 92.5 |

All data are expressed as mean ± standard deviation; $n = 3$.
TMRL = telmisartan + EUDRAGIT RL 100; TMRS = telmisartan + EUDRAGIT RS 100; TMS = telmisartan + EUDRAGIT S 100.

volume was noted down to calculate bulk density ($D_b$). The cylinder was then tapped mechanically 100 times to obtain the tapped volume for computing the tapped density ($D_t$) [16,22].

2.2.2.3. *Carr's index*. Carr index [23] and Hausner ratio [24] were calculated using following equations:

$$\text{Carr index} = (D_t - D_b) \times 100/D_t \quad (5)$$

$$\text{Hausner ratio} = D_t/D_b \quad (6)$$

### 2.2.3. *Particle-size analysis*

The sizes of the microspheres were determined using an optical microscope (Olympus, Tokyo, Japan) fitted with an ocular micrometer. The ocular micrometer was calibrated with a stage micrometer. A total of 100 microspheres were evaluated and the mean diameter was reported. The average particle size for each formulation ($n = 3$) is presented in Table 2.

### 2.2.4. *Scanning electron microscopy*

Scanning electron microscopy (SEM) was used for determining the surface morphology (JEOL JSM 5800; JEOL, Tokyo, Japan). The microspheres were fixed in slabs and coated with gold/palladium using a sputter coater. The SEM image of the TMRS-3 (i.e., microspheres containing 2-mg telmisartan) formulation is shown in Fig. 2.

### 2.2.5. *Determination of drug amount using high-performance liquid chromatography assay*

Drug content was determined by high-performance liquid chromatography (HPLC) using an LC-10ATVP HPLC pump, an SIL-10AF auto injector, an SPD-10A UV/Vis detector, and an SCL-10A VP system controller (all from Shimadzu, Kyoto, Japan). A Shim-pack VP-ODS (4.6 mm i.d. × 150 mm) packed with an adsorbent (5-μm; Shimadzu) was eluted with acetonitrile/methanol (60:40, v/v) isocratically. The elution was performed at 1.0 mL/minute using a sample volume of 20 μL. The UV detector was set at 296 nm for detection [2]. A linear correlation was achieved between drug content and peak area at 2–40 ng/mL (drug concentration). The equation describing the calibration curve for telmisartan was $y = 26{,}966x - 49{,}352$ ($R^2 = 0.999$), where $x$ is the concentration and $y$ is the peak area.

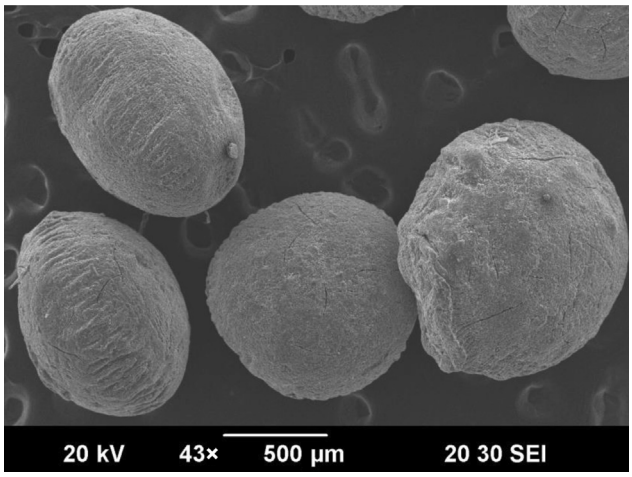


**Fig. 2 – Scanning electron microscopy image of the TMRS-3 formulation. SEI = secondary electron imaging; TMRS-3 = microspheres containing 2-mg telmisartan.**

### 2.2.6. *In vitro dissolution study*

The drug-release study was carried out in the USP dissolution apparatus II using 100 mg of the formulation at 37° ± 0.5°C. For simulation of physiological conditions, the study was carried out at three different pH conditions, namely, at pH 1.2 (simulated gastric fluid) and 6.8 and 7.4 (simulated intestinal fluid) [25].

Initially, the microspheres were treated with 900 mL of 0.1N (pH 1.2) hydrochloric acid containing 0.01% SLS for 2 hours [4]. After 2 hours, 25.92 g disodium hydrogen phosphate and 10.305 g dihydrogen potassium phosphate were added to increase the pH to 6.8 and the drug-release study was continued for another 4 hours. After the 6 hours, 2.142 g disodium hydrogen phosphate and 0.171 g sodium chloride were again added in order to increase the pH up to 7.4 and the study was continued for up to 24 hours [19,22,26]. The samples were withdrawn at suitable intervals and replaced with fresh medium. The aliquots were suitably diluted and drug content was determined by HPLC.

**Table 2 – Micromeritic properties of telmisartan microspheres.**

| Formulation code | Angle of repose (°) | Bulk density (g/mL) | Tapped density (g/mL) | Carr index | Hausner ratio | Particle size (μm) |
|---|---|---|---|---|---|---|
| TMS-1 | 26.32 ± 0.49 | 0.52 ± 0.02 | 0.61 ± 0.02 | 14.12 ± 0.21 | 1.17 ± 0.01 | 752.9 ± 4.9 |
| TMS-2 | 22.43 ± 0.91 | 0.53 ± 0.04 | 0.64 ± 0.02 | 18.18 ± 0.9 | 1.2 ± 0.03 | 769.3 ± 8.3 |
| TMS-3 | 22.19 ± 0.93 | 0.46 ± 0.02 | 0.54 ± 0.01 | 17.32 ± 0.8 | 1.2 ± 0.02 | 792.1 ± 6.3 |
| TMRL-1 | 19.45 ± 0.34 | 0.51 ± 0.01 | 0.60 ± 0.03 | 15.13 ± 0.95 | 1.17 ± 0.05 | 702.4 ± 7.3 |
| TMRL-2 | 20.43 ± 0.84 | 0.37 ± 0.05 | 0.43 ± 0.04 | 14.2 ± 1.3 | 1.16 ± 0.02 | 730.7 ± 4.8 |
| TMRL-3 | 23.89 ± 0.45 | 0.49 ± 0.03 | 0.57 ± 0.02 | 15.1 ± 1.01 | 1.16 ± 0.03 | 757.3 ± 6.5 |
| TMRS-1 | 15.98 ± 0.93 | 0.43 ± 0.03 | 0.53 ± 0.03 | 19.14 ± 1.03 | 1.23 ± 0.03 | 629.9 ± 7.3 |
| TMRS-2 | 18.39 ± 0.48 | 0.39 ± 0.06 | 0.45 ± 0.04 | 15.15 ± 1.3 | 1.15 ± 0.02 | 653.3 ± 4.5 |
| TMRS-3 | 15.29 ± 0.89 | 0.53 ± 0.09 | 0.60 ± 0.01 | 12.94 ± 1.1 | 1.14 ± 0.02 | 686.2 ± 5.8 |

All data are expressed as mean ± standard deviation; $n = 3$.
TMRL = telmisartan + EUDRAGIT RL 100; TMRS = telmisartan + EUDRAGIT RS 100; TMS = telmisartan + EUDRAGIT S 100.

#### 2.2.7. *In vivo studies*

The experimental protocol for *in vivo* drug permeation study was prepared and approved by the Institutional Animal Ethics Committee. Male albino rats (Wistar strain; average age, 6–8 weeks; average weight, 200 g) were housed in polypropylene cages under standard laboratory conditions with free access to food and water. The animals were divided into the following three groups (telmisartan dose, 10 mg/kg):

Group I = no treatment (control group)
Group II = telmisartan oral suspension (TOS)
Group III = TMRS-3 formulation

Suitable blood samples were removed at predetermined time intervals and processed for plasma separation [27–30]. The drug content was determined by HPLC assay.

### 2.3. *Release kinetics*

Data obtained from *in vitro* release studies were fitted to various kinetics equations (zero-order, first-order, and Higuchi models) to find out the mechanism of drug release from microspheres. The rate constants were also calculated for the respective models [31].

### 2.4. *Data and statistical analysis*

All data were presented as mean ± SD. Statistical analysis was performed using the GraphPad Prism Version 4 software (GraphPad Software, Inc., La Jolla, CA, USA). Analysis of variance or the paired *t* test was used as appropriate for statistical analysis, and the statistical significance was set at $p < 0.05$.

## 3. Results

### 3.1. *Micromeritic studies of microspheres*

White, spherical, and free-flowing microspheres were produced using the solvent evaporation method. The percentage yield varied from 68.7% to 92.5%, with the highest yield obtained for TMRS-3. The results show that increase in polymer ratio increases product yield.

It has been reported that higher molecular weight polymers show better precipitation of polymer at the boundary phase of the droplets owing to the increase of hydrophobicity [32]. Mean particle size has been shown to increase with increasing polymer concentration, which could be due to increase in relative viscosities.

All the formulations were free flowing as indicated by the angle of repose value less than 30°. The values of bulk and tapped densities have shown good packing ability. The values of Carr indices were 12.94–19.14% with the lowest $C_i$ value for TMRS-3, indicating its excellent compressibility. The Hausner ratio for the formulations was in the range of 1.14–1.23, showing their good flow properties.

After considering various micromeritic parameters, it can be inferred that TMRS-3 is the best formulation having the best flow properties with low angle of repose value (15.29°), lowest Carr index (12.94%), and low Hausner ratio (1.14).

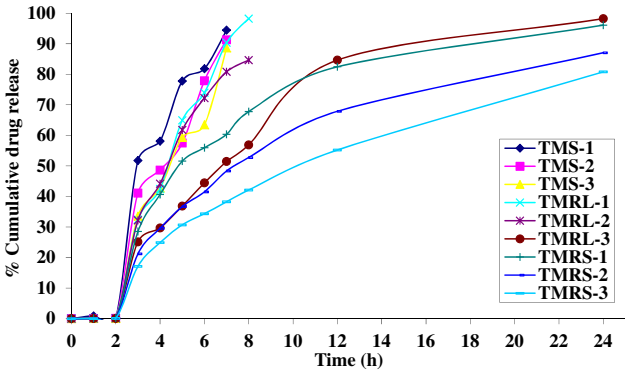


**Fig. 3 – *In vitro* release profile of microspheres (TMS, TMRL, and TMRS formulations) at different pH conditions (1–2 hours at pH 1.2; 3–6 hours at pH 6.8; and 7–24 hours at pH 7.4). TMRL = telmisartan + EUDRAGIT RL 100; TMRS = telmisartan + EUDRAGIT RS 100; TMS = telmisartan + EUDRAGIT S 100.**

### 3.2. *Drug-release behavior*

The drug-release behavior was studied up to 24 hours, simulating the physiological conditions using simulated gastric fluid (0.1N HCl, pH 1.2) and simulated intestinal fluid (pH 6.8 and 7.4). All the formulations showed negligible amounts of drug in the simulated gastric fluid; however, a change in the medium shows a difference in drug release. Further change in pH from 6.8 to 7.4 results in constant drug release up to 24 hours (Fig. 3).

### 3.3. *In vivo studies*

TMRS-3 was selected based on the physicochemical parameters and evaluated for *in vivo* permeation against TOS. The $C_{max}$ for TMRS-3 was three times more than that of TOS when

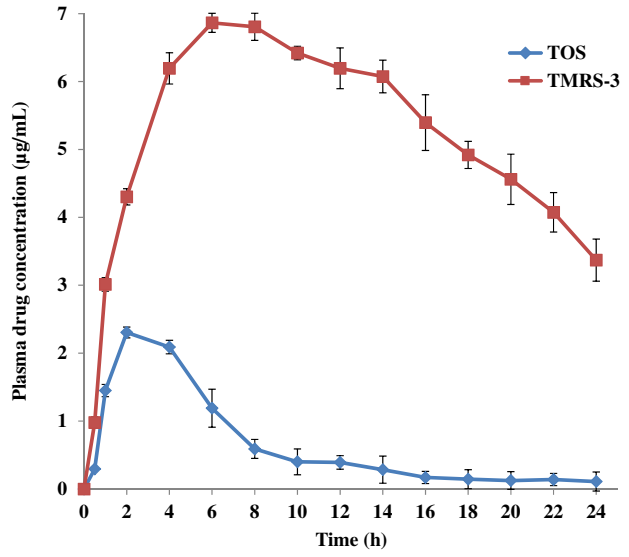


**Fig. 4 – Plasma drug concentration profiles of TOS and TMRS-3. TMRS-3 = microspheres containing 2-mg telmisartan; TOS = telmisartan oral suspension.**

**Table 3 – $C_{max}$, $t_{max}$, and $AUC_{0\rightarrow24}$ values for TOS and TMRS-3 formulations.**

| Formulation code | $C_{max}$ (μg/mL) | $t_{max}$ (h) | AUC (μg h/mL) |
|---|---|---|---|
| TOS | 2.305 ± 0.08 | 2 | 15.86 ± 0.98 |
| TMRS-3 | 6.8641 ± 0.14 | 6 | 127.6 ± 1.73 |

All data are expressed as mean ± standard deviation; $n = 6$; ($p \leq 0.05$).
AUC = area under the curve; TMRS-3 = microspheres containing 2-mg telmisartan; TOS = telmisartan oral suspension (10 mg/kg).

administered at equivalent doses. The corresponding $t_{max}$ was modified from 2 to 6 hours (Fig. 4). TMRS-3 had the highest plasma drug content, which was reflected by its higher bioavailability (TMRS-3 had 8.5 times more bioavailability than TOS; Table 3).

### 3.4. *Release kinetics*

The drug-release mechanism was studied by comparing the respective correlation coefficients for different release models (Table 4). It was observed that the drug release was diffusion controlled in the TMRS formulation.

## 4. Discussion

The microspheres were formulated using different grades of EUDRAGIT polymers, which vary in molecular weight and the resulting viscosities as well as in behavior at different pH values. Based on these results, it can be inferred that as the drug polymer ratio increases, product yield also increases.

The actual drug loading increased with an increase in theoretical drug loading. It has been reported that as the molecular weight of the polymer increases, its hydrophobicity also increases, thereby leading to better precipitation of polymer at the boundary phase of the droplets; however, the molecular weights for EUDRAGIT RS 100 and RL 100 were the same. The difference lies in their behavior when they come in contact with water. EUDRAGIT RL 100 has more permeability than EUDRAGIT RS 100.

Particle-size distribution is affected by the interaction between the dispersed phase and the dispersion medium. In our study, the mean particle size increases with the increase in polymer concentration due to increase in relative viscosity.

All the formulations have shown free-flowing nature with good packability. The formulations having 1:1 drug-to-polymer ratio demonstrated enhanced release properties. The maximum drug release was for TMS-1 (telmisartan + EUDRAGIT S 100), whereas the minimum drug release was for TMRS-3. The drug release was decreased with increase in polymer content. This could be explained based on particle-size distribution. Increase in polymer content increases particle size, which subsequently decreases the effective surface area. In addition, the path length traveled by the drug molecule is also increased. The formulation containing EUDRAGIT RS 100 showed the slowest drug release, because it is the least permeable polymer due to the presence of less quaternary groups than that in EUDRAGIT RL 100. By contrast, EUDRAGIT S 100 dissolves at and above pH 7 as it is a pH-dependent polymer. The study also shows the drug release at pH 6.8 from EUDRAGIT S 100, which may be due to the pore formation after swelling of the polymer.

The efficiency of the selected formulation (TMRS-3) was evaluated in rats for *in vivo* parameters because an *in vivo* study in humans is not a practical option. However, animal studies can give a realistic assumption of drug content in the living system. Controlled drug release from TMRS-3 can also provide for maximal absorption of telmisartan in the tissues.

The release mechanism was studied by comparing the values of correlation coefficients, and the drug release was found to be controlled by diffusion of drug through the microsphere matrix (TMRS formulation). The Higuchi model was found to be the best fitted for drug release from telmisartan microspheres of TMRS formulations.

## 5. Conclusion

Telmisartan microspheres were formulated and evaluated for drug release in simulated physiological conditions. The selected formulation was evaluated in rats for *in vivo* drug absorption. It was observed that the content of the polymer manipulates the physical parameters along with the drug-

**Table 4 – Release kinetic studies of telmisartan microspheres.**

| Formulation code | Zero-order model | Higuchi model | | First-order model | *Korsmeyer–Peppas* model | |
|---|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $K_H$ (release rate constant) | $R^2$ | $n$ (release exponent) | $R^2$ |
| TMS-1 | 0.9647 | 0.9621 | 33.284 | 0.93 | 1.6654 | 0.9351 |
| TMS-2 | 0.967 | 0.9446 | 29.238 | 0.8939 | 1.9404 | 0.9532 |
| TMS-3 | 0.9522 | 0.9366 | 26.714 | 0.8588 | 1.102 | 0.9674 |
| TMRL-1 | 0.9835 | 0.9863 | 29.897 | 0.8364 | 1.0751 | 0.9217 |
| TMRL-2 | 0.9615 | 0.9794 | 27.714 | 0.9709 | 1.0273 | 0.9133 |
| TMRL-3 | 0.8626 | 0.9356 | 19.834 | 0.9877 | 0.7116 | 0.9505 |
| TMRS-1 | 0.9098 | 0.9907 | 21.654 | 0.9892 | 0.7159 | 0.8991 |
| TMRS-2 | 0.919 | 0.9918 | 17.698 | 0.9849 | 0.6716 | 0.9481 |
| TMRS-3 | 0.9576 | 0.9953 | 15.103 | 0.9813 | 0.5605 | 0.9729 |

TMRL = telmisartan + EUDRAGIT RL 100; TMRS = telmisartan + EUDRAGIT RS 100; TMS = telmisartan + EUDRAGIT S 100.

release pattern of the microsphere. We obtained good yields of microspheres with adequate encapsulation efficiency, with the highest for TMRS-3. The particle size increased with increase in polymer content.

The release kinetic study has shown that drug release from telmisartan microspheres (TMRS formulations) follows the Higuchi model as the drug release occurs by diffusion.

The formulations have shown good drug release in simulated intestinal medium, which is the desired medium for drug absorption. In addition, the release continues at a constant rate in this medium.

## Conflicts of interest

All contributing authors declare no conflicts of interest.

## Acknowledgments

We are very thankful to IPCA (Ratlam, Madhya Pradesh, India) and Evonik Degussa India Pvt. Ltd. (Saki Naka, Mumbai, India) for their generosity in providing the samples of the drug telmisartan and EUDRAGIT polymers. The authors also thank I.T.S. Paramedical College (Pharmacy), Ghaziabad (Uttar Pradesh, India) for providing the adequate facility to carrying out this work.

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