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

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Abstract: Due to the low solubility and poor bioavailability of Ticagrelor (TIC), the current study developed a structured bioadhesive core-shell drug delivery system to address it. Ticagreior solid dispersion (T-SD) was fabricated using the uniaxial electrostatic spray method. Ticagrelor bio adhesive solid dispersion (T-BSD) was also prepared using the coaxial electrostatic spray technique. The adhesion of T-BSD to each intestinal segment was determined using biological adhesion test. The compartment model was used to study the plasma concentration-time curve and related pharmacokinetic parameters. The results of bioadhesion tests showed a positive adhesion effect of T-BSD in each intestinal segment. The maximum plasma concentration (C_{max}) of T-BSD was increased to 777.08ng/mL compared with the free drug (367ng/mL). Similarly, $t_{1/2}$, MRT and T_{max} of T-BSD (12.1h, 9.4h, 4h) were higher than the free drug (11.2h, 8.6h, 1h), respectively. The relative bioavailability of T-BSD was further increased to 430% compared with the free drug. The findings collectively revealed that the coaxial-electrospray technique could be a promising way to improve the bioavailability of TIC.

Keywords: Ticagrelor; uniaxial electrostatic spray; coaxial electrostatic spray; solid dispersion; bioadhesion

INTRODUCTION

Ticagrelor (TIC), a type of new cyclopentyltriazolylpyrim-idin, is a selective inhibitor of purine P_2Y_{12} receptor on vascular smooth muscle. It can prevent the formation of blood clots in blood vessels by inhibiting the activity of ADP (adenosine diphosphate), which stops the formation of arterial thrombosis (Leonardo C *et al*., 2018； Chen Gang, 2015; Philippe Gabriel S, 2010). Brilinta, its commercial product, was developed by AstraZeneca and also approved by FDA in 2011 (GU Chunmei *et al*., 2014). TIC is also a kind of BCS IV drugs and therefore, its poor solubility in water will greatly hinder the absorption process (Caren Gobetti, 2014) and result in low bioavailability (Joon Ho Ahn *et al*., 2020; Ioanna Xanthopoulou *et al*., 2018). The dissolution rate and permeability of TIC are the key factors that increase the bioavailability of the drug.

Previous studies have shown that various methods such as solid dispersion, comminuted TIC API and cyclodextrin inclusion technology can change the dissolution of the drug (Yadav M *et al*., 2021). The solid dispersion is the main technology among these methods (Wang Yan *et al*., 2017; Sung-Jin Kim *et al*., 2019; Young-Guk Na *et al*., 2019). However, solid dispersions based on melting and traditional solvent mechanisms have some limitations to develop into core-shell microspheres (Jinkun Huang *et al*., 2017). A newly developed preparation technology of solid dispersion using electrostatic spray in this study is likely to eliminate the aforementioned lapses. Electrostatic spray technology is a new method to produce fibrous or spherical materials by electrostatic force (Parhizkar LM and Reardon PJT, 2017; Nath SD *et al*., 2013; Dormer NH *et al*., 2013). The spherical or fibrous particles can be obtained by adjusting the voltage and flow rate of electrostatic spray (Annelies Smeets., 2019).

Carbomer is a crosslinked polymer that expands to form a viscous gel. Since the 1950, Carpohol polymers are widely used in thickening agents, suspension agents, gel matrix, biological adhesive material, controlled release preparation mechanism material and so on (Abdul Ahad *et al*., 2017). The bioadhesive technology facilitates the attachment of the formulations to the gastrointestinal tract and also increases drug retention time and then prolongs the absorption time of drugs at the site to improve their bioavailability (Adel Penhasi and Albert Reuveni, 2019).

In this study, a novel micron-size particulate formulation of TIC via coaxial electrospray technique was developed to address the problem of poor solubility and low bioavailability of TIC. The residence time of TIC *in vivo* can be increased and drug absorption can be enhanced by

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using biological adhesive material as shell and solid dispersion as core layer.

MATERIALS AND METHODS

Materials

Ticagrelor (TIC) was purchased from Aikemu Chemical Co., Ltd (Zhengzhou, China). Poloxamer188 was purchased from BASF New Materials Co., Ltd. PEG4000 and PVP-VA was obtained from Fengli Jingqiu Trading Co., Ltd (Beijing, China). HPMC K4M and Carbomer 940 were obtained from Shanghai Aladdin Bio-Chem Technology Co., Ltd (Shanghai, China). Chromatographic grade methanol and acetonitrile were purchased from Tedia Company, Ohio, USA. Deionized water was made in the laboratory and all other chemical reagents were obtained from Guoyao Chemical Regents Co. (Beijing, China).

Equilibrium solubility studies

To achieve a supersaturation state, an equal but excess amount of TIC was added to different media with different pH values and tween-80 content. These mixtures were kept in a water bath oscillator (37±1°C) for 72h. The solutions were filtered using a 0.45 μm filter membrane. The primary filtrate was first discarded and the subsequent filtrate was taken and analyzed using UV absorbance at 300 nm.

In vivo absorption of Ticagrelor in the intestine of rats

Male Sprague-Dawley rats (180-220 g) were obtained from the Jiangsu University Animal Center (Zhenjiang, China). The experiments were approved by the Animal Ethics Committee of Jiangsu University. On the basis of Doluisio's Technique, with a slight modification, the in situ “closed-loop” perfusion method was used to determine the absorption rate coefficient of TIC in 3 intestinal segments (duodenum, jejunum, ileum) (Fatmanur Tugcu-Demiroz *et al*., 2014).

Briefly, 18 rats were fasted for 4h (take water freely) and randomly divided into 3 groups. Each group was perfused with different concentrations of TIC solution (10μg/mL, 15μg/mL, 20μg/mL). SD rats were anesthetized with pentobarbital sodium, the rats were immobilized on a heated surface maintained at a temperature of 37°C with a mid-abdominal incision. Three 10 cm long intestinal segments (the duodenum, jejunum and ileum) were cut and cannulated at both ends (table 1). The bile duct was ligation to avoid hepatoenteric circulation and bile salt deposition. The intestinal contents were cleared by flushing the three intestinal segments with 37°C normal saline. Cotton wool pads cover the abdomen to prevent evaporation of peritoneal fluid and heat loss during the experiment. The TIC solution was diluted with a K-R solution (containing phenol red) and then introduced into each segment. The different segments were circulated at 2.5mL·min^{-1} and 37°C. Samples were taken at 0.5, 1, 1.5, 2, 2.5, 3h and the same volume of blank medium was added. Again, samples were centrifuged at 10, 000 r·min^{-1} for 10 min and the concentration of the drug was determined 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

Equations (1-2) were used to calculate the volume of the circulating solution and the amount of residual drug in the intestine, respectively. The absorption rate (A) and absorption rate constant (Ka) of TIC were calculated by equations (4-5), respectively.

$$Vtn = \frac{(V_{tn-1} - 2) \times C'_{tn-1} + 2 \times C'_{t0}}{C'_{tn}} \quad (1)$$

$$P_{tn} = C_{tn} \times V_{tn} + 2 \times \sum_{t=1}^{n-1} C_{tn} \quad (2)$$

$$A/\%(h^{-1}) = \frac{P_{t0} - P_{tn}}{P_{t0} \times tn} \times 100\% \quad (3)$$

$$Ka = \frac{ln\, P_{t0} - ln\, P_{tn}}{tn} \quad (4)$$

C'_{t0} is the concentration of phenol red before circulation; C'_{tn} is the concentration of phenol red in circulating solution at t_n; C'_{t1} is the initial concentration of TIC in circulating solution; V_{t1} is the initial volume of circulating solution; C_{tn} is the concentration of TIC in circulating solution at t_n; V_{tn} is the volume of circulating solution at t_n; t_n is the perfuse time of circulating solution; P_{t0} is the initial amount of TIC in circulating solution; P_{tn} is the amount of TIC in circulating solution at t_n。

Preparation of T-SD single-axis electrospray technology

The electrospray solution containing TIC and Poloxam 188 with a mass ratio of 1:3 was weighed and dissolved in 5 mL of trichloromethane to obtain a final TIC concentration of 10% (w/v). The solution was connected to a conductive needle (inner diameter of 0.5 mm) after transferring into a syringe. Herein, an electrostatic spinning machine with a syringe pump and collecting plate, a high-voltage power supply (positive voltage of 18kV and negative voltage of -2kV), an injection pump speed of 0.15mm/min and the distance between the injection pump and the collecting plate of 18cm was used in the preparation. The TIC-solid dispersion particles (T-SD) were then collected on the aluminum foil with an 18 cm receiving distance (Sharvil Patil and Abhijeet Mahadik, 2017; Annelies Smeets *et al*., 2020).

Characterization of T-SD

Particle size analysis of T-SD

T-SD samples were dried in a vacuum oven at (105±2) ℃ for 20 min. The dried T-SD samples were tested for particle size with a Helos/BF particle size analyzer. The test mode adopted was the dry method.

DSC

Differential Scanning Calorimeter (DSC, DSC 7020, Hitachi, Japan) was used to analyze TIC, solid dispersion excipient (T-SD) and TIC and excipient (Poloxam188) physical mixture (Takurou N and Murakami, 2007). The blank aluminum plate was used as a control. Temperature range for each sample was set at 20 to 200°C at a heating rate of 10.0 °C·min^{-1}, using static air as purging gas with a sample weight of 10mg.

Preparation of T-BSD using coaxial electrospray technology

The core layer solution comprised TIC and poloxamer188 with a mass ratio of 1:3 was dissolved in 5mL of trichloromethane to obtain a final TIC concentration of 10% (w/v). The sheath layer solution also consisted of 150 mg of Carbomer 940 dissolved in 10mL of water：ethanol mixture (1:8). Coaxial injector nozzle model (18G/21G) was used so as to have a coaxial electrospinner consisting of two co-centric stainless-steel channels. The two syringe pumps were interlinked with a shell layer flow rate of 0.1 mm/min， and that of the core layer at a velocity of 0.15 mm/min. Other parameters such as the electric potential, receiving distance and preparation of T-SD were all the same and further set up as a single-fluid mode. The T-BSD was prepared by injecting the liquid from the syringe at the same time. The positive and negative voltages were adjusted to 18kV and -2kV and the receiving distance was 18cm. Under the action of applied electric field, T-BSD samples can be obtained on aluminum foil paper (Weihong Yin *et al*., 2021).

Characterization of T-BSD

Scanning electron microscope

The morphologies of the T-BSD particles were observed under a scanning electron microscopy (JEOL, Tokyo). Prior to the test, the particles were deposited on silicon with conducting resin, which was provided using gold, to improve their conductivity (Sultanova Z *et al*., 2016; Chen R *et al*., 2022).

Bioadhesion

Twelve (12) SD rats were executed and three 10 cm long intestinal segments (duodenum, jejunum and ileum) cut off for further studies. The substances in the intestinal segments were washed with normal saline. Each intestinal segment was placed in a semicircle tube inclined at 45°C and flushed using the intestinal circulation solution for 10 min at 37°C. T-SD and T-BSD samples (10 mg each) were weighed, respectively and evenly sprinkled on the intestinal mucosa. The flow rate of peristaltic pump was set at 6ml/h for continuous flushing. After 3 hours, the T-SD and T-BSD were scraped off the mucosa and the TIC content analyzed according to the analysis method under "intestinal absorption methodology" section to calculate the retention rate.

In vitro dissolution study

Drug released from T-BSD, T-SD and TIC were studied according to the United States Pharmacopoeia (USP) type II dissolution method. Briefly, T-BSD, T-SD and TIC samples (equivalent to 10 mg TIC each) were dissolved in 900mL HCl solution containing 0.01% Tween-80 (pH 1.2) at 37°C and stirred mechanically at 50 rpm for 1.5 hours. Each sample was collected at the time intervals of 5 min, 10 min, 20 min, 30 min, 60 min and 1.5h (Jiaming Chen *et al*., 2018), The solutions were filtered using 0.45 μm microfiltration membrane and the primary filtrate discarded while the subsequent filtrate was analyzed using UV at 300 nm. The cumulative dissolution rate (%) was calculated as the weight ratio of released TIC to total TIC.

In vivo study

Animal studies

180-220g male SD rats (UJS-LAER-AP-2018030809) were fasted for 12h before the experiment, but allowed to drink water. The rats were randomly divided into two groups (n = 6) and orally administered with the TIC API, T-SD or T-BSD suspended in 0.5% CMC-Na solution with TIC dose of 9mg·Kg^{-1}, respectively. Aliquots (0.5mL each) of blood samples were harvested at 0.08, 0.17, 0.25, 0.50, 0.75, 1, 2, 3, 4, 6, 8, 12, 24 and 24 hours after oral administration. Blood samples were centrifuged at 10, 000 r·min^{-1} for 5min, the sediment was discarded and plasma was collected and stored at -20ºC. All studies were conducted in accordance with the Principles of Laboratory Animal Care (NIH publication no.85-23, revised in 1985).

Analysis of TIC in plasma samples

The content of TIC in plasma was determined by internal standard method. 190μL of plasma sample was mixed with 10μL of internal standard (150μg/ml Eltrombopag olamine) solution and vortexed for 5min to make it even. 200μL of methanol was added to each sample and centrifuged at 10000 rpm for 10 min to obtain a supernatant. The supernatant was then analyzed using an HPLC system which was equipped with LC-20AT HPLC pump (Shimadzu, Japan), SPD-20AVP UV Spectrometer detector (Shimadzu, Japan) and Diamonsil C_{18} column (150 mm x 4.6 mm, 5μm particle size; Dikma, China). The sample injection volume was 20μL and the wavelength of 300 nm. The analytical temperature of the sample was 30°C. The flow rate of mobile phase (Acetonitrile-ammonium acetate, 50:50 v/v) was 1mL/min. The methods used in the analysis were validated as required. (Vinicius R *et al*., 2019).

Pharmacokinetic Study

The $t_{1/2}$, C_{max}, T_{max}, AUC $_{0\text{-}24h}$ and other parameters were calculated according to the drug duration curve. The absorption rate of T-BSD microspheres in vivo was calculated by Wagner-Nelson method.

The calculation of relative bioavailability is shown in Equation 5.

$$Fr = \frac{AUC_T}{AUC_R} \times 100\ \% \quad (5)$$

AUC_T is the AUC of the T-BSD and AUC_R is the AUC of the TIC API. The data of T-BSD and TIC API were analyzed with the SPSS statistical package using an analysis of variance to assess any significant ($P<0.05$) difference.

RESULTS

Equilibrium solubility studies

The equilibrium solubility of ticagrelor in four media, namely water, pH1, pH4.5 and pH6.8 buffers were7.77, 13.95, 4.36 and 4.13μg/mL, respectively, table 2. After adding 0.01%, 0.02% and 0.05% Tween-80 to water, pH1, pH4.5 and pH6.8 buffers the solubility of Ticagrelor increased.

In vivo absorption of Ticagrelor in the intestine of rats

The absorption rate and absorption constant of 10μg/ml TIC in jejunum were the highest (14.34±2.34% and 0.4012±0.0689h^{-1}), followed by duodenum (12.94±3.23% and 0.3856±0.04528h^{-1}) and that of ileum were the lowest (11.78±3.56% and 0.2056±0.06512h^{-1}), respectively, tables 3 and 4. The absorption rates and absorption constants decreased with the increase in TIC concentration.

Characterization of T-SD

Particle size of T-SD

The average particle size of T-SD was 762.9 nm with the polydispersity coefficient of 0.34.

DSC

The TIC displayed an obvious endothermic characteristic peak at 140 ℃while the solid dispersion excipients showed an endothermic characteristic peak at 56°C, fig. 2. The endothermic peaks from the physical mixture of TIC and solid dispersion excipients were a simple superposition of the first two spectra, except that the peak intensity is weakened. The results it showed that TIC was still in crystal form in the physical mixture.

Characterization of T-BSD

Scanning electron microscope

SEM images showed that the T-BSD samples were in regular spherical particles, fig. 3.

Bioadhension for T-BSD

The retention rates of T-BSD in the different intestinal sections (duodenum-31%, Jejunum-42% and Ileum-50%) were higher than the rates of T-SD (duodenum-12%, Jejunum-14% and Ileum-16%), fig. 4.

In vitro dissolution study

As the fig. 5 shows, the in vitro dissolutionrate of TIC was very slow, thus only 9% at 5 min and only 50% at 90 min. In contrast, the dissolution rate of T-SD reached over 50% at 5min, which suggested a significant increase in the dissolution of TIC using electrostatic spraying.

In vivo study

Fig. 6 showed TIC plasma concentration-time profiles of the T-SD, T-BSD and reference preparations. Tigriorin reached the maximum plasma concentration at 1.5 h while that of T-SD and T-BSD were at 2.5h and 5h, respectively.

The pharmacokinetic parameters and the relative bioavailability were summarized in table 5. The C_{max} of T-SD and T-BSD were almost the same and significantly higher than that of the bulk drug. The $t_{1/2}$ of T-SD was decreased while that of T-BSD was increased compared with the bulk drug.

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	29.56	76.46
pH1.0	13.95	29.55	43.74	73.80
pH4.5	4.36	15.68	35.26	61.97
pH6.8	4.13	9.53	25.93	71.52

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

Concentration (μg/mL)	percentage (%)		
	Ileum	duodenum	jejunum
10	11.78±3.56	12.94±3.23	14.34±2.34
15	7.34±1.45	8.45±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		Ka (h^{-1})	
(μg /mL)	Ileum	duodenum	jejunum
10	0.2056±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

Table 5: Pharmacokinetic parameters of TIC API and T-BSD

Parameter	TIC	T-SD	T-BSD
$t_{1/2}$ (h)	11.21	9.28	12.09
T_{max} (h)	1	2	4
C_{max} (μg·L^{-1})	367.32	713.13	777.08
MRT(h)	8.618	7.277	9.441
$AUC_{0\text{-}24}$ (μg·h·L^{-1})	2481.935	5444.625	10682.58
Relative bioavailability	100%	219.4%	430.4 %

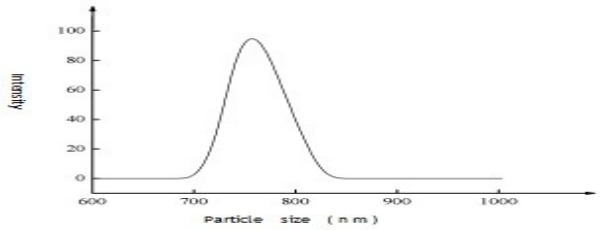

Fig. 1: Particle size distribution of T-SD.

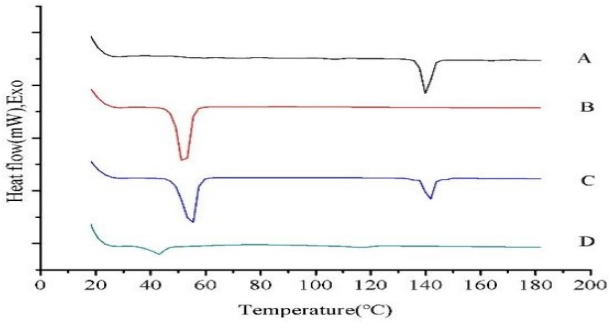

Fig. 2: DSC diagram of T-SD and excipients (A: TIC; B: solid dispersion excipient; C: TIC and excipient physical mixture; D: TIC solid dispersion).

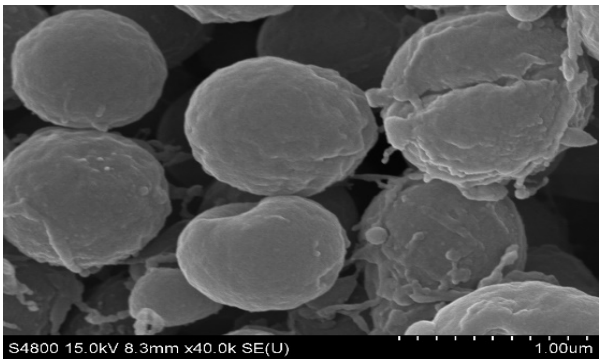

Fig. 3: T-BSD electron microscopy

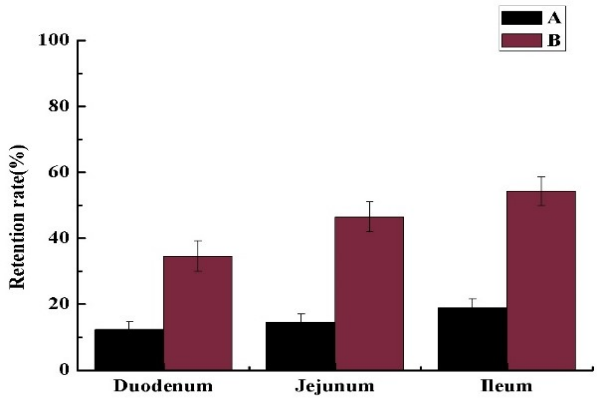

Fig. 4: Retention rate of each intestinal segment (A: T-SD; B: T-BSD)

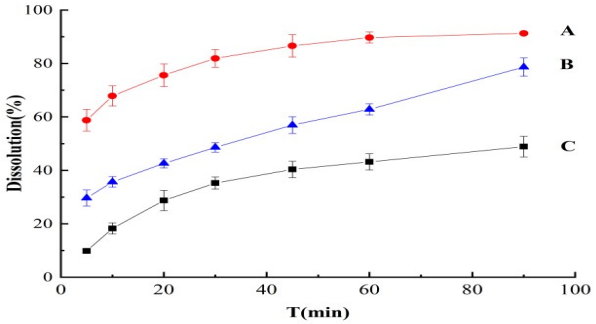

Fig. 5: Dissolution of solid dispersion, bioadhesive preparation and drug substance (A: solid dispersion; B: bioadhesive preparation; C: bulk drug)

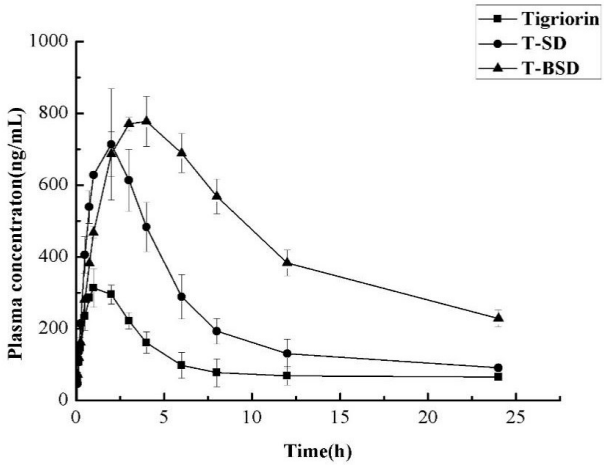

Fig. 6: Drug-time curve after single-dose intragastric administration of SD rats (n=6)

DISCUSSIONS

The solubility of Ticagrelor in the four different media without Tween 80 was very low (< 0.1 g/100 g) after 72 hours of shaking at 37°C. This situation was expected because of the insoluble nature of the drug. However, the solubility significantly increased with the addition of Tween 80. Only a small amount of TIC was absorbed in the different parts of the small intestine (jejunum, duodenum and ileum) which may be due to the poor solubility of TIC. The best absorption site of the TIC in the small intestine was the jejunum. The K_a value decreased due to the increase in the concentration of TIC from 10μg/ml to 20μg/ml, which indicated that facilitated diffusion and active transport may be the main absorption mechanism of TIC. The main site of drug absorption is the small intestine and the retention time of the drug in the small intestine should be prolonged as much as possible. TIC is mainly absorbed in the middle and upper part of the small intestine and its bioavailability can be improved by prolonging the residence time in the gastrointestinal tract. (Sachin Rathod *et al*., 2018).

The uniaxial electrostatic spray method was used to prepare T-SD to improve the low solubility of TIC. T-SD has uniform particle size. In the differential scanning calorimeter of the solid dispersion of TIC, the endothermic characteristic peak of TIC disappeared completely. This indicated that the form of TIC after the preparation of T-SD changed, thus no longer in the crystal form but rather in the amorphous form (He T and Jokerst Jv, 2020).

Due to the addition of the shell adhesion material, the viscosity of the whole solution system was increased with the particle size of T-BSD being about 1μm. The retention rate of T-BSD in the various intestinal segments of rats was greatly improved compared with T-SD without bioadhesive materials, The increased drug dissolution was very important in improving the bioavailability of the drug. The drug dissolution rate of T-BSD sample was slower than that of T-SD, which could be due to the fact that most of the drugs are wrapped in the shell material which reduceds the release rate with a sustained-release effect. However, the T-BSD hads the benefit of solubilization and quick release compared with TIC (Zhou L, 2015). There was no significant difference in C_{max} between the two preparations, but significant difference in T_{max} and $AUC_{0\text{-}24h}$. Thus, the T_{max} increased from 1.0 hours (reference) to 2.0 hours (T-SD test) and 4.0 hours (T-BSD test), which indicated an in vivo sustained-release property. The relative bioavailability of T-SD preparation also increased significantly by 219.4% compared with the T-BSD preparation (430.4%). The aforementioned results indicated that the mucoadhesive TIC-resinate microspheres can increase absorption and bioavailability of TIC (Hongfei Liu *et al*., 2018).

CONCLUSION

A novel insoluble drug delivery system was constructed based on electrostatic spray technology and bio-adhesive materials to improve the properties of BCS IV drugs. In this study, a novel TIC-loaded microparticle with a core-shell structure was fabricated using coaxial electrospray, which improved the dissolution properties of TIC particles. In addition, pharmacokinetic studies in rats showed that with the application of bioadhesive carrier in sheath layer, the in vivo bioavailability of TIC was significantly increased. The findings revealed a promising novel drug release system that simultaneously increased the dissolution and enhance the bioavailability of the fat-soluble drug which was absorbed in the upper GI tract.

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