

Investigation of Solubility Enhancement Approach of Ticagrelor

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Abstract

The aim of this study was to increase the solubility and enhancement of dissolution rate of poorly water-soluble drug ticagrelor this was done through formulating and evaluate ticagrelor nanoparticles using solvent antisolvent technology. Ticagrelor is a practically water-insoluble drug which acts as an antiplatelet medicine. Fifteen formulas were prepared, and different stabilizing agents were used with various concentrations such as poly vinyl pyrrolidone (PVPK-30), poloxamer 188 (PXM) and hydroxypropyl methyl cellulose (HPMC). The ratios of drug to stabilizers used to prepare the nanoparticles were 1: 0.5, 1:1 and 1:2.

The prepared formulas were evaluated for the sake of particle size, dissolution study, Fourier transform infrared spectroscopy, differential scanning calorimetry, and scanning electron microscopy. On the other hand, the increasing dissolution rate as the particle surface area can be increased due to the reduction of particle size to the nano range. The results showed that hydroxy propyl methyl cellulose (HPMC) (F 12) was found to be the best stabilizer.

Keywords: Ticagrelor, Nanoparticles, Particle Size, hydroxy propyl methyl cellulose.

دراسة وسائل زيادة الذوبان للتيكاكريلور

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الخلاصة

الهدف من هذه الدراسة هو زيادة ذوبان وتعزيز انحلال جسيمات نانوية لعقار التيكاكريلور باستخدام تكنولوجيا الترسيب من مضاف المذيب. تيكاكريلور هو دواء غير ذائب في الماء وهو دواء يعمل على منع تخثر الصفائح الدموية. تم اعداد خمسة عشر صيغة باستخدام بوليمرات استقرار مختلفة استخدمت بتركيز مختلفة مثل الفانيل بايريلدون المتعدد (PVP)، بولوكسامير وهيدروكسي بروبيل المثيل السليلوز (HPMC) وكانت نسب الدواء الى المثبتات المستخدمة في اعداد الجسيمات النانوية هي 1:0.5، 1:1، 1:2. تم تقييم الصيغ المعدة من حيث الحجم الحبيبي للجسيمات، دراسة انحلال وكذلك دراسة التوافق (مطابقة الأشعة تحت الحمراء وقياس المسح التفاضلي) تقاضلية المسح الكالوري متري والمجهر الالكتروني. من ناحية أخرى يزداد تحرر الدواء كلما صغر حجم الجسيمات النانوية لزيادة المساحة السطحية للجسيم. وأظهرت النتائج ان هيدروكسي بروبيل المثيل السليلوز (HPMC) (F12) هو افضل بوليمر استقرار للجسيمات النانوية.

الكلمات المفتاحية: تيكاكريلور، الجسيمات النانوية، الحجم الحبيبي، هيدروكسي بروبيل المثيل السليلوز.

Introduction

Many problems may arise from the poor solubility of drug candidates in the field of drug research and development. The aqueous solubility⁽¹⁾ of the drug is a critical determinant of its dissolution rate, and its limited dissolution rate that can arise from the low solubility which can frequently result in a low bioavailability of the orally administered drugs. Also, a drug with aqueous solubility lower than 100 µg/mL, can present a dissolution-limited absorption. In such a case, dose escalation may be required until the blood drug concentration reaches the therapeutic drug concentration range⁽²⁾.

The dissolution rate is often the rate-determining step in the drug absorption for poorly soluble drugs only. The challenge facing these drugs is to enhance the rate of dissolution or solubility. Moreover, dissolution subsequently improves absorption and bioavailability. Such formulation methods targeting dissolution enhancement of poorly soluble substances are continuously introduced⁽³⁾. The released enhancement of poorly soluble drugs may be carried out by an increase of the drug surface area, the drug solubility, or by formulating the drug in its dissolved state.

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Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of a water-insoluble drug such as micronization, adsorption onto high surface area carriers, lyophilization, co-grinding, formulation of inclusion complexes⁽⁴⁾.

One of these different solubility enhancement techniques is the Nanotechnology which is Nano-sized particles having attractive characteristics and receiving at the same time considerable attention in the last decade. Polymeric nanoparticles (PNPs) are solid particles or particulate dispersions with size in the range of 10–1000 nm. Since these particles are small in size, the surface area is very large, so the percentage of atoms or molecules on the surface can be increased significantly⁽⁵⁾.

Ticagrelor molecular formula and molecular Mass: $C_{23}H_{28}F_2N_6O_4S$ (522.57 gm/mole). Ticagrelor is a crystalline powder with an aqueous solubility of approximately 3.5 μ g/ml at room temperature⁽⁶⁾. Ticagrelor exhibits no pKa value within the physiological range can be categorized as a class IV drug (low solubility, low permeability) with a mean absolute bioavailability of ticagrelor in healthy volunteers is 36 %⁽⁷⁾.

This study aims to increase the solubility and enhancement of dissolution rate of poorly water-soluble drug ticagrelor this is done through formulating and evaluate ticagrelor nanoparticles by using solvent antisolvent technology.

Materials and Methods

Materials

Ticagrelor powder was purchased from (AOPharm, China). Poly vinyl pyrrolidone PVP K-30, Poloxamer 188, HPMC, Sodium Starch Glycolate (HI Media Laboratories, India). Methanol (GCC Analytical reagent, UK). brij35 (Polyoxyethylene (23) lauryl ether) (Riedel De Haen Ag Seelze, Hannover, Germany). Magnesium stearate (Barlocher, GMBH, Germany).

Methods

Preparation of ticagrelor nanoparticles

Ticagrelor nanoparticles had been prepared by using solvent/antisolvent precipitation technique (Nanoprecipitation method). A certain amount of pure drug of ticagrelor had been completely dissolved in methanol/water miscible solvent.

The obtained drug solution had been injected at a speed of 1ml/min using syringe infusion pump into the water containing one of the stabilizers (PVP, PXM, and HPMC) with

continuous stirring. Precipitation of solid drug particles occurred immediately upon mixing. The precipitated nanoparticles had been sonicated at 37 °C for 30 minutes and then lyophilized using Freeze Drying System (Labconco, USA) to obtain the nanoparticles powder⁽⁸⁾.

The composition and variable conditions of preparation of different formulas of nanoparticles were shown in table (1).

Table 1. Composition of ticagrelor nanoparticles formulas.

Formula No.	Polymer	Solvent: antisolvent ratio Methanol: Water	Drug: Polymer ratio
F1	PVP	1:10	1:0.5
F2	PVP	1:10	1:1
F3	PVP	1:10	1:2
F4	PVP	1:05	1:1
F5	PVP	1:15	1:1
F6	PXM	1:10	1:0.5
F7	PXM	1:10	1:1
F8	PXM	1:10	1:2
F9	PXM	1:05	1:1
F10	PXM	1:15	1:1
F11	HPMC	1:10	1:0.5
F12	HPMC	1:10	1:1
F13	HPMC	1:10	1:2
F14	HPMC	1:05	1:1
F15	HPMC	1:15	1:1

Formulation variables affecting the properties of the prepared nanoparticles

To study the factors affecting the properties of the prepared nanoparticles, different formulas were utilized in these studies as follow:

Effect of polymer concentration

The effect on a physical characteristic of prepared nanoparticles studied with different concentrations of the same polymer like PVP (F1, F2, and F3), PXM (F6, F7, and F8), HPMC (F11, F12, and F13). The results of this factor were recorded.

Effect of solvent: antisolvent ratio

The effect of different solvent: antisolvent ratio on a physical characteristic of the prepared nanoparticles studied utilizing formulas (F2, F4, and F5) with PVP as stabilizer, (F7, F9, and F10) with PXM as stabilizer, (F12, F14, and F15) with HPMC as stabilizer. The results of this factor were recorded.

Effect of polymer type

The effect on a physical characteristic of prepared nanoparticles was studied with different polymer type like:

- I- At low polymer: drug ratio: F1, F6, and F11.
- II- At high polymer: drug ratio: F3, F,8 and F13.
- III- At low solvent: antisolvent ratio: F4, F9, and F14.
- IV- At high solvent: antisolvent ratio: F5, F10, and F15.

The results of this factor were recorded.

Evaluation of ticagrelor nanoparticles**Particle size analysis**

Samples of all prepared nanoparticles were analyzed using ABT-9000 nano laser particle size analyzer, and particle size distribution curves were obtained. Also, the average particle size, polydispersity index (PDI) for each sample were recorded⁽⁹⁾.

Determination of ticagrelor content in nanoparticles

To determine the drug content of the prepared nanoparticles, 200 mg sample of each prepared formula was placed in a glass mortar and thoroughly triturated using methanol. After thoroughly rinsing all equipment, the total mixture was transferred to a volumetric flask, and the volume was completed to 100 ml with methanol (96%). The resultant dispersion was sonicated for 15 min to ensure complete dissolution of ticagrelor. The mixture was filtered through an ordinary filter paper, and the absorbance of ticagrelor was determined spectrophotometrically. The amount of drug inside the nanoparticles was determined applying the equation of the calibration curve⁽¹⁰⁾.

Determination of percentage of yield and entrapment efficiency

Nanoparticles after being dried were weighed, and the yield was calculated as a percentage of the total weights of starting material (polymer and drug) introduced into the system (this represents the theoretical weight of nanoparticles) and the actual weight of nanoparticles obtained. The percent yield was calculated using the following equation⁽¹¹⁾.

$$\% \text{ Yield} = \frac{\text{Actual weight of nanoparticles gained}}{\text{Theoretical weight of nanoparticles}} \times 100$$

The entrapment efficiency of nanoparticles was determined from the theoretical and actual drug contents. The latter being determined from the results of the assay, described in section of drug content The percent entrapment efficiency was calculated the following equation.

$$\% \text{ Entrapment Efficiency (EE)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Determination of Ticagrelor nanoparticles saturation solubility

Saturation solubility of the selected formulas of ticagrelor nanoparticles was carried out using the shake flask method for different test media water, HCl buffer pH 1.2 with 1 % Brij 35 and phosphate buffer solution pH 6.8 with 1 % Brij 35. An excess amount of the drug nanoparticles was added to 10 ml of medium in a test tube and stirred in a water bath with the shaker at 37±2°C for 48 hours. Filtered samples were analyzed spectrophotometrically for drug content⁽¹²⁾.

Nanoparticles surface morphology studies**Scanning Electron Microscopy (SEM)**

Scanning electron microscopy was utilized to observe surface properties and as well as the particle size of nanoparticles. Scanning electron microscope of ticagrelor nanoparticles was operated with a secondary detector at different acceleration voltage and different magnification values.

Preparation of nanoparticles incorporated tablets of ticagrelor

Ticagrelor nanoparticles of the selected formulas with all excipients (except the lubricant) as listed in table (2) were accurately weighed and passed through 20 mesh sieve. The powder was blended in a poly bag by tumbling for 15 minutes. The blending was continuing for further 1 minute after addition of magnesium stearate as a lubricant. The final mixture was compressed using a 9-mm single punch tablet machine at 10KN compression force⁽¹³⁾

Table 2. Composition of nanoparticles incorporated tablets.

Composition (mg)	Formulation No.		
	F 2	F 7	F 12
Amount of nanoparticle equivalent to ticagrelor	90	90	90
Sodium starch glycollate	3 %	3 %	3 %
Magnesium stearate	2 %	2 %	2 %
Mannitol up to total weight	300	300	300

***In vitro* dissolution study**

The prepared tablets were subjected to dissolution study. The USP paddle method was used for the *in vitro* dissolution studies. In this method, HCL solution (pH1.2) with 1 % Brij 35 and phosphate buffer solution (pH 6.8) with 1 % Brij 35 were used as dissolution medium. The rate of stirring was 75 ± 2 rpm. The amount of ticagrelor was 90 mg in all formulations. The dosage forms were placed in 900 mL of both media and maintained at $37 \pm 0.1^\circ\text{C}$. At appropriate time intervals (5, 10, 15, 20, 30, 40, 50,60,70,90 and 100 minutes), five mL of the samples were taken and filtered through a 0.45-mm Millipore filter. The dissolution medium was then replaced by five mL of fresh dissolution fluid to maintain a constant volume. The samples were then analysed at λ_{max} of ticagrelor by UV-spectrophotometer. The mean of three determinations was used to calculate the drug release from each of the formulations.

Results and Discussion***Evaluation of the prepared nanoparticles******Particle size analysis***

Samples of all the prepared nanoparticles formulas were analysed by using ABT-9000 Nano Laser Particle Size Analyzer, and particle size distribution curves were obtained. Also, the average particle size and polydispersity index (PDI) of each sample were recorded in table 3.

Effect of polymer concentration

The results were shown in figure 1-3 of the nanoparticle of the three polymers (PVP, PXM, and HPMC) indicated that changing polymer concentration had an impact on ticagrelor nanoparticles mean size. Increasing polymer concentration to certain level led to increasing in mean particle size but observed only higher than drug: polymer equal ratio. These results could be explained by increasing polymer concentration which can caused more coating of drug particles until a particular concentration was reached where all drug particles were coated with a polymer. Then the increasing polymer concentration would led to increase the thickness of the polymer coat around each particle, or it may resulted in the aggregation of many particles and increased in the mean particle size⁽¹⁴⁻¹⁶⁾.

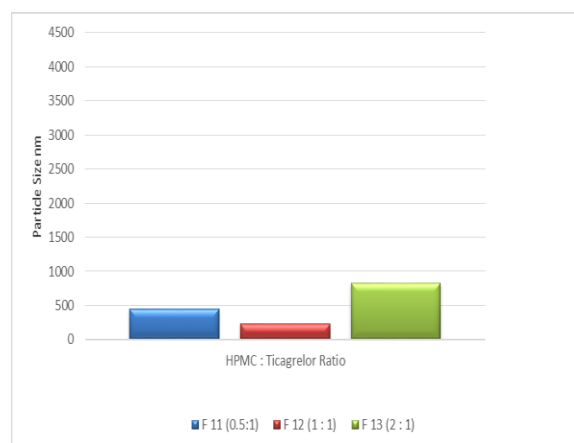
Effect of solvent: antisolvent ratio

The effects of changing the ratio of injected drug-solvent solution to stabilizer antisolvent solution on the mean size of the nanoparticles formed have been shown in figure 4-6. These figures illustrate that the solvent: antisolvent ratio 1:10 was the best ratio among the

other ratios and this, in turn, manifested that the former gave the lowest mean particle size for all types of polymer⁽¹⁷⁾.

Table 3. Particle size range of the prepared nanoparticles.

Formul a No.	Particle size range (nm)	Effectiv e particle size average (nm)	PDI
F 1	722.2-773.6	854	0.005
F 2	199.2-415.9	297.6	0.027
F 3	669-4126.5	1661.5	0.358
F 4	2107.7-10000	9471.7	0.221
F 5	41.4-10000	8086	0.475
F 6	285.3-2236.3	798.7	0.480
F 7	149.4-490.2	299.1	0.04
F 8	3695.7-4662.4	4151	0.005
F 9	1-10000	11303.4	0.402
F 10	7060.6-10035.6	10867.7	0.269
F 11	431.9-460.7	451.2	0.005
F 12	195.3-240.6	229.6	0.05
F 13	340.6-2031	831.9	0.343
F 14	3980.3-4524	5104.3	0.319
F 15	416.9-10000	4281.7	0.370

**Figure 3. Effect of HPMC: Ticagrelor on Ticagrelor nanoparticle size**

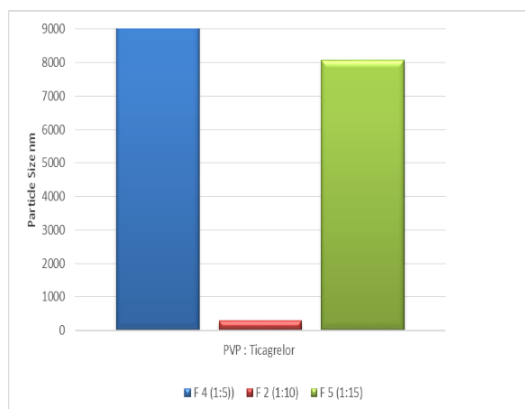


Figure 4. Effect of solvent: antisolvent ratio using PVP on ticagrelor nanoparticle size.

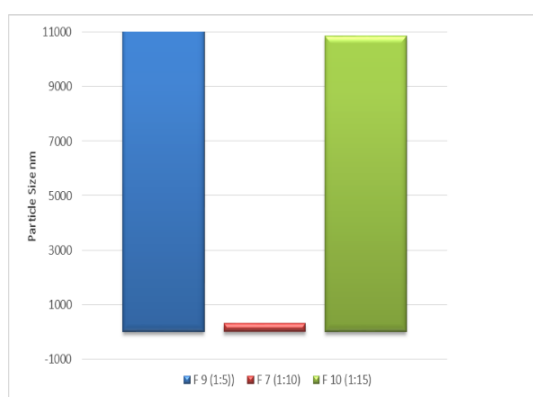


Figure 5. Effect of solvent: antisolvent ratio using PXM on ticagrelor nanoparticle size.

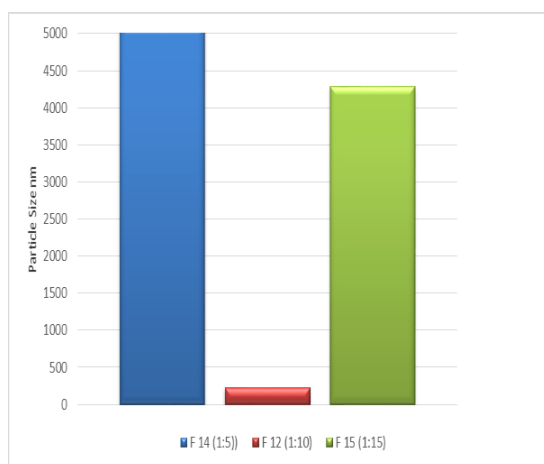


Figure 6. Effect of solvent: antisolvent ratio using HPMC on ticagrelor nanoparticle size

Effect of polymer type

The effect of polymer type on nanoparticle size was studied at two factors: I. drug: polymer ratio and II. levels of solvent: antisolvent ratio. At low drug: polymer ratio (1: 0.5), the polymers produce small particle size in the order of HPMC<PVP<PXM as shown in figure (7) and at high drug: polymer ratio (1:2), the order was

HPMC<PVP<PXM as illustrated in figure (8). It was noticed that there were significant differences in nanoparticles mean size between formulas using different polymer type as a stabilizer. These differences may be attributed to the difference in affinity of polymers to the drug particles. On the other hand, at low and high antisolvent: solvent ratio figure (9 and 10), the order of polymer produced small particle size was HPMC<PVP<PXM.

Polyvinylpyrillidone K-30 and HPMC were polymeric non-ionic stabilizers; they stabilize the system by steric stabilization which can be accomplished by adsorbing polymers onto the drug particle surface by an anchor segment that strongly interacts with the dispersed particles, while the other well-solvated tail part extends into the bulk medium. Moreover, the PVPK-30, is a well-known efficient polymeric stabilizer forming adsorption layers on drug nanoparticles,⁽¹⁸⁾ whereas the poloxamer 188 is an anion ionic surfactant⁽¹⁹⁾.

The formulations containing PVP K-30 and HPMC as stabilizers had a small particle size in comparison with the formulation containing poloxamer 188 that gave larger particle size. Poloxamer188 (pluronic F68)[®] is a block copolymer, responsible for the hydrophobic interaction with the drug molecule, the crystal growth inhibition is mainly due to the hydrophobic polypropylene oxide group (PPO) in the pluronic polymer, while the hydrophilic polyethylene oxide (PEO) chains provide steric hindrance upon aggregation⁽²⁰⁾. Poloxamer188 can form a valuable mechanical and thermodynamic barrier at the interface that hinders the approach and coalescence of individual emulsion droplets at their optimum level. Although this mechanism of poloxamer 188 gave larger particle size in all three ratios 0.5:1, 1:1 and 1:2 drug: the polymer in formulas F6, F7, and F8; respectively, the formulas that contain poloxamer188 as a stabilizer had large particle size. Such a thing may be attributed to the insufficient affinity, of poloxamer188 to ticagrelor, and possess a slow diffusion rate and ineffective adsorption onto the drug particle surface in the water-methanol mixture. However, if there is no affinity between the particle surface and the polymer, the attractive forces between two particles become dominant due to depletion of polymer from the gap of two particles (reduction force)⁽²¹⁾.

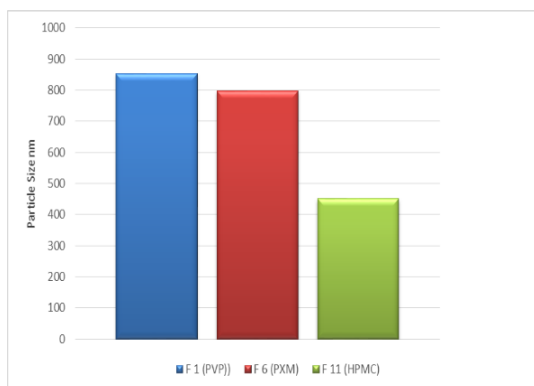


Figure 7. Effect of polymer type at low drug:polymer ratio (1: 0.5) on nanoparticles size

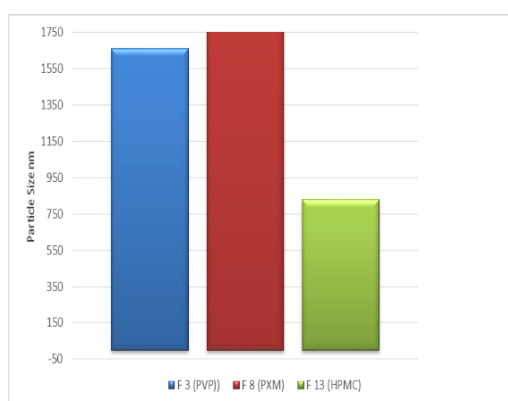


Figure 8. Effect of polymer type at high drug:polymer ratio (1: 2) on nanoparticles size.

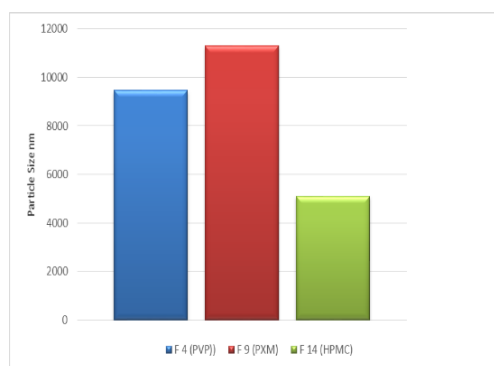


Figure 9. Effect of polymer type at low solvent:antisolvent ratio (1:0.5) on nanoparticles size

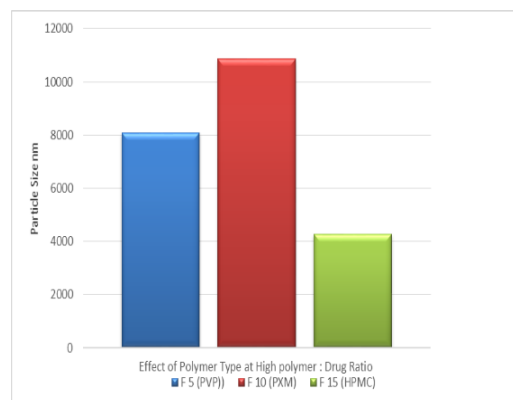


Figure 10. Effect of polymer type at high solvent:antisolvent ratio (1: 15) on nanoparticles size

Polydispersity index of the prepared nanoparticles

PDI shows in table 4 is an index of width or spread or variation within the particle size distribution and indications of the long-term stability of nanoparticles. Monodisperse samples have a lower PDI value, whereas higher values of PDI indicate a wider particle size distribution and the polydisperse nature of the sample. The usual range of PDI values is 0 - 0.05 (monodisperse standard), 0.05 - 0.08 (nearly monodisperse), 0.08 - 0.7 (mid-range polydispersity), and >0.7 (very polydisperse) ⁽²²⁾. The PDI results of the selected formulas (F2, F7, and F12) showed high uniformity in particle size of the prepared nanoparticles since it was in the monodisperse range which mainly attributed to the efficiency of the preparation method.

Table 4. Polydispersity index of selected formulas

Formula No.	Particle size (nm)	Polydispersity index (PDI)
F2	297.6	0.027
F7	299.1	0.04
F12	229.6	0.05

Percent yield and entrapment efficiency of prepared ticagrelor nanoparticles

The percentage yield and entrapment efficiency of ticagrelor nanoparticles of the selected formulas were shown in the table (5). The high yield percent and entrapment efficiency of the prepared nanoparticles indicated that technique applied in preparation of nanoparticles was good enough for such preparations.

Table 5. The percent yield and entrapment efficiency of selected formula

Formula No.	% yield	% EE
F2	91.5	90
F7	89	87.2
F12	95	92.5

Saturated solubility study of the prepared nanoparticles

The solubility of ticagrelor nanoparticles of the selected formulas in different solvents was determined as shown in the table (6). Ticagrelor nanoparticles saturation solubility increased in all of the three selected formulas (F2, F7, and F12). The saturation solubility's of Ticagrelor nanoparticles of the selected formulas in water increased 8.191, 7.121 and 9.376 folds relative to a pure drug for formulas F2, F7 and F12, respectively. The increase in saturation solubility was mainly due to nanonization effect^(23, 24).

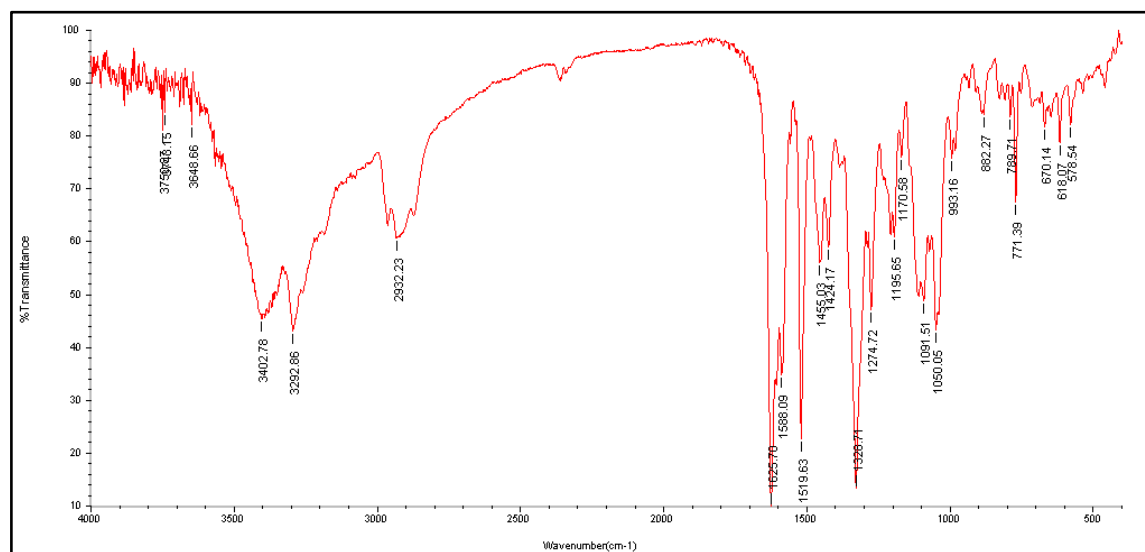
Table 6. Solubility data of the ticagrelor nanoparticle selected formulas in different media

Solvent	Solubility of selected formulas (mg/L)		
	F2	F7	F12
Water with 1% Brij 35	29	28	30
HCl solution pH 1.2 with 1% Brij 35	31.53	28.8	32.8
Phosphate Buffer pH 6.8 with 1% Brij 35	29.144	28	30.2

Drug compatibility study**Fourier Transforms Infra-Red Spectroscopy**

The Fourier Transforms-Infra Red spectrum gives some information about the functional groups that may interact with excipient during formulation. The IR spectrum of Ticagrelor figure (11) (12) showed the characteristic peak.

The spectra of the selected formulas F12 represented in figures revealed the presence of central peaks of drug which indicated that there was no noticeable interaction between drug and polymer during the preparation of nanoparticles.

**Figure 11. FTIR Spectrum of pure ticagrelor powder**

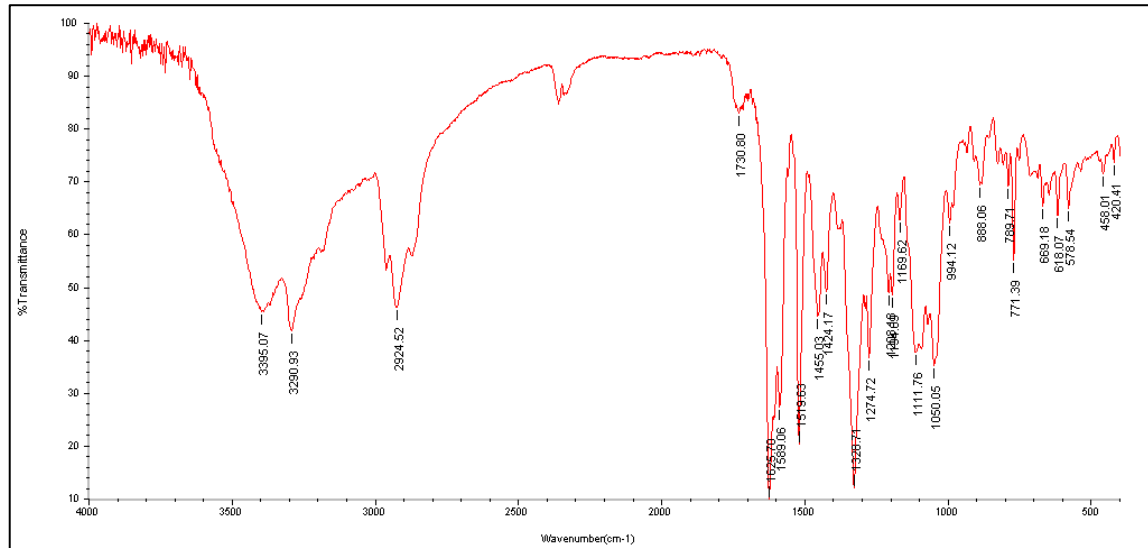


Figure 12. FTIR Spectrum of F12 (HPMC) nanoparticles

Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry thermogram of Ticagrelor showed a sharp endothermic peak at corresponding to its melting point which indicated a pure crystalline state of the drug as shown in figure (13) (14).

Also the thermogram of nanoparticles of the selected formula F12 as shown in figures indicated reducing in the crystallinity and conversion of more percentage of drug to amorphous form

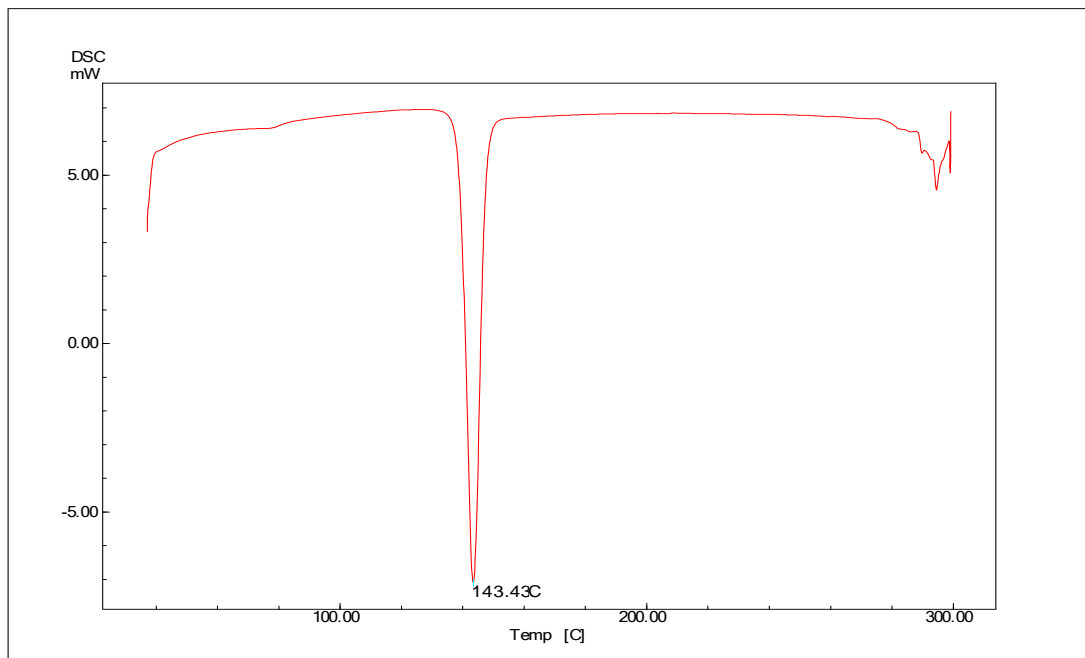


Figure 13. DSC thermogram of pure ticagrelor

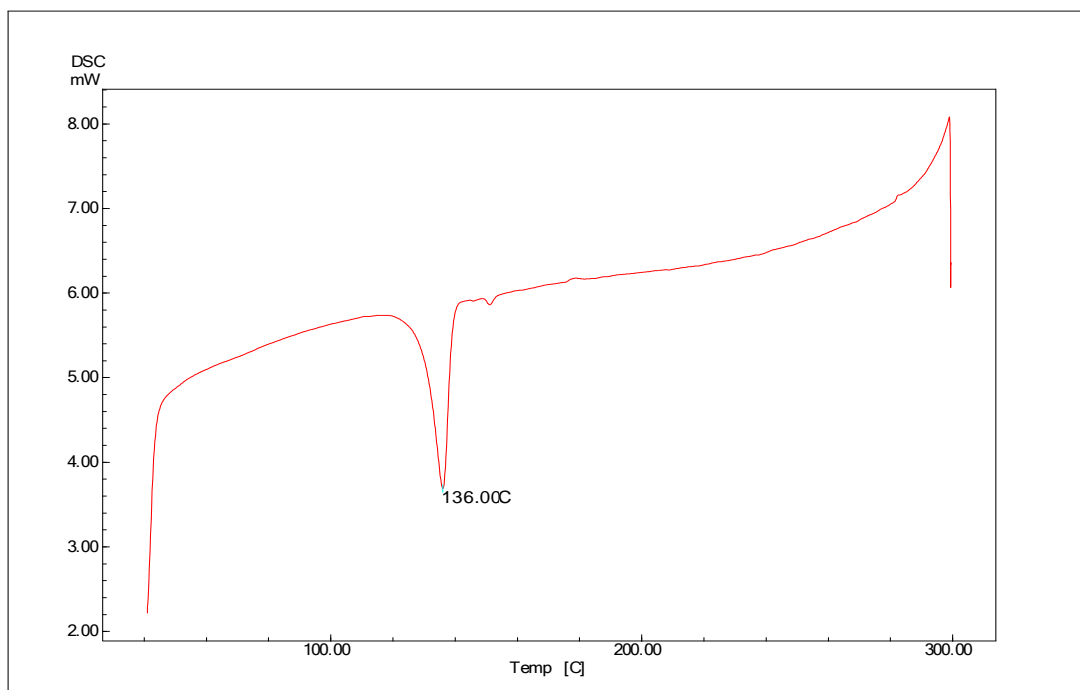


Figure 14. DSC thermogram of F12 (HPMC) ticagrelor nanoparticles.

***In vitro* dissolution study results**

The results of dissolution study of marketed tablet (Birlinta®) in different buffer pH figure (15) showed similarity with nanoparticle formulas representing by similarity factor (f_2) and dissolution efficiency (DE), generally in both media; in HCL buffer pH 1.2 (DE=85%) and in Phosphate buffer pH 6.8 (DE=89%). On the other hand, figures (16-19) showed the considerable improvement in dissolution represented by the dissolution efficiency of nanoparticles incorporated tablets of 88 % and 92 % for the F 12 and this mainly due to nanosizing of the particles which consequently enhanced the solubility. These results expected according to Noyes– Whitney equation where the solid dissolution rate is directly proportional to its surface area exposed to the dissolution medium (25-28).

The similarity factor f_2 is a measure of the similarity in the percent of dissolution between two curves. Current FDA guidelines (29) suggest that the dissolution profiles are considered similar if f_2 is greater than 50 (50–100), which is equivalent to an average difference of 10% at all sampling time points (30, 31).

The f_2 result agreed with the current FDA guidelines as shown in table 7.

Table 7. Similarity factor (f_2) and dissolution efficiency (DE%) of ticagrelor nanoparticles.

Formula No.	f_2		DE %	
	pH 1.2	pH 6.8	pH 1.2	pH 6.8
Birlinta®			89	85
F2	79	73	87	83
F7	64	54	85	80
F12	75	70	92	88

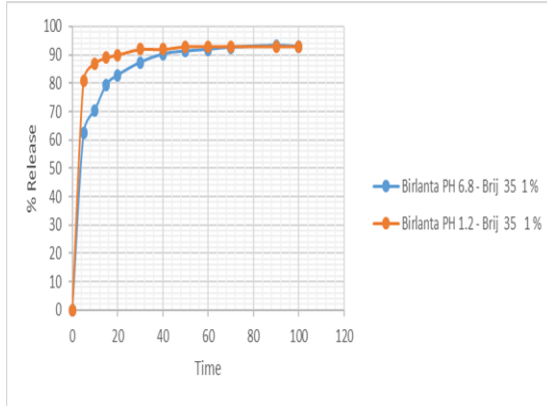


Figure 15. Dissolution profile of Birlanta in HCL buffer pH 1.2 and 6.8 with 1 % Brij.

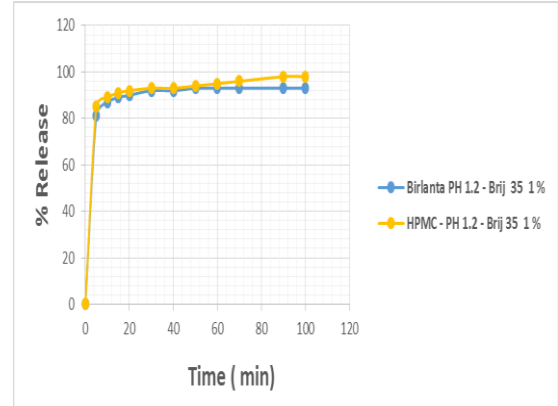


Figure 18. Dissolution profile of nanoparticle of selected formula F 12 incorporated in tablets in buffer pH 1.2 with 1 % Brij 35.

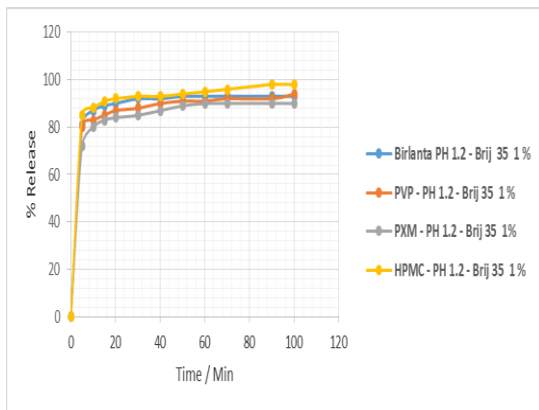


Figure 16. Dissolution profile of nanoparticle of selected formulas (F2, F7 and F12) incorporated in tablets in phosphate buffer pH 1.2 with 1 % Brij 35.

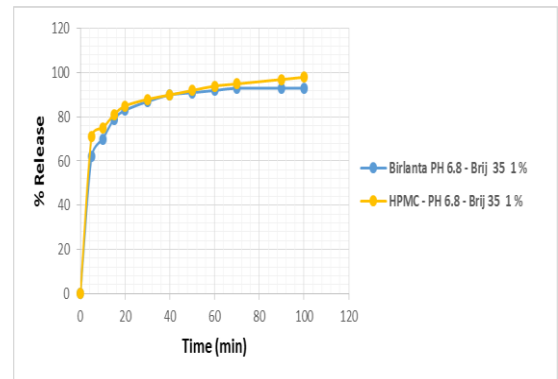


Figure 19. Dissolution profile of nanoparticle of selected formula F12 incorporated in tablets in phosphate buffer pH 6.8 with 1 % Brij 35.

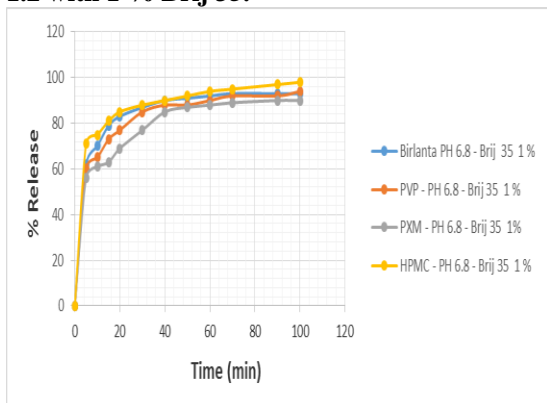


Figure 17. Dissolution profile of nanoparticle of selected formulas (F2, F7, and F12) incorporated in tablets in phosphate buffer pH 6.8 with 1 % Brij 35.

Further characterization of the optimum nanoparticle formula

Depending on the results of previous studies which demonstrate in a watertight way that formula F12 (HPMC) was the suggested formula for preparation of nanoparticle with optimum properties, thus it was subjected to advance analysis.

Scanning Electron Microscope (SEM)

The images of the SEM at different magnification as shown in figure (20) of nanoparticles obtained from the selected formulas (F12) indicated uniform submicron sized particles.

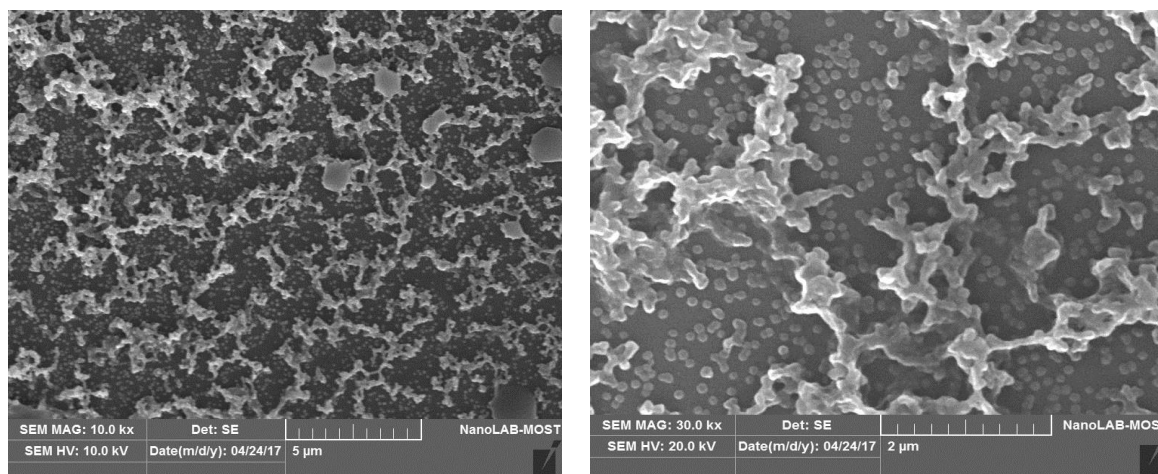


Figure 20. Scanning electron microscope image of F12 (HPMC) nanoparticles at different magnification

Conclusions

Depending on the result of the studies, one can conclude the following; the polymer, drug, and solvent: antisolvent ratio, in addition to polymer type, showed the considerable effect on the nanoparticle size.

The optimum formulation variables were 1:1 and 1:10 ratio for the drug: polymer ratio and solvent: antisolvent ratio respectively. Among the three polymers used, HPMC produced the smallest nanoparticle size. The optimum formula (F12) nanoparticles increment in saturated solubility about nine times that of pure drug. The dissolution efficiency of the Ticagrelor optimum formula nanoparticles F12 incorporated in tablet showed increment to (DE=92% and 88%) (pH 1.2 and pH 6.8), respectively in comparison to that of the marketed tablet (DE=89% and 85%). Also, similarity factor f_2 was 75 and 70 at pH 1.2 and pH 6.8, respectively for selected formula. Analysis by DSC and SEM of nanoparticles of selected formula (F12) indicated reducing in the crystallinity and changing to amorphous form of the drug.

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