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Modeling of ticagrelor bioadhesive solid dispersion based on coaxial electrostatic spray to enhance oral bioavailability and improve drug release

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Abstract: In order to address ticagrelor's (TIC) low solubility and poor bioavailability, the current study created a structured bioadhesive core-shell drug delivery system. The uniaxial electrostatic spray technique was used to create ticagreior solid dispersion (T-SD). The coaxial electrostatic spray method was also used to create ticagrelor bio adhesive solid dispersion (T-BSD). Using a biological adhesion test, the adhesion of T-BSD to each segment of the intestinal tract was identified. The plasma concentration-time curve and associated pharmacokinetic parameters were studied using the compartment model. The outcomes of bioadhesion tests revealed that T-BSD had a favorable adhesion effect in every intestinal segment. T-maximum BSD's plasma concentration (Cmax) increased from the free drug's (365ng/mL) level to 575.08ng/mL. The t1/2, MRT, and Tmax of T-BSD (12 h, 9.4h, and 4h, respectively) were all longer than those of the free drug (11.2h, 8.6h, and 1h). T-relative BSD's bioavailability increased even more in comparison to the free drug, reaching 430%. Collectively, the results showed that the coaxial-electrospray method might be a promising means of enhancing TIC's bioavailability.

Keywords: Uniaxial electrostatic spray Ticagrelor, coaxial electrostatic spray, bioadhesion, solid dispersion

INTRODUCTION

A new cyclopentyltriazolylpyrimidine called ticagrelor (TIC) selectively inhibits the purine P2Y12 receptor on vascular smooth muscle. By inhibiting the activity of ADP (adenosine diphosphate), which prevents the development of arterial thrombosis, it can prevent the formation of blood clots in blood vessels (Leonardo C et al., 2018; Chen Gang, 2015; Philippe Gabriel S, 2010). Its commercial product, Brilinta, was created by AstraZeneca and authorised by the FDA in 2011. (GU Chunmei et al., 2014). Since TIC is also a type of BCS IV drug, its

poor solubility in water will significantly impede the absorption process and lead to low bioavailability (Caren Gobetti, 2014). (Joon Ho Ahn et al., 2020; Ioanna Xanthopoulou et al., 2018). The main elements that boost the drug's bioavailability are the permeability and dissolution rate of TIC. Previous research has demonstrated that different techniques can alter how a drug dissolves, including solid dispersion, comminuted TIC API, and cyclodextrin inclusion technology (Yadav M et al., 2021). The primary technology used in these techniques is solid dispersion (Wang Yan et al., 2017; Sung-Jin Kim et al., 2019; Young-Guk Na et al., 2019). Nevertheless, core-shell microsphere development from microspheres based on melting and conventional solvent mechanisms is constrained in some ways (Jinkun Huang et al., 2017). The lapses mentioned above are likely to be eliminated by a newly created preparation technique of solid dispersion using electrostatic spray in this study. A novel technique for using electrostatic force to produce fibrous or spherical materials is called electrostatic spray technology (Parhizkar LM and Reardon PJT, 2017; Nath SD et al., 2013; Dormer NH et al., 2013). Electrostatic spray's voltage and flow rate can be adjusted to produce spherical or fibrous particles (Annelies Smeets., 2019). Crosslinked polymer carbomer expands to create a viscous gel. Carpohol polymers have been used in a variety of products since the 1950s, including thickening agents, shock absorber agents, gel matrix, biological adhesive materials, controlled release preparation mechanisms, and more (Abdul Ahad et al., 2017). The bioadhesive technology makes it easier for formulations to adhere to the gastrointestinal tract, as well as prolonging drug absorption times at the site to increase their bioavailability (Adel Penhasi and Albert Reuveni, 2019). To address the issue of TIC's poor solubility and low bioavailability, a novel coaxial electrospray technique was used to create micron-size particulate formulations of TIC. The TIC's in vivo residence time *Corresponding author: articlepharmacyliu@163.com increases and improves drug absorption when solid dispersion is used as the core layer and biological adhesive material acts as the outer shell.

MATERIALS AND METHODS

The Ticagrelor, Poloxamer188, PEG4000, PVP-VA, HPMC K4M and Carbomer 940, Chromatographic grade methanol and acetonitrile were purchased from sigma company (Karachi, Pakistan).

Equilibrium solubility studies

To various media with various pH values and tween-80 contents, an equal but excessive amount of TIC was added in order to reach a supersaturation state. For 72 hours, these mixtures were left in an oscillator with a water bath set at 37°C. A 0.45 m filter membrane was used to filter the solutions. The subsequent filtrate was taken and examined using UV absorbance at 300 nm after the primary filtrate was first discarded.

In vivo absorption of Ticagrelor in the intestine of rats

The Quaid-i-Azam University Animal Center provided male Sprague-Dawley rats (180–220 g). The Quaid-i-Azam University Animal Ethics Committee gave the studies the go-ahead. The in situ "closed-loop" perfusion method was used to determine the absorption rate coefficient of TIC in 3 intestinal segments (duodenum, jejunum, and ileum), based on Doluisio's Technique with a

minor modification (Fatmanur Tugcu-Demiroz et al., 2014). 18 rats were divided into 3 groups at random after being fasted for 4 hours while drinking water freely. Different concentrations of TIC solution (10 g/mL, 15 g/mL, and 20 g/mL) were perfused into each group. Pentobarbital sodium was used to anaesthetize SD rats before they were immobilised on a heated surface that was kept at a temperature of 37°C using a mid-abdominal incision. The duodenum, jejunum, and ileum, three 10 cm long intestinal segments, were cut and cannulated on both ends (table 1). To prevent hepatoenteric circulation and bile salt deposition, the bile duct was banded. By flushing the three intestinal segments with normal saline at 37°C, the intestinal contents were cleared. To prevent peritoneal fluid from evaporating and heat loss during the experiment, cotton wool pads are placed over the abdomen. Each segment was then filled with a diluted version of the TIC solution that had been mixed with a K-R solution that contained phenol red. The various segments were circulated at a rate of 2.5 mL per minute and 37 °C. At 0, 1, 1.5, 2, 2.5, and 3 hours, samples were collected, and the same volume of blank medium was added. Once more, samples were centrifuged for 10 minutes at 10,000 rpm to determine the drug concentration using a High Performance Liquid Chromatography.

Table 1: The specific location of the intestinal segments

Intestine	Site
Duodenum	Starting 2 cm distal to stomach pylorus
Jejunum	Starting 4 cm after duodenal exit
Ileum	Starting12 cm distal to cecum point

Preparation of T-SD single-axis electrospray technology

To achieve a final TIC concentration of 10% (w/v), the electrospray solution containing TIC and Poloxam 188 with a mass ratio of 1:3 was weighed and dissolved in 5 mL of trichloromethane. After being transferred into a syringe, the solution was connected to a conductive needle with an inner diameter of 0.5 mm. Here, a high-voltage power supply with a positive voltage of 18 kV and a negative voltage of -2 kV, an injection pump running at 0.15 mm/min, and a distance of 18 cm between the injection pump and the collecting plate were used in the preparation. Following collection on aluminum foil with an 18 cm receiving distance, the TIC-solid dispersion particles (TSD) were observed (Sharvil Patil and Abhijeet Mahadik, 2017; Annelies Smeets et al., 2020).

Analysis of T-particle SD's size characteristics

T-SD samples were dried for 20 min. at (1052) °C in a vacuum oven. Using a Helos/BF particle size analyzer, the dried T-SD samples were examined for particle size. The dry method was used as the test mode. In order to examine the physical mixture of TIC, solid dispersion excipient (T-SD), and TIC and excipient (Poloxam188), a DSC Differential Scanning Calorimeter (DSC, DSC 7020, Hitachi, Japan) was used (Takurou N and Murakami, 2007). As a control, a blank aluminum plate was used. With a sample weight of 10 mg and a temperature range of 20 to 200 oC, each sample was heated at a rate of 10.0 °C per minute.

Preparation of T-BSD using coaxial electrospray technology

To achieve a final TIC concentration of 10% (w/v), the core layer solution, which consisted of TIC and poloxamer188 in a mass ratio of 1:3, was dissolved in 5 mL of trichloromethane. In addition, 150 mg of carbomer 940 were dissolved in a 10 mL mixture of water and ethanol for the sheath layer solution (1:8). A coaxial electrospinner made of two co-centric stainless-steel channels was created by using a coaxial injector nozzle model (18G/21G). The core layer flow rate of the two syringe pumps was 0.15 mm/min, and the shell layer flow rate was 0.1 mm/min. The preparation of T-SD, receiving distance, and other parameters were all the same and further configured in a single-fluid mode. By simultaneously injecting the liquid from the syringe, the T-BSD was prepared. The receiving distance was 18 cm, and the positive and negative voltages were set to 18kV and -2kV, respectively. On aluminum foil paper, T-BSD samples can be obtained under the influence of an applied electric field (Weihong Yin et al., 2021).

Characterization of T-BSD

Scanning electron microscope

The T-BSD particles' morphologies were examined using scanning electron microscopy (JEOL, Tokyo). To increase the conductivity of the particles before the test, conducting resin that was made using gold was deposited on silicon (Sultanova Z et al., 2016; Chen R et al., 2022).

Study of in vitro dissolution

The United States Pharmacopoeia (USP) type II dissolution method was used to study the drug released from T-BSD, T-SD, and TIC. In a nutshell, samples of T-BSD, T-SD, and TIC (each corresponding to 10 mg TIC) were dissolved in 900 mL of an HCl solution containing 0.01% Tween-80 (pH 1.2) and mechanically stirred at 50 rpm for 1.5 hours. According to Jiaming Chen et al. (2018), each sample was taken at intervals of 5 min, 10 min, 20 min, 30 min, 60 min, and 1.5 h. The solutions were filtered using a 0.45 m microfiltration membrane, with the primary filtrate being discarded while the subsequent filtrate was subjected to UV analysis at 300 nm. The weight ratio of released TIC to total TIC was used to calculate the cumulative dissolution rate (%).

Animal studies, in vivo Male SD rats weighing 180–220g (UJS–LAER–AP-2018030809) were allowed to drink water during the 12-hour fasting period prior to the experiment. The rats (n = 6) were randomly assigned to one of two groups and were then given an oral dose of the TIC API, T-SD, or T-BSD suspended in a 0.5% CMC-Na solution. Blood was drawn in aliquots (0.5mL each) at 0, 0, 15, 0, 25, 0, 50, 0, 55, 1, 2, 3, 4, 6, 8, 12, and 24 hours after oral administration. Plasma was collected and stored at -20oC after being centrifuged at 10,000 rpm for 5 minutes. Sediment was removed from the blood samples. Every study followed the Guidelines for the Care and Use of Laboratory Animals (NIH publication no.85-23, revised in 1985).

Analysis of TIC in plasma samples

An internal standard method was used to determine the plasma's TIC content. For evenness, 190 l of plasma sample was combined with 10 l of an internal standard solution (150 g/ml Eltrombopag olamine). Each sample received 200 litres of methanol before being centrifuged at 10,000 rpm for 10 minutes to collect the supernatant. After that, the supernatant was examined using an HPLC system that included a Shimadzu, Japan-made LC-20AT HPLC pump, SPD-

20AVP UV Spectrometer detector, and Diamonsil C18 column (150 mm x 4.6 mm, 5 m particle size). The injection volume for the sample was 20 L, and its wavelength was 300 nm. The sample's analytical temperature was 30oC. Mobile phase (acetonitrile and ammonium acetate, 50:50 v/v) flowed at a rate of 1 mL/min.The analysis's methodology underwent the necessary validation. 2019 (Vinicius R et al.). Study of Pharmacokinetics According to the drug duration curve, the t1/2, Cmax, Tmax, AUC 0-24h, and other parameters were calculated. The Wagner-Nelson method was used to determine the absorption rate of T-BSD microspheres in vivo.

RESULTS

Studies on equilibrium solubility

The equilibrium solubility of ticagrelor was 5.57, 13.95, 4.36, and 4.13 g/mL in water, pH1, pH4.5, and pH6.8 buffers, respectively (table 2). Ticagrelor became more soluble in water, pH1, pH4.5, and pH6.8 buffers when 0.01%, 0.02%, and 0.05% Tween-80 were added.

Table 2: Balanced Solubility of Ticagrelor in different media.

Solution	0.00% Tween-80	0.01% Tween-80	0.02% Tween-80	0.05% Tween-80
H_2O	7.77	16.40	29.46	76.46
pH1.0	13.94	29.44	43.74	73.80
pH4.4	4.36	14.68	34.26	61.97
pH6.8	4.13	9.43	24.93	71.42

Rat intestinal in vivo absorption of ticagrelor

The jejunum had the highest absorption rate and absorption constant for 10 g/ml TIC (14.34 2.34% and 0.4012 0.0689h-1, respectively), followed by the duodenum (12.94 3.23% and 0.3846 0.04428h-1), and the ileum had the lowest absorption rates (11.48 3.46% and 0.2046 0.06412h-1, respectively). With an increase in TIC concentration, the absorption rates and constants decreased (Table 3 and 4).

Table 3: Absorption rates of different concentrations of TIC in different intestinal segments.

Concentration (µg/mL)	percentage (%)		
	Ileum	duodenum	jejunum
10	12.78±3.46	12.94±3.23	14.34±2.34
14	7.34±1.44	8.44±0.98	10.01±1.17
20	6.06±1.87	6.12±1.02	7.23±2.10

Table 4: Absorption constants of different concentrations of ticagrelor in different intestinal segments

Concentration (µg /mL)	Ka (h^{-1})		
	Ileum	duodenum	jejunum
10	0.2046±0.06512	0.3856±0.04528	0.4012±0.0689
15	0.1846±0.03074	0.3367±0.01278	0.3416±0.04326
20	0.1378±0.02686	0.2795±0.03456	0.2918±0.08723

T-SD characteristics

The polydispersity coefficient for T-SD was 0.34 and the average particle size was 762.9 nm.

DSC

Fig. 2 shows that the solid dispersion excipients showed an endothermic characteristic peak at 56 °C while the TIC showed a clear endothermic characteristic peak at 140 °C. With the exception of the weakened peak intensity, the endothermic peaks from the physical mixture of TIC and solid dispersion excipients were just a superposition of the first two spectra. The findings indicated that TIC was still present in the physical mixture as crystals.

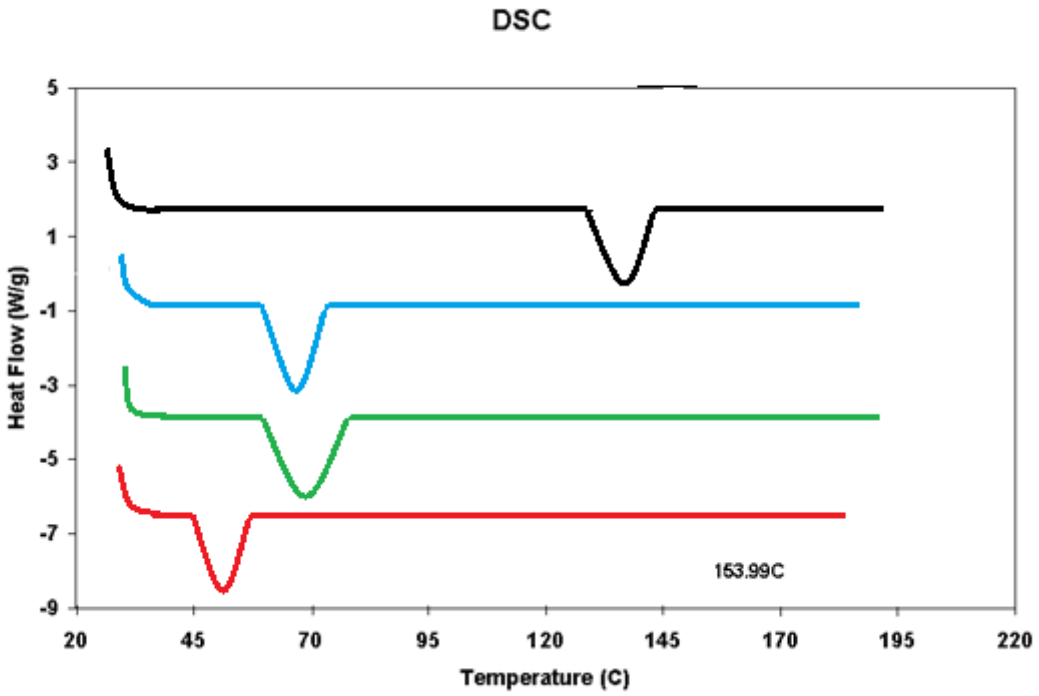

Fig. 2: DSC diagram of T-SD and excipients (A: TIC; B: solid dispersion excipient; C: TIC and excipient physical mixture; D: TIC solid dispersion).

Characterization of T-BSD Scanning electron microscope

The T-BSD samples were in uniform, spherical particles, according to SEM images (fig. 3). T-BSD bioadhesion Figure 4 shows that T-BSD retention rates were higher than T-SD retention rates in the various intestinal sections (duodenum, Jejunum, and Ileum, respectively, 31%, 42%, and 50%).

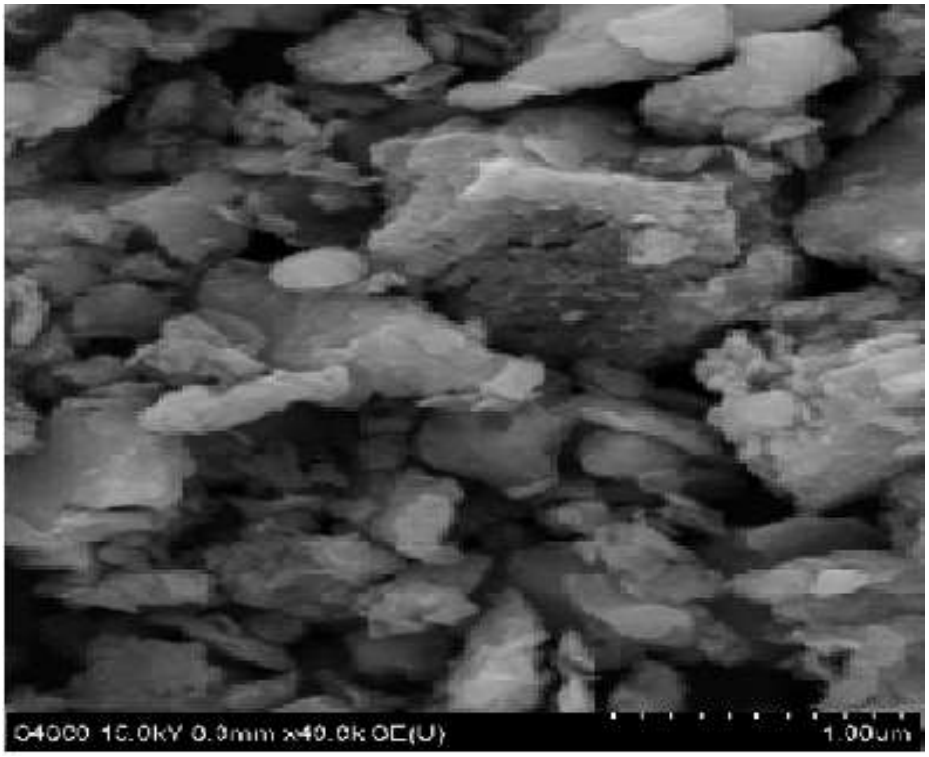

Fig. 3: T-BSD electron microscopy.

Study of in vitro dissolution

The in vitro dissolution rate of TIC was extremely slow, with only 9% dissolving after 5 minutes and 50% after 90 minutes. The dissolution rate of T-SD, on the other hand, increased significantly by over 50% at 5 minutes, suggesting that electrostatic spraying significantly increased the dissolution of TIC.

The T-SD, T-BSD, and reference preparations' TIC plasma concentration-time profiles are displayed in table 5. Tigriorin's plasma concentration peaked at 1.5 hours, whereas T-SD and T-did BSD's so at 2.5 and 5 hours, respectively. Table 5 provides an overview of the pharmacokinetic parameters and the relative bioavailability. Nearly identical and significantly higher than that of the bulk drug was the Cmax of T-SD and T-BSD. When compared to the bulk drug, the t1/2 of T-SD was lower while that of T-BSD was higher.

Table 5: Pharmacokinetic parameters of TIC API and TBSD.

Parameter	TIC	T-SD	T-BSD
$t_{1/2}$ (h)	11.21	9.28	12.09
Tmax (h)	1	2	4
Cmax (μg·L-1)	367.32	713.13	777.08
MRT(h)	8.618	7.277	9.441
AUC0-24 (μg·h·L-1)	2481.935	5444.625	10682.58
Relative bioavailability	100%	219.4%	430.4 %

DISCUSSIONS

After 72 hours of shaking at 37oC, the solubility of ticagrelor in the four different media without Tween 80 was very low (0.1 g/100 g). The drug's insoluble nature made this situation predictable. Tween 80, on the other hand, significantly improved the solubility. Due to TIC's poor solubility, only a small amount of it was absorbed in the jejunum, duodenum, and ileum, three different parts of the small intestine. The jejunum in the small intestine served as the TIC's optimal absorption site. When the concentration of TIC was increased from 10 g/ml to 20 g/ml, the Ka value decreased, suggesting that facilitated diffusion and active transport may be the primary method of TIC absorption. The small intestine is the primary site of drug absorption, so it is important to maximise the drug's time in the small intestine. The bioavailability of TIC can be increased by extending the time it spends in the gastrointestinal tract because it is primarily absorbed in the middle and upper part of the small intestine. (Sachin Rathod and colleagues, 2018).

In order to increase the low solubility of TIC, T-SD was prepared using the uniaxial electrostatic spray technique. The particle size of T-SD is constant. The endothermic characteristic peak of TIC completely vanished in the differential scanning calorimeter of the solid dispersion. This showed that the form of TIC had changed after the preparation of T-SD, no longer being in the crystal form but instead being in the amorphous form (He T and Jokerst Jv, 2020). The addition of the shell adhesion material increased the viscosity of the entire solution system, with T-BSD particles being about 1 m in size. When compared to T-SD without bioadhesive materials, the retention rate of T-BSD in the various intestinal segments of rats was significantly increased. The improved bioavailability of the drug was greatly aided by the increased drug dissolution. The fact that most drugs are wrapped in a material called a shell that slows the release rate with a sustained-release effect may be the reason why the T-BSD sample's drug dissolution rate was slower than that of the T-SD sample. However, compared to TIC, the T-BSD had the advantages of solubilization and quick release (Zhou L, 2015). Between the two preparations, there was no discernible difference in Cmax, but there was a discernible difference in Tmax and AUC0-24h. As a result, the Tmax increased from 1.0 hours (the reference) to 2.0 hours (the T-SD test) and 4.0 hours (the T-BSD test), indicating an in vivo sustained-release property. When compared to the T-BSD preparation (430.4%), the relative bioavailability of the T-SD preparation increased significantly by 219.4%. According to the aforementioned findings, TIC-resinate microspheres can boost TIC absorption and bioavailability (Hongfei Liu et al., 2018).

CONCLUSION

To enhance the qualities of BCS IV drugs, a novel insoluble drug delivery system was created using electrostatic spray technology and bio-adhesive materials. This study used coaxial electrospray to create a novel TIC-loaded microparticle with a coreshell structure, which enhanced the TIC particle's dissolution characteristics. The in vivo bioavailability of TIC was also significantly increased with the use of a bioadhesive carrier in the sheath layer, according to pharmacokinetic studies in rats. The results showed a promising novel drug release system that

simultaneously improved the bioavailability of the fatsoluble drug that was absorbed in the upper GI tract and increased the dissolution of the drug.

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