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SPRAY DRIED DISPERSIONS: A VIABLE APPROACH TO IMPROVE BIOAVAILABILITY, TICAGRELOR AS A MODEL DRUG

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ABSTRACT

The present study aimed to investigate the processability of API-Hydrophilic carrier composite into formulation of solid dispersion and therefore to reveal the benefits of the composite formation in *IN-VIVO* performance. Spray dried dispersions (SDDs), consisting of active component embedded with hydrophilic polymer, were manufactured by Spray dryer. Release profile as well as *IN-VIVO* performance of the formulation with reference product was compared. Simple and economical spray drying method based on the solvent evaporation method was developed for the formulation of Ticagrelor solid dispersion. Initial characterization of physical mixtures, pure drug, reference product and solid dispersions were carried out by *in vitro* dissolution, dissolution efficiency, permeation study, wetting study, solubility study, FT-IR, differential scanning calorimetry (DSC) and *IN-VIVO* bioavailability study. DSC study showed that Ticagrelor was present in its amorphous form. FT-IR study showed there is no incompatibility between any polymeric systems with drug components. Improvement in the solubility and dissolution rate was observed for all samples. During ageing study, almost no decrease of *in vitro* drug dissolution was observed as compare with freshly prepared solid dispersions. Solid dispersions showed more than 75% Ticagrelor release after 45 min during dissolution test. *IN-VIVO* bioavailability study shows more than two fold increase in bioavailability compare to market formulation. The result showed that the spray drying process of a liquid feed is an attractive and promising alternative to obtain enhanced solubility of drug in solid dispersions. Thus,

present study demonstrated the high potential of spray drying process technique for obtaining stable free flowing solid dispersions of poorly water-soluble drugs using various solubilizing polymers.

KEYWORDS: Spray dried dispersions, Solubility, Dissolution rate, Spray drying technique, Solubilizing polymers, Anti-static agent, *IN-VIVO* bioavailability study.

INTRODUCTION

Ticagrelor is a platelet aggregation inhibitor. Like the thienopyridines prasugrel, clopidogrel and ticlopidine, ticagrelor blocks adenosine diphosphate (ADP) receptors of subtype P2Y12. In contrast to the other antiplatelet drugs, ticagrelor has a binding site different from ADP, making it an allosteric antagonist, and the blockage is reversible. Moreover, the drug does not need hepatic activation, which might work better for patients with genetic variants regarding the enzyme CYP2C19 (although it is not certain whether clopidogrel is significantly influenced by such variants).[1,2]

The chemical name (IUPAC) of Ticagrelor is (1S,2S,3R,5S)-3-[7-{[(1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5- (propylthio)-3H-[1,2,3]triazolo[4,5- d] pyrimidin-3-yl]-5-(2- hydroxyethoxy)cyclopentane-1,2-diol corresponding to the molecular formula C23H28F2N6O4S. The CAS number of Ticagrelor is 274693-27-5. The molecular mass is 522.57.[12,3]

Ticagrelor is a powder with a melting point 140-142° C The drug substance has low water solubility (0.016 mg/mL at 20 ±5°C). It does not exhibits pH dependent solubility in aqueous buffers. Ticagrelor is a BCS Class 4 compound (low solubility, low permeability).[1,3,4]

Four polymorphs have been identified. This form has been used in all pre-clinical and clinical studies and it does not convert to any other form on storage.

Therefore, various formulation approaches have been followed to improve the dissolution rate as well as the bioavailability of Ticagrelor.

SD was selected for evaluation as an alternative drug delivery system to enable a higher drug loading per unit dose. SD of Ticagrelor has been focused on water-soluble carrier only. Solubilization of poorly soluble drugs such as Ticagrelor within the GIT is considered a crucial step in the oral absorption process. The selection of suitable carriers has extensively

been reviewed. The use of water-soluble carriers such as Kolliphor and Gelucire class carriers with solubilising properties have been studied as tools to enhance the solubility of poorly water soluble drugs.[3-6]

The spray-drying technique is extensively used in the pharmaceutical industry to produce dispersions, micro particles, as an alternative to emulsification methods. This technique transforms the liquid feed into a dry powder in one step and is feasible for the scaling-up of the microencapsulation, continuous particle processing operations and can be applied to a wide variety of materials. Spray drying can be also used to enhance the solubility and improve particulate design. Solid dispersions (SD) are used to increase bioavailability of poorly soluble APIs. Through proper formulation and selection of excipients, the SD technology is applicable to compounds with a broad range of physiochemical properties.[7] [8]

Solvent evaporation method by spray drying technique was chosen as the appropriate method to develop the SD. The primary objective of this study was to optimize SD formulation using attainable manufacturing process as well as pharmaceutically acceptable excipients. The second goal was to characterize formulated solid dispersions (SD) for solubility/ Bioavailability enhancement and for short term stability study as per ICH guidelines.[4,7,9-13]

MATERIALS AND METHODS

Materials

Ticagrelor was gifted from Alembic Research Center, Gujarat, INDIA. Gelucire 50/13 (Stearoyl Macrogoglycerides EP, solid pastilles) and Gelucire 44/14 (Lauroyl Macrogoglycerides EP, semi-solid) were generous gift from Gattefosse, Mumbai, INDIA. Lutrol F 68 and Lutrol F127 were obtaining from BASF Corporation, Mumbai, INDIA. All other chemicals and solvents were of analytical grade.

Methods

Phase Solubility Study: Phase Solubility study was conducted as per the method reported by M. Cirri et.al.[14] Drug and carrier as per the specified drug: carrier ratio were weighed accurately and added to pure drug with 10 ml of water in screw capped bottles. All the bottles were shaken in incubator shaker at 24°C and 37°C for 24 h. The container with drug and water was used as control. After 24 h the solutions were filtered using (0.4 nm) filter paper and the filtrates were diluted. The absorbances were measured in spectra at 295 nm. From the absorbance the solubility of the drug were calculated.

Preparation of Physical Mixtures

Physical mixtures containing the base pellets, drug, carrier and other excipients were prepared in the same proportions used for SD preparation in order to allow comparison between them. The ingredients were slowly mixed with a spoon in a glass flask. These physical mixtures were tested for their physical properties and Ticagrelor solubility.

Preliminary trials for selection of Hydrophilic polymer

In this study, Hydrophilic polymers were used to formulate solid dispersion. Different grade of Gelucire and Kolliphor were evaluated for the preparation of solid dispersion. Different Drug: polymer ratio was selected based on phase solubility data as describe in table no 1.

Preparation of the Solid Dispersions feed system

After several trials, it was found that ethanol and dichloromethane (DCM) in 60:40 ratio was able to adequately dissolve both API as well as hydrophilic polymer and easy to feed into spray drying process. Solid dispersions of Ticagrelor and various polymers in different ratios were prepared using spray drying process. Add polymer slowly in this solvent and continue stir for 30 minutes or till clear solution is obtained. Add Talc (ultramicronized) to above solution with continuous stirring for at least 15 minutes or till homogeneous dispersion is obtained. Drug dispersion system prepared using above prepared dispersion and add drug slowly till dispersion become homogenous. This mixture was homogenized with a magnetic stirrer at 300-600 rpm. The suspensions obtained by this procedure were spray dried in a laboratory-scale spray dryer.

Spray drying Process

The drying process was studied in a laboratory-scale spray dryer (model LU 222 Advanced Labultima, Mumbai, INDIA) equipped with a two-fluid pneumatic atomizer. The cylindrical drying chamber is made of borosilicate glass and is 130 mm in diameter and 510 mm in height. The maximum water evaporation capacity is 0.5 L per hour at the air inlet temperature of 180 °C. The following set of conditions was kept fixed for all experiments: suspension feed rate of 3 ml/min, atomization air pressure 4.0 kg/cm^2, drying air flow rate 45 Nm^3/hr, Inlet temperature 70 °C, outlet temperature 40-45 °C, Vacuum -110 to -120 mm H_2O.

Optimum solid dispersion batch was finalized to Tablet formulation and characterized for further study.

Characterization of SD

Saturation Solubility

Saturation solubility studies were conducted as per the method reported by J.Hecq et.al.[15] To evaluate the increase in solubility of Ticagrelor after spray drying (with hydrophilic carriers) or only by the presence of excipients (physical mixtures), saturation solubility measurements were conducted. The known excess (approximately 50 mg) of Ticagrelor was added to 10 ml of dissolution media. Samples were rotated at 20 rpm in a water bath (37 °C) for 48 hours. The samples were then filtered, suitably diluted and analyzed by UV spectrophotometer at 295 nm.

Drug Content

SD equivalent to 90 mg of Ticagrelor were weighed accurately and dissolved in a suitable quantity of methanol. The solutions were filtered through a membrane filter (0.45 mm). The drug content was determined at 295 nm by UV spectrophotometer (Shimadzu 1800) after suitable dilution.

Determination of Flow properties & Percent Yield

Bulk and tapped density: The volumes corresponding to 30 gm samples of SDDs powders were determined in a 100 mL graduated cylinder. Tapped density was determined with the help of a tap density tester to allow a controllable and reproducible level of tapping.

Hausner's ratio (HR) and Carr's index (CI): HR and CI were used to indicate the compressibility properties of the materials and were calculated using the measured values of the tapped and the bulk density of the powders. According to their definitions,

HR = Bulk density/tapped density

CI% = (tapped density-bulk density/tapped density)* 100.

Angle of repose: Angle of repose was determined by the funnel method. A 5-g sample of powder was allowed to flow down in a glass funnel onto a flat circular base with known diameter. The height of the heap formed was measured with a calliper and angle of repose was calculated, using following formula,

Angle of repose $\Theta = \tan^{-1}(H/r)$

Where H= height of the heap formed, r= radius of circle formed

Percent yield

The percent yield of Ticagrelor pellets was determined by using the following formula,

Percent yield= (Weight of prepared pellets/weight of drug + carriers)* 100

Flodex study

Determine appropriate Disk size to free flow of the blend and evaluate flow characteristics of the SDDs.

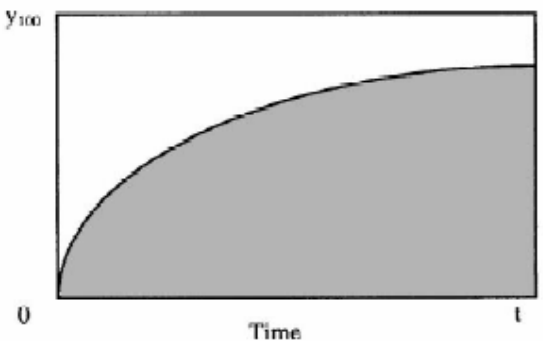
***In vitro* Drug Release Study**

Dissolution is a critical parameter for Ticagrelor, as it is a poor water-soluble drug. Dissolution studies were carried out for all the developed formulations. Dissolution of marketed Ticagrelor formulation was also carried out for comparison.

Dissolution test was performed using USP apparatus type II for 75 min. Samples of spray dried dispersions equivalent to 90 mg of the drug and reference product were added to the dissolution medium 0.2% w/v Polysorbate 80 in water at a temperature of 37°C ± 0.5°C, which was stirred at 75 rpm. At suitable time intervals (10, 20, 30, 45, 60 and 75), 10 ml samples were withdrawn and analyzed at λmax of 295 nm using UV visible spectrophotometer. Equal volume of fresh medium prewarmed at the same temperature was added in to the dissolution medium after each sampling to maintain its constant volume throughout the test. Each test was performed in triplicate and calculated mean values of cumulative drug release were used while plotting the release curves.

Dissolution efficiency (%): Dissolution efficiency (DE) represents the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100 % dissolution in the same time.

$$D.E. = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\%$$



Where y is the drug percent dissolved at time t

Wetting study and Permeation study

The funnel method of Ticagrelor and selected batches were investigated as per the method reported by M.C. Gohel et.al[16] and permeation study through Cellulose nitrate membrane method reported by Sunil Kumar et.al[17] respectively.

Differential scanning calorimetry

Modulated DSC analysis was conducted using a Shimadzu Instruments Model TA- 60 (Japan) equipped with a refrigerated cooling system. Samples were weighed to 5 ± 0.5 mg in aluminum crimped pans. Samples were heated at a rate of 10 °C/min from 30 to 300 °C with modulation temperature amplitude of 0.5 ºC and a modulation period of 40 seconds for all studies. Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 40 ml/min. The thermogram for pure Ticagrelor and various polymer based spray dried dispersions of Ticagrelor were obtained.

FT-IR study

Drug-excipients interactions play a vital role in the release of drug from formulation. The pure Ticagrelor and its mixture with polymer and drying aids were mixed with IR grade KBr and were scanned over a range of 400-4000 cm^{-1} using FTIR instrument (FTIR-1700, Shimadzu, Kyoto, Japan).

***IN VIVO* study**

Performed Open label, Balanced, Randomized, Two-Treatment, Two-sequence, Two-Period, Single dose, Crossover design, Oral Bioavailability study of Two different formulation of Ticagrelor (Test Vs. reference) in normal healthy Albino rabbits subject in group of 6 under fasting condition. After administration of a dose of Ticagrelor, about 1ml of blood sample was collected through marginal ear vein up to 24hr.

Study protocol

The protocol for in vivo pharmacokinetic study of Ticagrelor was approved, under protocol no. **IP/PCOL/FAC/20/36**, by the Institutional Animal Ethics Committee (IAEC), Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India. This study was carried out to predict the comparative in vivo drug release behaviour of Ticagrelor SDDs (optimized batch) and reference product. 12 Albino rabbits, having weight between 2.0 to 2.5 Kg, were taken for the study. Rabbits were randomly divided in two groups- one group for suspension of reference product and another group for suspension of test product. Animals were kept under

fasting condition overnight with free access of water. Suspension (in water) of both Ticagrelor SDDs (optimized batch) and reference product were orally administered to the animals in dose equivalent to 63 mg/kg body weight of Ticagrelor. After oral administration of both the suspensions to the respective groups of animals, 1.0 ml of blood sample were collected from the marginal ear vein at 0, 0.25, 0.5, 0.75, 1, 1.25, 2, 3, 6, 12 and 24 h time intervals.

Assay method: The drug from the plasma samples are extracted by optimizing a method for extraction. 500µl rabbit plasma is taken in a screw-capped plastic tube and 2.5 ml of Acetonitrile is added in plasma sample and vortexes for 1 min to extract Ticagrelor. Blood samples were centrifuged at 10,000 rpm for 10 min at 4 °C in refrigerated centrifuge (BL-150R, Biolab, Mumbai, India) to separate the plasma from other blood components. Plasma samples were stored at −20 °C until further HPLC analysis for the drug content. The developed method for the determination of drug is optimized for chromatographic conditions. The volume of injection was 10 µL. All solutions were filtered through a 0.45 µm filter before injection into the column. The flow rate was set at 1.0 mL/min with a mobile phase of (Potassium dihydrogen phosphate buffer, pH5.5: Acetonitrile) (55: 45 v/v). The mobile phase was filtered under vacuum through a 0.45 µm modified hydrophilic PTFE membrane and degassed ultrasonically for 30 min prior to use. The column temperature was maintained at 25 °C. Peak areas (in volts) were used as the measured analytical response, with detection at 295 nm.

RESULTS

Phase solubility study: Phase solubility study of Ticagrelor was conducted as per the method reported by M. Cirri et.al.[14] Table: 1 gives the phase solubility data. The solubility of Ticagrelor was found to be increasing constantly on increasing the concentration of the carrier when physically mixed with the drug. The negative ΔG values of the formulations indicate the spontaneity of the process at low temperature. The thermodynamic Parameters results proved the solubilisation effect of the carrier on the drug.

Table. 1: Phase solubility data to determine ΔG value.

System	Slope	Intercept	Ka	Log Ka	ΔG (Kj/mol)
Lutrol F68	0.860	2.280	2.694	0.430	-0.585
Lutrol F127	0.820	2.360	1.930	0.286	-0.388
Gelucire 44/14	0.890	3.110	2.602	0.415	-0.564
Gelucire 50/13	0.860	3.210	1.914	0.282	-0.383

Characterization of Solid Dispersions

Powder Characterization

Flow properties for solid dispersion like Bulk density, Tapped density, Carr's index, Hausners ratio, Angel of repose and Flodex study were performed and found within optimum flowability. Optimum batch freely pass through 15 mm disk, found 66 flowability index which reflect medium flowability.

Saturated solubility study, Drug content and Percent yield

Aiming to characterize the SD obtained with highest solubility and acceptable yield, several physical-chemical analyses were carried out, like solubility, practical yield and drug content. All parameters for various polymeric systems were described in table 2. The solubility of Ticagrelor was determined in dissolution media. In every polymeric system polymer concentration increases solubility comparatively increased in a small scale.

Table. 2: Saturated Solubility and % yield data of pure API with various polymeric binary mixtures.

Sr No.	Batch no.	Polymer	Drug-polymer ratio	Solubility (µg/ml)	% yield
1	Pure drug	-	-	3.22	-
2	G50/3	Gelucire 50/13	1:3	29.54	65
3	P188/3	Kolliphor P188	1:3	23.42	68
4	P407/3	Kolliphor P407	1:3	15.28	72
5	G44/3	Gelucire 44/14	1:3	28.54	70
6	-	RLD	-	6.52	-
7	G50/1	Gelucire 50/13	1:1	14.54	65
8	G50/2	Gelucire 50/13	1:2	21.78	70

***In vitro* dissolution study**

Table 3 shows the release data and profile of Ticagrelor SD. The interpretation of the data and the profile showed that the cumulative percentage release (CPR) from Ticagrelor SD were higher than pure drug. The CPR from the batches was also found to be increased on increasing the concentration of the carrier incorporated in formulations.

%CPR, Mean Dissolution Time and %DE considered as characteristics parameters for obtained formulations. Results obtained from the batches prepared from various polymers are summarized in Table 3. As we increased the ratio of polymer compare to drug it increased the *in vitro* dissolution of Ticagrelor in comparison with pure drug and market product. Ratio of 1:3 (Drug: Gelucire 50/13) in solid dispersion was selected for optimization. In every

polymeric SD system as polymer concentration increases compare to drug it increases dissolution of drug so we selected highest concentration of all batches for further study.

Dissolution efficiency

In vitro drug release data obtained from various batches summarized in table 3 describe that dissolution efficiency of SD was much higher compare to pure drug and marketed formulation. All data were summarized in table 3.

Table. 3: Comparison of *in vitro* drug release, MDT and %DE from different formulations.

Sr No.	Time (Min)	Cumulative Percentage Release (CPR)*						
		Batch No						
		G50/1	G50/2	G50/3	G44/3	P188/3	P407/3	Reference
1	0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	10	32.933 (15.605)	43.067 (5.115)	47.600 (6.410)	24.267 (19.246)	33.267 (13.424)	29.400 (8.999)	39.000 (7.302)
3	20	69.100 (4.927)	63.967 (7.276)	67.600 (3.131)	42.100 (5.676)	44.333 (10.736)	40.267 (11.330)	68.967 (4.193)
4	30	73.300 (3.984)	74.300 (6.346)	84.933 (3.618)	58.333 (3.434)	65.233 (4.681)	55.667 (7.098)	79.267 (3.533)
5	45	76.000 (4.728)	79.067 (5.086)	93.767 (2.806)	79.833 (4.878)	76.267 (3.560)	78.633 (4.268)	85.167 (3.554)
6	60	94.500 (1.977)	94.267 (2.016)	97.433 (1.107)	94.900 (3.380)	93.333 (1.287)	95.433 (1.327)	94.633 (2.378)
7	75	97.100 (2.699)	99.733 (1.289)	101.367 (1.135)	99.433 (2.062)	97.933 (1.586)	99.600 (1.516)	98.633 (2.578)
Mean Disso. Time		0.30 hr	0.34 hr	0.30 hr	0.45 hr	0.41 hr	0.46 hr	0.32 hr
%DE at 45 min		46.96	47.57	55.50	48.17	46.53	47.37	51.81

Wetting study: The funnel method of Ticagrelor and selected batches were investigated as per the method reported by M .C. Gohel et.al[16] and Sunil Kumar et.al[17] respectively and findings are shown in Table 4. The wetting time of the pure drug was found higher indicating poor wettability of the drug. The wetting time of samples was found to be very less compare to pure drug. This behaviour may be attributed to increased wettability by the action of hydrophilic carrier used in the formulation.

Permeation study: The data for Cellulose nitrate membrane was given in the Table 4. It was observed that the amount of drug permeated from selected batches in both membranes was found to be higher than pure drug. The results can be considered as the evident for increase in release rate of Ticagrelor from Solid dispersions.

Table. 4: Permeability data and wettability data of various batches.

Batch codes	Drug: polymer ratio	Permeability (mg/ml/hr)		Wettability	
		Cellulose acetate membrane		Funnel method (min)	
		SDDs	PM	SDDs	PM
Pure drug	-	0.011		65	-
	1:3	0.044	0.022	48	52
	1:3	0.052	0.028	42	48
	1:3	0.038	0.018	44	54
	1:3	0.040	0.024	51	53

DSC study: DSC analysis demonstrated that Ticagrelor was rendered entirely amorphous in this formulation as indicated by the absence of the melting endotherm peak, which is seen with the Ticagrelor pure drug. In the binary mixture of drug and polymer suppression of endothermic peak was seen.

FT-IR study: The FTIR spectra of Ticagrelor SDDs showed characteristic peaks of Ticagrelor in all formulation.

***IN VIVO* study:** The collected plasma samples were analyzed using laboratory developed validated HPLC method. Pharmacokinetic parameters describe in table no 5 reveals more than 2 fold increase in the Cmax of test formulation in comparison of reference formulation. From the above discussion it is clear that improvement in solubility and dissolution rate of Ticagrelor from solid dispersion has been reflected in increase in Cmax and AUC in comparison to reference formulation. The study revealed improvement in the bioavailability of Ticagrelor from solid dispersions.

The comparative plasma concentration time profile of optimized batch and reference product in rabbits were plotted and are shown in Fig. 1, while pharmacokinetic parameters were calculated using PK Solver. PK Solver is a freely available add-in program in Microsoft Excel for pharmacokinetic and pharmacodynamics data analysis. A marked increase of more than two fold in peak plasma concentration (C) was observed after administration of Ticagrelor SDDs (15.394 ± 0.54 µg/ml) as compared to Reference product (6.866 ± 0.824 µg/ml). Peak plasma concentration was achieved with in (T) 90 min in both cases. A marked increment (more than two fold) in bioavailability of Ticagrelor was observed after oral administration of Ticagrelor SDDs, with an increase in AUC max (133.090 µg h/ml vs. 69.492 µg h/ml) as compared to Reference product. The increase in bioavailability could be due to an increase in saturation solubility and dissolution velocity of the Ticagrelor SDDs.

Table. 5: Pharmacokinetic parameters of Test vs Reference.

Parameters	Test	Reference
Dose	63 mg/kg	63 mg/kg
Cmax	15.394 ± 0.54 µg/ml	6.866 ± 0.824µg/ml
Tmax	1.5 hr	1.5 hr
AUC0-t	133.090 µg*hr/ml	69.492 µg*hr/ml
AUC0-∞	143.622 µg*hr/ml	75.161 µg*hr/ml
AUCt - ∞	10.532 µg*hr/ml	5.669 µg*hr/ml
Kel	0.112	0.118
T1/2	6.192 Hr	5.866 Hr

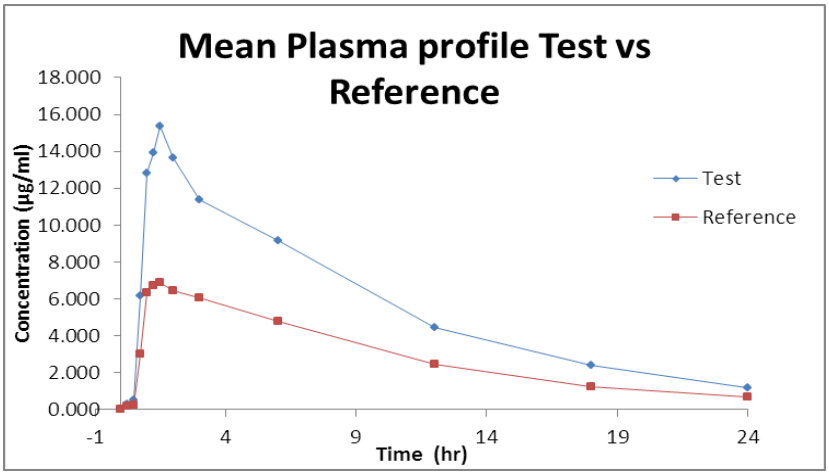


Figure. 1: AUC comparison Test vs Reference.

CONCLUSION

The results show that the spray-drying process for producing a solid dispersion of Ticagrelor starting from liquid feeds is an attractive and promising alternative to increase drug solubility, together with adequate pharmacotechnical properties. Spray drying can be used to obtain differentiated properties in the SD can be designed to optimize solid dispersion properties. It can also be concluded that the best condition to obtain SD containing Ticagrelor with adequate flow and compressibility properties and the best solubility was the one performed with 1:3 (Ticagrelor : Gelucire 50/13) combination.

In this study, Ticagrelor solid dispersions were successfully prepared by spray drying process using Hydrophilic polymers. Drug: Gelucire 50/13 1:3 ratio exhibited better solubility & Bioavailability of Ticagrelor as compared to other polymeric system. Formulation was characterized for in vitro drug release as well as *IN VIVO* bioavailability study. Results of DSC and FTIR are showing compatible drug-polymer system after process which resulted in increase in the solubility as well as in vitro dissolution. Significant enhancement in bioavailability of Ticagrelor was observed after oral administration of Ticagrelor SDDs tablet

as compared to Reference product. The results show that the spray-drying process for producing a solid dispersion of Ticagrelor starting from liquid feeds to SDDs is an attractive and promising alternative to increase drug solubility, together with adequate pharmacotechnical properties. It can also be concluded that the best condition to obtain SD containing Ticagrelor, the best solubility/bioavailability was the one performed with 1:3 (Ticagrelor: Gelucire 50/13) combination. Thus, the results obtained in the study are in support for the application of Hydrophilic carrier system in spray drying process in the preparation of Ticagrelor solid dispersion.

Declaration of interest: The authors report no conflicts of interest.

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REFERENCES

1. Yan-yu X, Yun-mei S, Zhi-peng Ch, Qi-neng P. Preparation of Ticagrelor proliposome: A new way to increase oral bioavailability of Ticagrelor in beagle dogs. Int. J. Pharm, 2006; 319: 162–168.
2. El-Samaligy MS, Afifi NN, Mahmoud EA. Evaluation of hybrid liposomes-encapsulated Ticagrelor regarding physical stability and in vivo performance. Int. J. Pharm, 2006; 319: 121–129.
3. Wu W, Wang Y, Que L. Enhanced bioavailability of Ticagrelor by selfmicroemulsifying drug delivery system. Eur. J. Pharm. Biopharm, 2006; 63: 288–294.
4. Woo JS, Kim TS, Park JH, Chi SC. Formulation and biopharmaceutical evaluation of Ticagrelor using SMEDDS. Arch. Pharm. Res., 2007; 30: 82–89.
5. Iosio T, Voinovicha D, Perissutti B, Serdoza F, Hasaa D, Grabnarb I, Dall'Acquac S, Zarad GP, Muntonid E, Pintoe JF. Oral bioavailability of Ticagrelor phytocomplex formulated as self-emulsifying pellets. Phytomedicine, 2010; 18, 505–512.
6. Sun NY, Wei XL, Wu BJ, Chen J, Lu Y, Wu W. Enhanced dissolution of Ticagrelor /polyvinylpyrrolidone solid dispersion pellets prepared by a one-step fluid-bed coating technique. Powder Technol, 2008; 182: 72–80.
7. Ford JL. The status of solid dispersions. Pharm. Act. Helv, 1986; 61: 69–88.

8. Fouad EA, EL-Badry M, Mahrous GM, Alanazi FK, Neau SH, Alsarra IA, The use of spray-drying to enhance celecoxib solubility. Drug Dev. Ind. Pharm, 2011; 37: 1463–1472.
9. Barker SA, Yap SP, Yuen KH, McCoy CP, Murphy JR, Craig DQM. An investigation into the structure and bioavailability of [alpha] tocopherol dispersions in Gelucire 44/14. J. Control Release, 2003; 91: 477–488.
10. Karatas A, Yüksel N, Baykara T. Improved solubility and dissolution rate of piroxicam using Gelucire 44/14 and labrasol. Farmaco, 2005; 60: 777–782.
11. Barakat NS. Etodolac-liquid-filled dispersion into hard gelatin capsules: An approach to improve dissolution and stability of etodolac formulation. Drug Dev. Ind. Pharm, 2006; 32: 865–876.
12. Lukovac S, Gooijert KEG, Gregory PC, Shlieout G, Stellaard F, Rings EHHM, Verkade HJ. Gelucire® 44/14 improves fat absorption in rats with impaired lipolysis. Biochim. Biophys Acta, 2010; 1801: 665–673.
13. Hilden LR, Morris KR. Physics of amorphous solids. J. Pharm. Sci., 2004; 93: 3-12.
14. Cirri M, Mura P, Rabasco AM, Gines JM, Moyano JR, Gozalez R. Characterization of Ibuproxam binary and ternary dispersion with hydrophilic carriers. Drug DevInd Pharm, 2004; 30: 65-74.
15. Hecq J, Deleers M, Fanara D, Vranckx H, Amighi K. Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. Int J Pharm, 2005; 299: 167-177.
16. Gohel MC, Patel LD. Processing of nimesulide PEG 400-PEG-PVP solid dispersions: preparation, characterization and in-vitro dissolution. Drug Dev Ind Pharm, 2003; 29: 299-310.
17. Sunil KB, Michael AR, Soumyajit M, Rao Y. Formulation and evaluation of rapidly disintegrating fenoverine tablets: Effect of superdisintegrant. Drug Dev Ind Pharm, 2007; 33: 1225-1232.