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ORIGINAL ARTICLE / ÖZGÜN MAKALE

PREPARATION AND EVALUATION OF COMPRESSION-COATED TABLETS FOR CHRONOPHARMACEUTICAL DRUG DELIVERY

KRONOFARMASÖTİK İLAÇ TAŞIYICI BASINÇLA KAPLANMIŞ TABLETLERİN HAZIRLANMASI VE DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: *This study aims to prepare and evaluate time-controlled drug delivery system of telmisartan. Telmisartan has low aqueous solubility, which is its major drawback. The solubility of the drug enhanced by using solid dispersion method and compression coated chronotherapeutic tablets were formulated.*
Material and Method: *Solid dispersion of telmisartan was prepared by melting method. Direct compression method was used to prepare telmisartan containing core tablets and tablets were coated by compression-coating method. Prepared tablets were characterized in terms of hardness, diameter, and thickness. In order to demonstrate the pulsatile release, the tablets were subjected to USP Apparatus II dissolution test.*
Result and Discussion: *Solid dispersion of telmisartan increased the solubility of telmisartan significantly ($p<0.05$). Compression-coated tablets were obtained with suitable hardness values (149.833±5.862-205.367±3.955 N) and telmisartan was released with lag times of 120-540 min which are suitable for chronopharmaceutic application.*
Keywords: *Chronopharmaceutical, compression-coated, pulsatile release, solid dispersions, telmisartan*

ÖZ

Amaç: *Bu çalışmada telmisartanın çözünürlüğünün artırılması için katı dispersiyonlarının hazırlanması amaçlanmıştır. Telmisartanın en önemli sorunu olan düşük çözünürlüğe sahip olmasıdır. Telmisartanın çözünürlüğü katı dispersiyon yöntemi kullanılarak artırılmış ve basınçla kaplanmış kronoterapötik tabletler formüle edilmiştir.*
Gereç ve Yöntem: *Telmisartanın katı dispersiyonları eritme yöntemi ile hazırlanmıştır. Telmisartan katı dispersiyonlarını içeren çekirdek tabletler doğrudan basım yöntemi ile hazırlanmış ve basınçla*

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kaplama yöntemi ile kaplanmıştır. Hazırlanan tabletler sertlik, çap ve kalınlık açısından karakterize edilmiştir. Tabletlerde pulsatil ilaç salımını göstermek amacıyla USP aparat II çözünme hızı testi yapılmıştır.

Sonuç ve Tartışma: *Telmisartan katı dispersiyonları telmisartanın çözünürlüğünü önemli ölçüde artırmıştır ($p<0,05$). Basınçla kaplanmış tabletler uygun sertlik değerleri (149.833±5.862-205.367±3.955 N) ve elde edilmiştir. Telmisartan, kronofarmasötik uygulamalara uygun şekilde 120-540 dk arasında değişen gecikme sürelerinden sonra hızla salınmıştır.*

Anahtar Kelimeler: *Basınçla kaplama, katı dispersiyon, kronofarmasötik, pulsatil salım, telmisartan*

INTRODUCTION

Circadian rhythm, which is a 24-hour clock related to the sleep-wake cycle, controls the rhythmicity of the biological systems. Biological disorders such as asthma, arthritis, duodenal ulcer, cancer, cardiovascular diseases, diabetes, and hypercholesterolemia can be influenced by circadian rhythm. As a result, they can display daily peaks and troughs [1]. Therefore, certain drug concentrations are required at the site of action at times appropriate to the circadian rhythm [2,3].

Some functions of cardiovascular system like blood pressure, heart rate, stroke volume are associated with circadian rhythm [4]. Capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. In other words, blood pressure is at its lowest during sleep and progressively rises during the early morning hours [2,4,5]. Hence, according to the circadian rhythm of the body, antihypertensive drugs are required in the early hours of the morning [6]. Considering the diseases which have some night or morning symptoms, more effective therapies can be achieved with modified release drug delivery systems [4] rather than conventional systems which release the drug right after the applications [2]. Pulsatile release drug delivery systems are thought to be suitable for chronotherapeutic purposes in order to achieve therapeutic drug concentrations at the time which the symptoms of the diseases arise by bedtime administration of drugs [4]. Pulsatile drug delivery systems, which are synchronized with the circadian rhythm of disease states and body functions, release the drugs immediately like a pulse after a lag time in which no or less than 10% of drug release occurs [2,7]. In this context, by bedtime administration, pulsatile drug delivery systems release the drug after a lag time and show their effects when the symptoms begin, and so keep the patients from unnecessary drug exposure and interruption of night's sleep due to the requirement of night-time dosing [8].

Telmisartan (2-(4-{[4-methyl-6-(1-methyl-1*H*-1,3-benzodiazol-2-yl)-2-proply-1*H*-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid) which is a widely used antihypertansive drug belongs to the group of angiotensin II type 1 (AT1) receptor antagonists. However, its low and variable bioavailability after oral administration due to its poor and pH dependent solubility is the major obstacle about telmisartan [9].

Among various other methods including micronization/nanonization, complexation or co-crystals, solid dispersion is one of the most efficient and successful solubility enhancement methods [10]. Solid dispersions are one-phase solid systems that comprising polymeric carrier in which the drug is incorporated [11,12]. In the solid dispersion method, the solubility of the drug is enhanced by altering the crystalline structure to an amorphous state with higher energy [13]. Solid dispersions can be constructed as binary or ternary systems. Binary solid dispersions compose of carrier and drug while ternary systems contain some excipients like surfactants, super disintegrants and, pH modifiers to enhance the solubility and stability of drug [14,15]. pH modifiers are vital components because of that solubility of two-thirds of water soluble active ingredients depends on pH [16]. It is suggested that pH modification of dosage forms can be a good strategy to enhance the solubility of drugs whose solubility are dependent on pH [17]. The solubility of telmisartan is significantly dependent on pH; it is insoluble in acidic mediums but spontaneously soluble in alkaline mediums [18,19], due to its free acid form [17,20]. Therefore, incorporating an alkalizer into telmisartan solid dispersions for changing microenvironmental pH can enhance the solubility of telmisartan, and subsequently minimize the supersaturation in the microenvironment can inhibit drug recrystallization and precipitation, improve solubility, dissolution rate, as well as oral bioavailability of telmisartan [20,21].

The aims of this study were i) to enhance the solubility of telmisartan through the formation of solid dispersion systems, ii) for administration at bedtime, to design pulsatile telmisartan tablets using compression coating method for delayed drug delivery that starts in the morning hours, when symptoms appeared.

MATERIAL AND METHOD

Materials

Telmisartan was obtained from Auctus Pharma Limited, Madhapur-Hyderabad. Poloxamer 188, sodium alginate (SA), hyroxypropyl methylcellulose (HPMC) 100 mPa.s were received from Sigma Aldrich, USA. HPMC 4000 mPa.s was supplied from Fluka, USA and cellulose acetate propionate (CAP) from Aldrich Chemistry, UK. Sodium carbonate was obtained from Riedel-de Haen AG, Seelze-Hannover. Avicel pH 102 and talc were provided from Aklar Kimya, Ankara-Turkey. Crosscarmellose sodium was supplied from JRS Pharma, Rosenberg, Germany and magnesium stearat was from Molychem, Mumbai-India.

Preparation of Solid Dispersions

The solid dispersions were prepared by a modified melting method (Table 1). Poloxamer 188 was melted at 60ºC, above the polymer's melting point and sodium carbonate was added to the molten polymer. After the molten polymer and alkali source were mixed homogeneously telmisartan was added and mixed with magnetic stirrer at 100 rpm for 45 minutes until it became a homogenous mixture. The homogenous mixture was cooled to room temperature to obtain a solid mass and the solidified masses were crushed and passed through 60 mesh sieve/ 250 µm microplate sieve.

Table 1. Composition of solid dispersions

Solid Dispersions	Ratios (telmisartan : poloxamer 188 : sodium carbonate)	Telmisartan (mg)	Poloxamer 188 (mg)	Sodium Carbonate (mg)
SD1	1:9:0	200	1800	-
SD2	1:9:1.5	200	1800	300
SD3	1:9:3	200	1800	600
SD4	1:6:1.5	200	1200	300
SD5	1:6:3	200	1200	600

Determination of Solubility of Pure Telmisartan and Solid Dispersions

The solubility examinations were performed according to the previously described shake flask method [22]. An excess amount of telmisartan, physical mixture, or solid dispersions was added to volumetric flasks containing 10 ml of phosphate buffer pH 7.5 and incubated in an orbital shaker at 100 rpm at 37ºC for 48 hours. Then the content was filtered through 0.45µm filter paper and analyzed at 295 nm with a UV-visible spectrophotometer after appropriate dilutions with phosphate buffer. All measurements were carried out in triplicate. The calculation of drug was performed using the calibration curve which was constructed by plotting the absorbance versus 2.5 to 20 ppm concentrations of telmisartan.

Preparation of Core Tablets

The core tablets were prepared by the direct compression method (Table 2). The ingredients except for talc and magnesium stearate were weighed and mixed for 5 minutes. Talc and magnesium stearate were added to the mixture and mixed for additional 5 minutes. The acquired mixture was compressed using a hydraulic press and 7 mm flat punches under 50 bar pressure for 20 sec.

Table 2. Core tablet formulations

Formulation Code	Telmisartan (mg)	Telmisartan Physical Mixture (mg)	Telmisartan Solid Dispersion (mg)	Avicel pH 102 (mg)	Cross-carmellose Sodium (mg)	Magnesium Stearate (mg)	Talc (mg)	Total (mg)
C1	10	-	-	131	6	1.5	1.5	150
C2	-	100*	-	41	6	1.5	1.5	150
C3	-	-	100*	41	6	1.5	1.5	150

* Equals to 10 mg telmisartan.

Preparation of Compression-coated Tablets

The prepared core tablets were subjected to compression coating using various compositions given in Table 3. The compression-coated tablets were prepared using a hydraulic press and 10 mm flat punches. 140 mg, half of the coating powder (CAP or blends of CAP and HPMC or SA) was filled to the die cavity to make a powder bed and the core tablet was manually placed in the center of the coating powder bed. The remaining half of the coating powder was then poured into the die and compressed at 50 bar for 20 sec.

Table 3. Coating layer compositions

Coating Layer	Formulation Code									
	CCT I	**CCT II**	**CCT III**	**CCT IV**	**CCT V**	**CCT VI**	**CCT VII**	**CCT VIII**	**CCT IX**	**CCT X**
CAP (mg)	280	252	210	140	252	210	140	252	210	140
SA (mg)	-	28	70	140	-	-	-	-	-	-
HPMC (100) (mg)	-	-	-	-	28	70	140	-	-	-
HPMC (4000) (mg)	-	-	-	-	-	-	-	28	70	140

Determination of the Physical Characteristics of the Tablets

Prepared tablets were characterized for hardness, thickness and diameter. The hardness of the core and coated tablets was measured by using Pharma Test hardness tester (model PTB 311, Key, Englishtown, NJ).

In vitro Drug Release Studies for Core and Compression-coated Tablets

In vitro drug release studies of the core and compression-coated tablets were carried out in 900 ml of pH 7.5 phosphate buffer at 37±0.5ºC at 75 rpm using USP dissolution apparatus II as described in USP 36. At specific time points, 5 ml of dissolution medium was withdrawn and replaced with a fresh dissolution medium. Withdrawn aliquots were filtered through 0.45 µm filter paper and analyzed at 295 nm with a UV-visible spectrophotometer. All measurements were carried out in triplicate.

Differential Scanning Calorimetry Studies

Thermal characteristics of telmisartan, poloxamer 188, sodium carbonate, their binary and ternary physical mixtures, as well as binary and ternary solid dispersions, were investigated by differential scanning calorimeter (DSC 60 with software of TA/60 WS, Shimadzu, Japan). Samples of about 2 mg were placed in sealed aluminum pans and heated under a nitrogen flow up to 300ºC, at the heating rate of 10ºC/min.

RESULT AND DISCUSSION

The focus of this study was to develop compression-coated tablets to obtain an immediate

telmisartan release when the highest blood pressure was seen in the early mornings, imitating the circadian cycle of the body after a lag time. For this reason, solid dispersion of telmisartan, a water-insoluble weak acidic drug, was prepared in order to increase the solubility. Then the core tablets containing telmisartan solid dispersion were compression-coated with CAP as the outer layer of coating agent and HPMC or SA as pore-forming agents in order to achieve pulsatile drug release for chronotherapy in hypertension.

Determination of Solubility of Free Telmisartan and Solid Dispersions

In the current study, solid dispersions which include different amounts of poloxamer 188 as carrier with or without the different amounts of sodium carbonate as alkalizer were prepared by melting method, as can be seen in Table 1.

Solubility profiles of the pure telmisartan and drug from SDs are presented in Figure 1. It is seen that the solubility of telmisartan is increased by approximately between 5.7 and 451.2 times in SD formulations with poloxamers 188 and sodium carbonate in comparison with pure drug. The SD containing poloxamers 188 and sodium carbonate in ratio 1:9:3 (SD3 coded solid dispersion) had the highest, while only Poloxamers 188 (SD1 coded formulation) had the lowest solubility of drug, respectively.

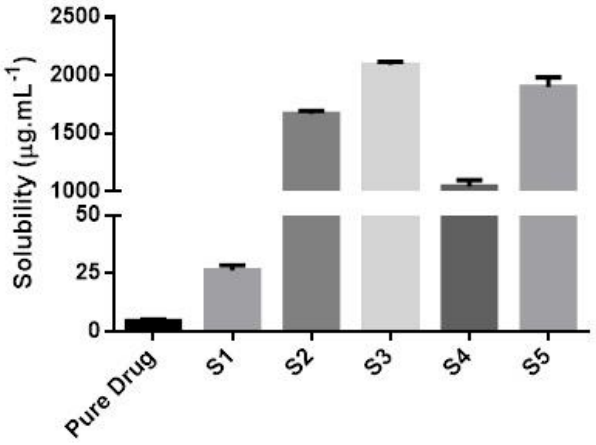

Figure 1. Solubility of pure telmisartan and telmisartan solid dispersions

These considerable differences between binary and ternary solid dispersions have shown that sodium carbonate played a crucial role in the solubilization of telmisartan and increasing amount of sodium carbonate for the same amount of poloxamer has enhanced solubility of telmisartan by changing the pH of the solid dispersion to alkali values. But surprisingly for the same amount of sodium carbonate, increased amount of poloxamer 188 has not significantly improved the solubility of telmisartan. According to these results SD5 which contains telmisartan: poloxamer 188: sodium carbonate 1:6:3 has showed the most promising solubility and so it has been selected for further experiments.

Determination of the Physical Characteristics of the Tablets

The hardness of tablets is the result of bonds between excipients and drug, and this network is formed by compression force during tableting. Moreover, lubricants reduce the friction between the dye and punches to allow smooth tableting with a reduced mechanical strength. Therefore, the hardness of core tablets which include magnesium stearate and talc as lubricant were lower than compression-coated tablets. On the other hand, the thickness and diameter values of all tablets meet the requirements (Table 4).

Table 4. Characterization of core tablets and compression-coated tablets

Formulation	Hardness (N)	Thickness (cm)	Diameter (cm)
C I	158.767±8.467	0.288±0.003	0.706±0.001
C II	56.700±3.517	0.327±0.003	0.704±0.001
C III	62.950±2.475	0.293±0.003	0.703±0.003
CCT I	195.433±2.281	0.475±0.005	1.004±0.001
CCT II	205.367±3.955	0.465±0.005	1.005±0.001
CCT III	179.467±7.132	0.455±0.005	1.005±0.001
CCT IV	149.833±5.862	0.443±0.003	1.010±0.002
CCT V	180.211±4.171	0.410±0.004	1.003±0.002
CCT VI	176.492±6.358	0.408±0.005	1.005±0.001
CCT VII	174.981±4.302	0.407±0.005	1.005±0.001
CCT VIII	178.973±5.180	0.425±0.004	1.002±0.001
CCT IX	179.209±3.129	0.424±0.005	1.005±0.002
CCT X	174.087±6.071	0.421±0.003	1.004±0.001

In vitro Drug Release Studies for Core and Compression-coated Tablets

Core Tablets

Core tablets were prepared with pure telmisartan, physical mixture and solid dispersion of telmisartan, and their dissolution profiles are given in Figure 2.

Telmisartan release from C1- and C2-coded formulations was found to be only 22.747% ± 1.292 and 56.323% ± 0.688, respectively. On the other hand, C3-coded formulation which contains solid dispersion of telmisartan demonstrated almost 100% drug release within the first 45 minutes, due to the enhanced aqueous solubility of telmisartan as a result of ternary solid dispersion. Hence, C3 formulation was selected as core tablet for further experiments.

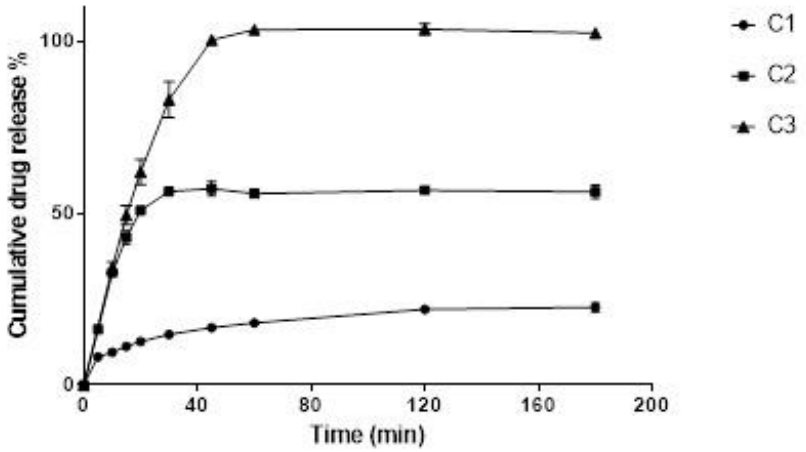

Figure 2. *In vitro* dissolution profiles of core tablets

Compression-coated Tablets

Pulsatile drug delivery systems can achieve chronotherapeutic purposes by mimicking the timing of the body. Being one of the pulsatile drug delivery strategies, compression-coated tablets consist of a core tablet which is made up of active ingredient and excipients and outer layer which determinate the

lag time and release profile according to its content that can be rupturable, swellable or erodible polymers [23,24].

The biggest advantage of these oral time-controlled drug delivery systems is providing a lag time after medication so that patient can benefit from drugs when the symptoms starts to arise special times in circadian cycle, especially diseases like cardiovascular diseases or asthma [25].

A variety of coating material can be used for compression-coating and according to these materials, drug release mechanisms change: rapture coating, swelling/eroding coating and permeation/diffusive coating [1,7,8,26]. Erodible coatings consist of hydrophilic polymers, for example HPMC, hydroxyethylcellulose and hydroxypropylcellulose, which go through swelling, dissolution and/or erosion when exposed to aqueous media and provide modified release of drug from the core. In rupture coating, delayed release of active ingredient is provided by disruption of the coating consisted of mixture of water insoluble polymeric material and water soluble materials as pore-forming agents. Disruption of the coating can be achieved by an adequate increase in core volume or hydration of the swellable polymers in the mixture of coating material together with insoluble polymer [8,26].

In this work, for compression-coating, CAP has been used as the main rupturable, eroding polymer and different grades of HPMC and SA have been used as pore-forming, swellable polymers and the effect of formulation of outer shell consisted of these hydrophobic and more hydrophilic polymers on the lag time and following drug release were investigated.

Cellulose esters are significant parts of the development of new drug delivery technologies due to their low toxicity, endogenous and/or dietary decomposition products, stability, film strength, compatibility with many of drugs, and ability to form micro- and nanoparticles [27].

CAP, a biodegradable and water-insoluble polymer [28] is used as an enteric coating material in capsules and tablet formulations. CAP can be used for coating with organic or aqueous solvent systems or for direct compression [29].

HPMC is a cellulose derivative approved by FDA and has been commonly used as a pharmaceutical additive for various purposes, especially in oral controlled drug delivery systems. HPMC is also a suitable compression-coating material for timed-release systems because of that the swelling upon contact with water and forming a hydrogel behavior of HPMC can control drug diffusion tightly [30]. SA is a hydrophilic polymer which has erodible properties. The erosion property of SA in coating layer leads to breakdown of coating [31]. Swellable polymers, like HPMC, have a crucial role in pulsatile drug delivery systems being either an erodible coating barrier or swelling force to break up rupturable coating layer [26].

The compression-coated tablets showed different release profiles with clear lag times followed by different release phases depending on coating layer compositions. Incorporation of pore-forming agents into coating layer resulted in release profiles with different lag times and release phases. Therefore, incorporation of HPMC or SA in CAP coating layer modulated the lag time and drug release profiles.

It can be a reason for extended lag time that HPMC and SA may form a viscous gel around CAP [32] and drug release from compression-coated tablets started when the outer shell took off by dissolution or erosion of the hydrophilic gel layer formed by HPMC or SA on the surfaces of core tablets [33].

The incorporation of the hydrophilic polymers (both SA and HPMC) into the coating layer contributed to the release of telmisartan. CCT I-coded tablet formulation which contained only CAP as coating agent did not show any telmisartan release while all other formulations which contained different amounts of SA or HPMC released telmisartan after variable lag times without premature release.

CCT II-IV, tablet formulations containing SA, demonstrated pulsatile release of telmisartan after different lag times depending on SA ratio in the coating layer. As can be seen in Figure 3 increased ratio of SA in the coating layer decreased the lag time due to hydration of the coating layer by the hydrophilic characteristic of SA [34]. CCT II-coded tablet with the lowest SA content showed the highest lag time prior to sustained telmisartan release whereas CCT III and IV showed faster drug release within 2 hours.

The mean lag time of the compression-coated tablets containing both HPMC-100 and HPMC-4000 decreased with increase in HPMC concentration from 10% to 25% but increased for 50% level (Figure 4 and 5). This initial decrease in mean lag times up to 25% concentration may be attributed to the dominating pore-forming properties, while further increase to 50% w/w was the consequence of

increased gelling properties of HPMC. During dissolution process, the coating layers which consist of 50% HPMC became elastic as a result of dominated gelling properties over pore-forming properties [35].

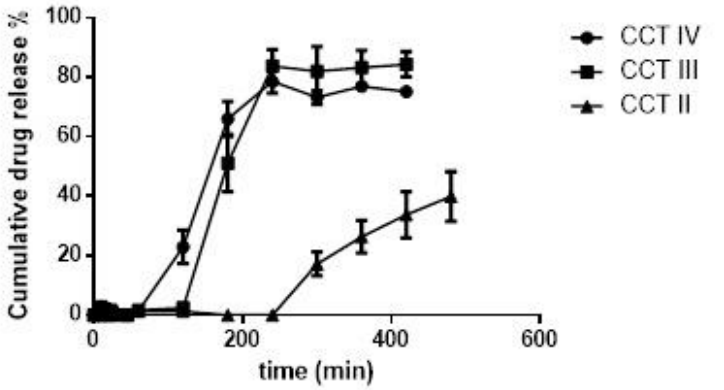

Figure 3. *In vitro* dissolution profiles of SA containing compression-coated tablets

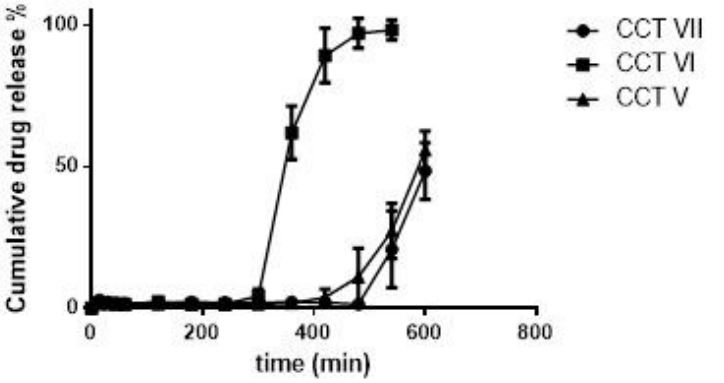

Figure 4. *In vitro* dissolution profiles of HPMC-100 containing compression-coated tablets

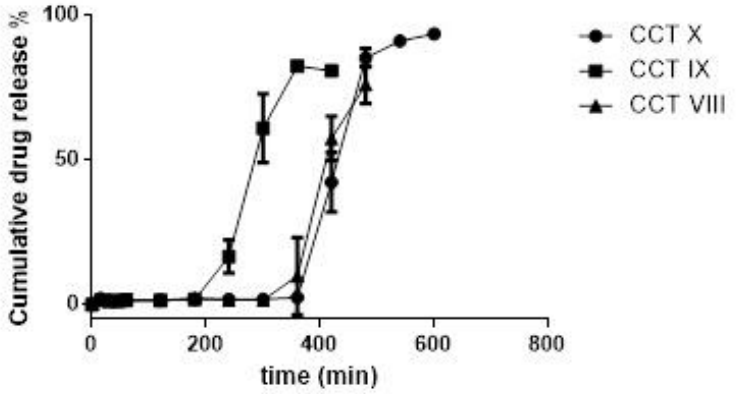

Figure 5. *In vitro* dissolution profiles of HPMC-4000 containing compression-coated tablets

Generally, it is expected that the retardation effect of polymers increases as the viscosity of the polymer increases due to the formed stronger gel with more viscous polymer on the core tablet [36,37]. But interestingly in our work, the lag times obtained from HPMC with higher viscosity grade were shorter than HPMC with lower viscosity grade for all ratios in the coating layer. In fact that swelling property of the polymer increases with increasing viscosity of the polymer [38]. This means HPMC with 4000 mPa.s viscosity swells more than HPMC with 100 mPa.s. The more swelling HPMC (4000 mPa.s) caused to remove the insoluble polymer, CAP coating on the core tablets earlier and release of telmisartan. After the lag time, the outer shell of the CAP coating on the core tablet broke into two halves to result in rapid drug release. The rupturing of the coating layer of the CCT X coded compression coated tablet which is the optimum compression-coated tablet formulation with approximately 6 hours of lag time and following rapid release was visualized by using a colored core tablet, and can be seen in Figure 6.

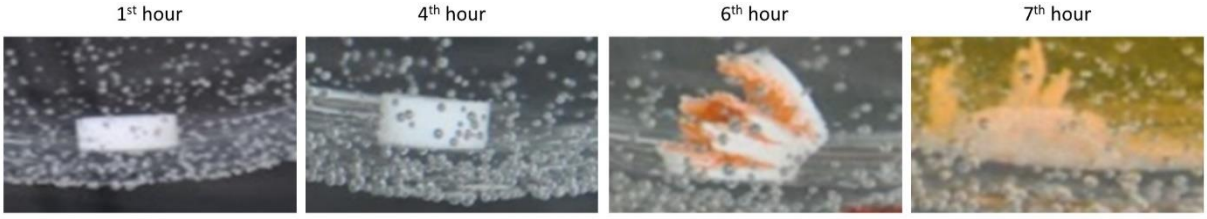

Figure 6. The images of CCT X-coded compression-coated tablets during *in vitro* dissolution tests

Differential Scanning Calorimetry Studies

DSC was used to determine the state of telmisartan in solid dispersion and physical mixtures and to identify possible drug–polymer or drug-alkali interactions. DSC is a thermal analysis which measures change of physical properties like phase transitions of a sample along with temperature against time. While temperature is increasing or decreasing, heat quantity absorbed or radiated by sample as temperature differences between sample and reference are measured [39].

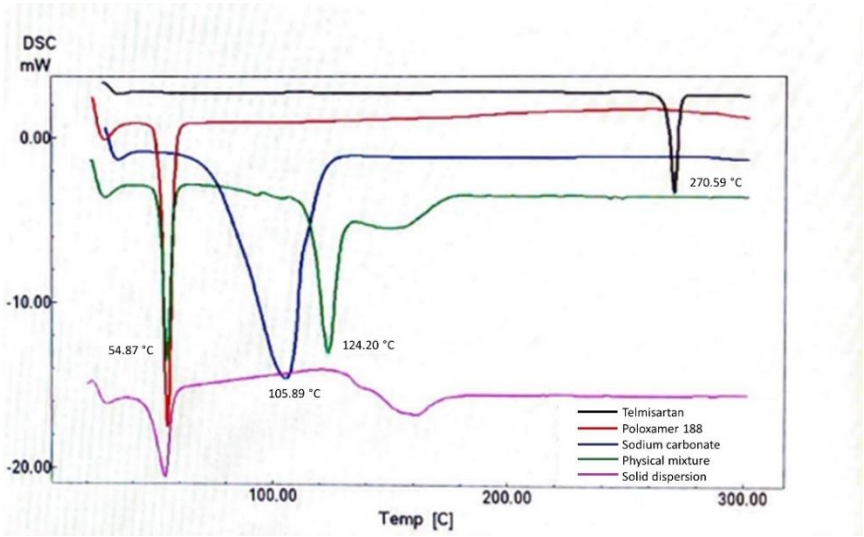

Figure 7. DSC thermograms of the pure telmisartan, poloxamer 188, sodium carbonate, their physical mixture and solid dispersion (SD5)

DSC thermograms of telmisartan, poloxamer 188 as well as their solid dispersions and physical mixture are shown in Figure 7. As can be seen in Figure 7, pure telmisartan, poloxamer 188, and sodium

carbonate showed endothermic peaks at 270.59°C, 54.86°C, and 105.89°C, respectively, corresponding to their melting point and indicating their crystalline structure. However, the sharp endothermic peak of telmisartan has disappeared in the DSC thermograms of solid dispersions and physical mixture. The absence of telmisartan endotherms can be attributed to either drug solubilization in molten polymer before melting point of telmisartan or change into an amorphous state during preparation process [40,41,42]. On the other hand, in the DSC thermogram of the physical mixture the shift of the sodium carbonate peak from 105.89 to 124.20°C may also be due to the relationship between telmisartan and sodium carbonate. These differences have explicated that there was a strong interaction between weak acidic telmisartan and alkali sodium carbonate [17].

This study showed that the solubility of telmisartan can be enhanced by the solid dispersion technique and telmisartan/sodium bicarbonate/poloxamer 188 ternary system can be considered suitable for pulsatile release tablet formulations. Formulations of pulsative compression-coated tablets containing solid dispersion of telmisartan are successfully developed. The tablets provided a desirable lag time followed by rapid and complete drug release to meet the challenges of chronopharmaceuticals. The *in vitro* drug release studies showed that the lag time of the tablet formulation could be modified by several factors such as core composition, the type and ratio of coating materials.

AUTHOR CONTRIBUTIONS

Concept: O.E., C.H.; Design: O.E., C.H.; Control: O.E., C.H.; Sources: O.E., C.H.; Materials: O.E., C.H.; Data Collection and/or Processing: O.E., C.H.; Analysis and/or Interpretation: O.E., C.H.; Literature Review: O.E., C.H.; Manuscript Writing: O.E., C.H.; Critical Review: O.E., C.H.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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