Solubility enhancement of BCS classified IV drug - Apixaban by preparation and evaluation of Mesoporous Nanomatrix

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ABSTRACT

Biopharmaceutics classification system (BCS) class IV compounds, exhibits low solubility, intestinal permeability and oral bioavailability among all the pharmaceutical class of drugs. Therefore, these drugs need a more compatible and efficient delivery system. Since, their solubility in various mediums will remains a limitation. Hence, the mesoporous Nanomatrix approach may prove to be a suitable solution ahead. Therefore, in the present study, the polymer-coated mesoporous material like Sylysia 350, Carbon, Tin Oxide are opted for the BCS class IV drug like Apixaban to attain higher solubility and dissolution. The prepared Nanomatrix was evaluated for its particle size, DSC, Solubility and dissolution studies. For this study, Apixaban was opted for formulating Sylysia 350, Carbon, Tin Oxide based Mesoporous Nanomatrix system. Nanomatrix was prepared by the Amorphous solid dispersion method using probe sonication. The mesoporous Nanomatrix of Apixaban showed improvement in the solubility in water by approx.7 folds when Apixaban used in combination with Sylysia 350 and Polymer HPMC K15M. From the present study, we can conclude that the optimized Apixaban mesoporous Nanomatrix may prove to be a suitable potential option for solubility enhancement, increase *in-vitro* drug release and effective delivery of BCS class IV drugs.

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INTRODUCTION

The therapeutic effectiveness of a drug depends on its bioavailability as well as on the solubility of drug molecules. Solubility is the phenomenon of dissolution of a solute in the solvent to give a homogenous system and is one of the important parameters to achieve the desired concentration of drug in the systemic circulation to produce a pharmacological response. Nearly 40% of the new chemical entities currently being discovered have poor solubility in water. More than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. Low aqueous solubility is the major problem encountered with the formulation development of new chemical entities as well as for the generic development. To achieve high absorption of a drug, it should be present in the form of an aqueous solution at the site of absorption (Lachman *et al.*, 1991). The insufficient dissolution rate of the drug is the limiting fac-

tor in the oral bioavailability of poorly water-soluble compounds. In such cases, dose-escalation would be required until the blood drug concentration reaches the therapeutic drug concentration range. This dose-escalation sometimes causes topical toxicity in the gastrointestinal tract upon oral administration, and such toxicity could lead to a reduction in patient compliance. The formulation design of a drug product with a high dose is generally difficult due to significant higher tablet weight. Increasing drug load might result in poor powder properties and may have different in-process challenges during granulation and compression. In addition to this, the manufacturing cost would also increase since a large amount of active pharmaceutical ingredient (API) might be consumed to develop and manufacture the drug product. The poor solubility of new drug candidates might also affect the chemical properties during the drug discovery stage. During clinical trials, the poor solubility and bioavailability of a drug substance might result in limited therapeutic potential, thereby leading to insufficient clinical outcomes (Kawabata *et al.*, 2011). Different factors affecting solubility, solubility enhancement techniques, its importance and applications has been reported for poorly water-soluble drugs (Savjani *et al.*, 2012; Sikarra *et al.*, 2012; Kadam *et al.*, 2013; Bharti *et al.*, 2015; Patil *et al.*, 2017) Use of porous media like mesoporous Sylysia 350 has been investigated as a potential means to increase the solubility of poorly soluble drugs and to stabilize the amorphous drug delivery system. These materials have nano-sized capillaries, Porous and the large surface area which enable the materials to accommodate high drug loading and promote the controlled and fast release. Therefore, mesoporous Sylysia 350 has been used as a carrier in the solid dispersion to form Mesoporous Nanomatrix. Mesoporous Sylysia 350 is also being used as an adsorbent in a conventional solid dispersion, which has many useful aspects. Various methods are available for incorporation of drugs into mesoporous materials like solvent deposition methods, mechanical activation and vapor-phase mediated mass transfer (Chaudhari and Gupte, 2017).

MATERIALS AND METHODS

Apixaban was obtained as gift samples from Dr. Reddys Laboratories Limited, Hyderabad, India. The Mesoporous material like Sylysia 350, Carbon and Tin oxide were procured from SD Fine Chem Limited, Hyderabad, India and all other chemical used were of analytical grade from Loba Chemie Pvt. Ltd., Mumbai, India.

Mesoporous Nanomatrix

Different trials were performed for selection of different Mesoporous materials, solvents and polymer to prepare Mesoporous Nanomatrix (Wang *et al.*, 2011; Jia *et al.*, 2011; Zhang *et al.*, 2013b, 2014; Yin *et al.*, 2018; Zhang *et al.*, 2013a).

Trials for selection of Mesoporous material

Based on a literature survey, different trials for Apixaban and Mesoporous materials in the ratio of 1:1 and 1:3 were performed and evaluated for Apixaban solubility.

Trials for selection of solvent

Different solvents like Dimethyl Sulfoxide (DMSO), Dichloromethane (DCM) and Acetonitrile (solvent class 2 & 3) acceptable to be used in the pharmaceutical as per US FDA Safety guidance (Q3C) for the use of solvents in pharmaceuticals were evaluated. The addition criteria for selection of solvents are based on good solubility for Apixaban and the carrier like HPMC K15M and PVP K30 (Liberman *et al.*, 1989; Kim, 2013).

Trials for the screening of polymer for preparation of Apixaban–Sylysia 350 /Polymer mesoporous Nanomatrix

The different polymer like PVP K30 and HPMC K15M were screened for the preparation of Apixaban–Sylysia 350 /Polymer mesoporous Nanomatrix by solid dispersion method.

Procedure for preparation of Trials of Mesoporous Nanomatrix

The weighed quantity of Apixaban (10 mg), mesoporous polymer Sylysia 350 (10 mg) and carrier polymer HPMC K15M or PVP K30 (10 mg) was dissolved separately in 1 mL volume of Dichloromethane solvent. Then, allowed to a dispersion of the above Apixaban solution (10 mg/mL) into prepared the 1 mL of Sylysia 350 dichloromethane suspension (10 mg/ml) in a round flask and further sonicated for 30 minutes. Then, again allowed the dispersion of carrier solution (HPMC K15M or PVP K30) into the above Apixaban Sylysia 350 dichloromethane suspension with continues stirring for 24 h. The above-prepared suspension was evaporated under reduced pressure at a temperature of 40°C till to dry. Further, the obtained Nanomatrix was vacuum dried in a hot air oven at room temperature for 48 hr. The dried solid dispersion Nanomatrix was stored in a desiccator for further evaluation (Yin *et al.*, 2018).

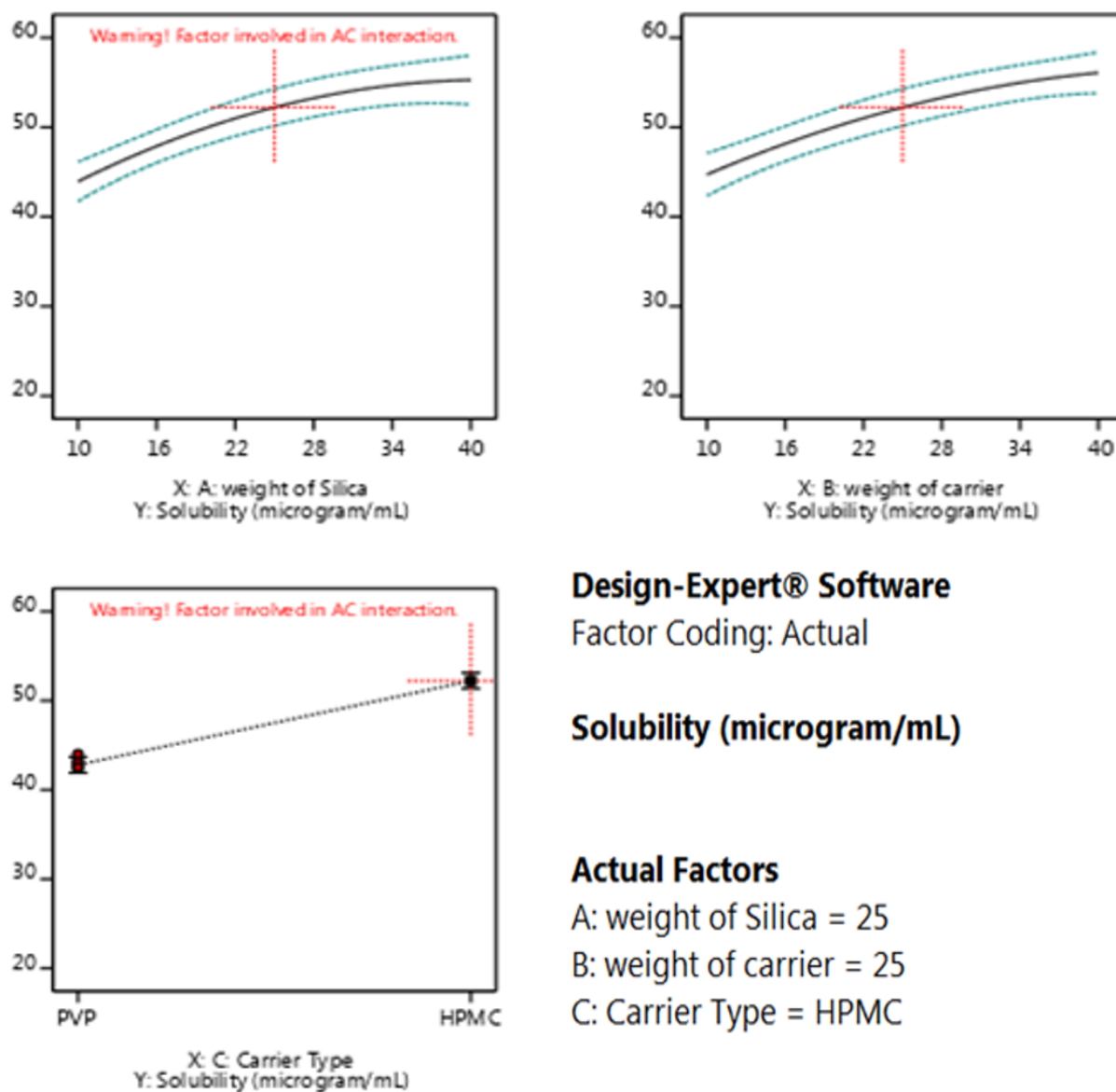**Screening of Apixaban–Sylysia 350/polymer Nanomatrix by DOE**

Figure 1: Normal Plot

Table 1: Trials for selection of mesoporous material

Batch no.	Mesoporous material	Ratio (Drug: mesoporous material)	Drug Quantity (mg)	Mesoporous Quantity (mg)	Solubility (μg/ml) N=3
APX1	Sylysia 350	1:1	10	10	3.03±0.23
APX2	Sylysia 350	1:3	10	30	4.92±.0.15
APX3	Carbon	1:1	10	10	2.77±0.20
APX4	Carbon	1:3	10	30	2.92±0.12
APX5	Tin oxide	1:1	10	10	3.01±0.14
APX6	Tin oxide	1:3	10	30	3.14±0.21

Table 2: Solubility of Apixaban

Solvents	Solubility, N=3	Observation/Inference
Water	2.86 ± 0.13 μg/mL	Practically Insoluble
DMSO	5.23 ± 0.25 mg/mL	Freely soluble
DMF	3.16 ± 0.32 mg/mL	Freely soluble
Dichloromethane	4.34 ± 0.26 mg/mL	Freely soluble
Ethanol	214.83 ± 0.65 μg/mL	Slightly soluble
Methanol	243.26 ± 0.31 μg/mL	Slightly soluble
Acetonitrile	196.76 ± 0.92 μg/mL	Slightly soluble

Table 3: Trials batches for a screening of polymer for preparation of Apixaban–Sylysia 350 /Polymer Mesoporous Nanomatrix

Batch no.	Ratio	Drug	Mesoporous material	Carrier	Solubility (μg/mL), N=3
APX	-	Apixaban	-	-	2.86 ± 0.13
APX7	1:1:1	Apixaban	Sylysia 350	HPMC K15M	21.54 ± 0.43
APX8	1:1:1	Apixaban	Sylysia 350	PVP K30	15.34 ± 0.55

Table 4: I-optimal DOE screening design details

File Version	11.0.3.0			
Study Type	Response Surface		Subtype	Randomized
Design Type	I-optimal	Coordinate Exchange	Runs	16
Design Model	Reduced Cubic		Blocks	No Blocks
Build Time (ms)	107.00			

Table 5: Selected Factors and its range forI-optimal DOE screening design

Factor	Name	Units	Type	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	Weight of Sylysia 350	-	Numeric	10.00	40.00	-1 ↔ 10.00	+1 ↔ 40.00	23.19	11.48
B	Weight of carrier	-	Numeric	10.00	40.00	-1 ↔ 10.00	+1 ↔ 40.00	24.88	11.69
C	Carrier Type	-	Categoric	PVP	HPMC			Levels:	2

Based on the considerable good solubility as compared to the other, the carrier (s) was selected to formulate the Apixaban nanomatrix. However, based on initial learning, the Sylysia 350 and Polymer weight and Carrier/polymer type were selected as a factor for the DOE, and solubility of each DoE run is considered as a response to the DOE. The API concentration i.e., 10 mg and solvent type DCM, was kept constant to all DOE run. The statistical optimization of various process parameters for the experiment was done using Design-Expert® software.

Evaluation of Apixaban Nanomatrix

Solubility Studies

The plain Apixaban and prepared trials of Apixaban mesoporous Nanomatrix were evaluated for comparative solubility study in distilled water. The Apixaban/Sylysia 350/Polymer mesoporous Nanomatrix was added into 10 mL of aqueous solution in a test tube and was shaken at 37°C in a water bath. After 48-hr equilibrium, the saturated solution was rapidly filtered through a 0.45-μm millipore filter and diluted with distilled water and it was analyzed by UV Spectrophotometer at a specific wavelength

(Working document QAS/17.699/Rev2, 2018).

Drug content
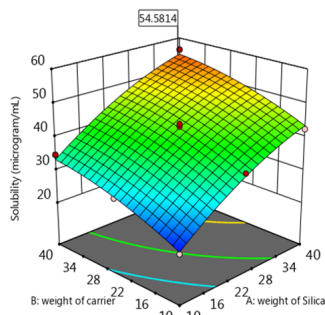
Figure 2: Contour surface plot for PVP K30 polymer
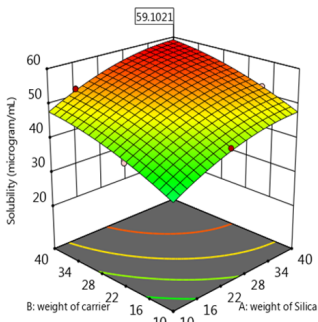
Figure 3: Contour surface plot for HPMC K 15M polymer

Based on obtaining data from the solubility study of Apixaban Nanomatrix, the optimized batch was further evaluated for drug content. The test was estimated by dissolving 10 mg of mesoporous Nanomatrix in 10 mL of DCM. The samples were sonicated for 15 min and filtered through Whatman filter paper 0.45μm and analyzed by using UV Spectrophotometer and absorbance were taken.

Particle size measurement and Polydispersity Index

Based on obtaining data from the solubility study of Apixaban Nanomatrix, the optimized batch was further evaluated for mean particle size distribution and the polydispersity index by particle size analyzer.

Differential Scanning Calorimetry (DSC)

The optimized batch was evaluated for DSC (Mettler Toledo) study to get the compatibility reactions.

In vitro drug release study

The *in-vitro* drug release was performed in USP apparatus Type II (Electrolab Dissolution tester USP TDT-08L) using the paddle method at 75 rpm of rotation speed. The phosphate buffer pH 6.8

(900mL) was used as a dissolution medium and media temperature maintained at 37 $\pm$ 0.5ºC during the study. An accurately weighed amount of the Apixaban plain drug and Nanomatrix (all equivalent to 10 mg of Apixaban) were transferred into separate vessels of the dissolution apparatus. 10mL aliquot was removed at predetermined time intervals i.e., 10, 20, 30, 40, 50, 60 minutes from dissolution medium and replace with same buffer solution maintained at 37 $\pm$ 0.5ºC for maintaining sink condition and the samples were filtered through a 0.45-μm millipore filter and analyzed by using UV Spectrophotometer at specific wavelength (Liberman *et al.*, 1989).

Formulation Immediate Release Tablet

Based on the above-mentioned evaluation parameters, the optimize Apixaban Nanomatrix was further selected to formulate the immediate-release tablets. The tablets were prepared by direct compression method using the different composition of diluents, binders and lubricants (Liberman *et al.*, 1989).

Procedure for preparation of Immediate Release Tablet

The required quantity of Apixaban plain drug and optimized Nanomatrix were weighed separately. The other excipients (Lactose Monohyderate, Microcrystalline cellulose and Sodium starch glycolate), as mentioned in the formula composition, were also weighed and shifted together through #20 sieve. The sifted blend was mixed together for 10 min in a polybag. The required quantity of Magnesium Stearate, as mentioned in the formula composition, was weight and shifted through #40 sieve. The sifted Magnesium Stearate was mix together with the blend of Step 2 in a polybag for 1 min. The Lubricated blend of the prepared granule mixture was compressed manually on a compression machine fitted with 6 mm diameter round shape Punch and 6 mm Die were selected and tablet were formulated by direct compression method.

Evaluation of compressed Tablet

In vitro drug release of an immediate-release tablet

The drug release from the Immediate release tablet of Apixaban was performed by the In-vitro dissolution test in the USP apparatus Type II (Electrolab Dissolution tester USP TDT-08L) using paddle at 75 rpm rotation speed in 900 ml of phosphate buffer pH 6.8 as a dissolution medium by maintaining temperature 37$\pm$0.5ºC. 10mL aliquots were removed at predetermined time intervals i.e., 10, 20, 30, 40, 50, 60 minutes from dissolution medium and replace with the same buffer solution maintained at 37 $\pm$

0.5ºC for maintaining sink condition. The samples were filtered through a 0.45-μm millipore filter and analyzed for the drug release using a UV Spectrophotometer at a specific wavelength of 278 nm (Liberman *et al.*, 1989).

Assay of Tablet

Weighed accurately 20 tablets and an average weight of twenty tablets was calculated. These tablets were crushed and powdered using mortar and pestle. Powder equivalent to 50mg Apixaban was accurately weighed and transferred to a 50 mL of volumetric flask. Sample was sonicated for 30min and diluted up to mark with diluent [water: acetonitrile (60:40 v/v)]. The solution was filtered through a 0.45-μm millipore filter. This filtered solution was further diluted to 10 μg/mL with diluent and analyzed for the drug release using a UV Spectrophotometer at the wavelength of 278 nm. This procedure was performed in triplicate.

RESULTS AND DISCUSSION

Mesoporous Nanomatrix

Trials for selection of mesoporous material

Based on a literature survey, the different mesoporous materials, as mentioned in Table 1 in the ratio of 1:1 and 1:3, were evaluated for solubility of Apixaban and Mesoporous material.

The screening outcome of the above trials resulted that the batch APX2 contains the ratio of 1:3 of Apixaban and Sylysia 350 was showing the maximum solubility as compared to the other mesoporous materials like Carbon and Tin Oxide. Hence, Sylysia 350 mesoporous material was finalized for further trials.

Trials for selection of solvent

The solubility of Apixaban in different solvents were evaluated and discussed in Table 2.

Different solvents like DMSO, DCM and Acetonitrile (solvent class 2 & 3) acceptable to be used in the pharmaceutical as per US FDA Safety guidance (Q3C) for the use of solvents in pharmaceuticals were evaluated. These selected solvents are showing good solubility for Apixaban. The DCM is showing good solubility and lower boiling points (400 0C) as compared to the other evaluated solvents like DMSO (1890 0C) & Acetonitrile (820 0C). Hence, DCM was selected for further trials.

Trials for a screening of polymer for preparation of Apixaban–Sylysia 350/Polymer Nanomatrix

The different polymers like PVP K30 and HPMCK15M were screened for preparation of Apixaban–Sylysia 350/Polymer mesoporous Nanomatrix by solid dispersion method. The comparative solubility results of these polymers with mesoporous Nanomatrix against the Apixaban API is presented in Table 3.
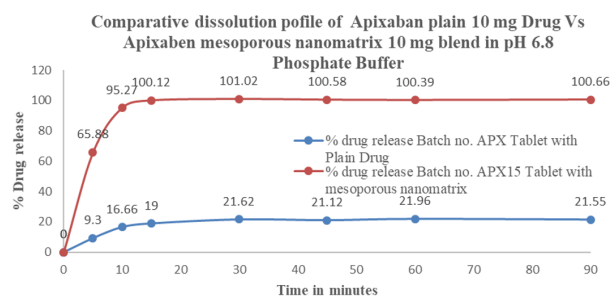

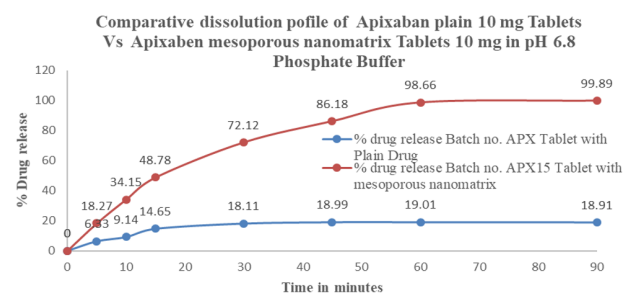**Figure 7: Comparative in vitro drug release Study in pH 6.8 phosphate buffer**

Figure 8: Comparative in vitro drug release study of immediate-release Apixaban Tablet in pH 6.8 phosphate buffer

The HPMC K15M carrier is showing considerable good solubility as compared to the other evaluated carrier PVPK30. Hence, the HPMC K15M carrier was selected for further trials.

DOE Screening Apixaban–Sylysia 350/polymer Nanomatrix by Solubility

The comparative solubility results for the selected I-Optimal screening DOE are presented in Tables 4 and 5 and Table 6 respectively. The ANOVA for the selected DoE model is presented in Table 7 and the normal plot is shown in Figure 1 and Contour surface plot for PVP K30 and HPMC K 15M are presented in Figure 2 and Figure 3 respectively.

Actual Equation-PVP

Solubility (microgram/mL) = 3.03889 + 1.30007 * weight of Sylysia 350 + 0.783127 * weight of carrier + -0.0116353 * weight of Sylysia 350^2 + -0.00808981 * weight of carrier^2

Actual Equation-HPMC

Solubility (microgram/mL) = 20.9758 + 0.959774 * weight of Sylysia 350 + 0.783127 * weight of carrier + -0.0116353 * weight of Sylysia 350^2 + -0.00808981 * weight of carrier^2

Distribution Results (Contin)

Peak	Diameter (nm)	Std. Dev.
1	298.0	278.8
2	0.0	0.0
3 0.0 4	0.0	0.0
5	0.0	0.0
Average	298.0	0.0
		278.8
Residual :	5.492e-003	(O.K)

Cumulants Results

Diameter	(d)	:192.4	(nm)
Polydispersity Index (P.I.)		:0.319	
Diffusion Const.	(D)	:2.557e-008	(cm²/sec)
			(°C)

Measurement Condition

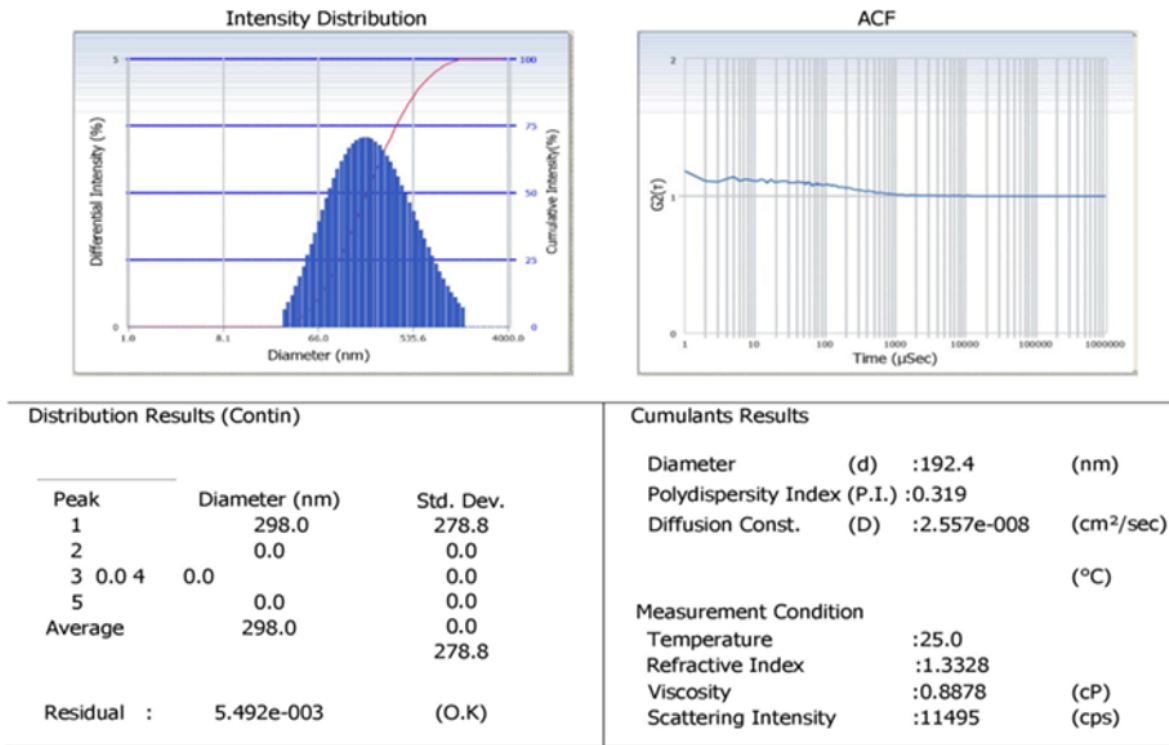|		
Temperature	:25.0	
Refractive Index	:1.3328	
Viscosity	:0.8878	(cP)
Scattering Intensity	:11495	(cps)

Figure 4: Particle size distribution and Polydisperasity index of optimized APX 15
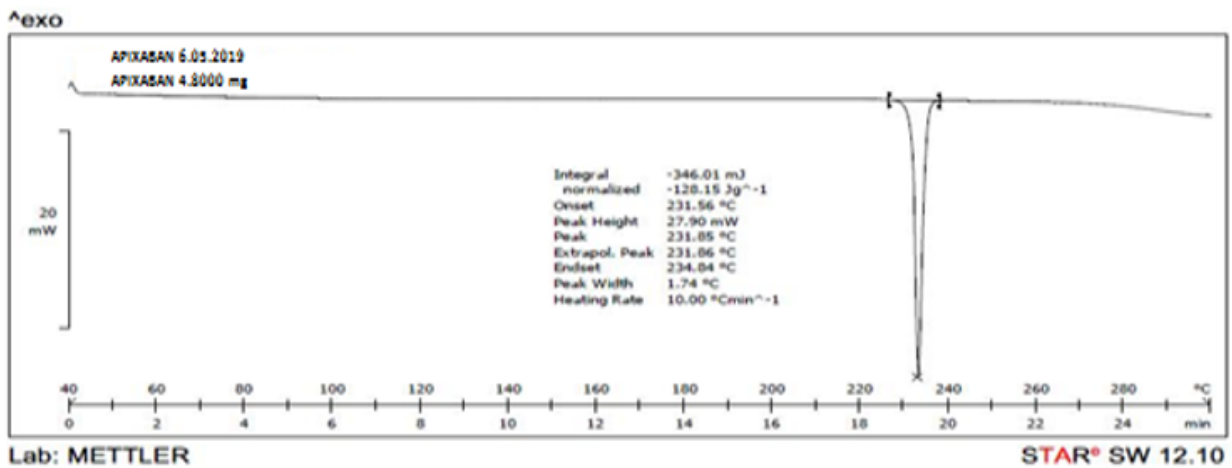

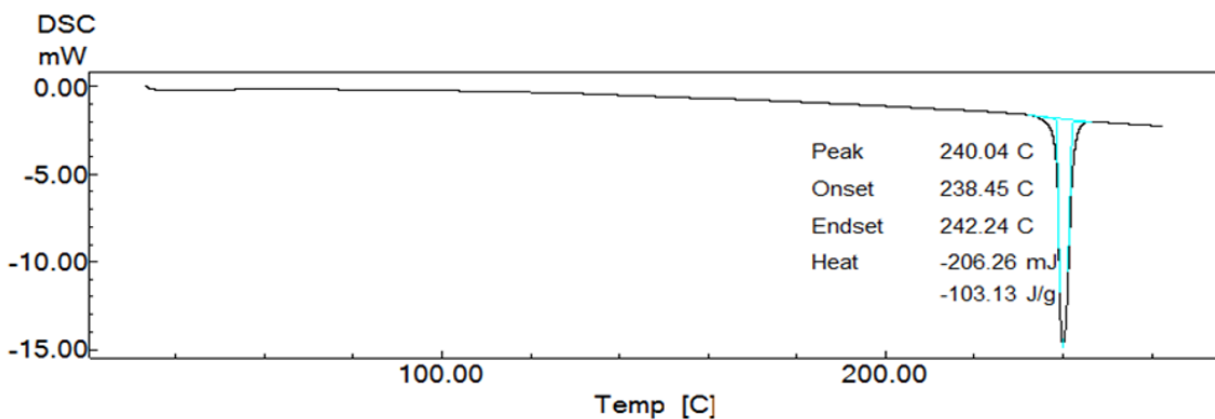**Figure 5: DSC Thermogram of optimized APX 15**

Figure 6: DSC Thermogram of API (Apixaban)

Table 6: Solubility response of Apixaban–Sylysia 350/polymer Nanomatrix by DOE screening

DOE Run	Batch no.	Factor 1	Factor 2	Factor 3	Response
		A: weight of Sylysia 350	B:weight of carrier	C: Carrier Type	Solubility (μg/mL) N=3
1	APX9	40	10	PVP K30	42.44±0.21
2	APX10	10	21	HPMC K15M	41.62± 0.15
3	APX11	25	40	PVP K30	43.56±0.42
4	APX12	10	21	HPMC K15M	42.19±0.55
5	APX13	23	10	HPMC K15M	44.72±0.32
6	APX14	25	25	PVP K30	42.5±0.47
7	APX15	37	38	HPMC K15M	58.19±0.38
8	APX16	10	40	PVP K30	34.72±0.73
9	APX17	16	40	HPMC K15M	52.18±0.77
10	APX18	10	10	PVP K30	21.34±0.29
11	APX19	40	18	HPMC K15M	52.19±0.53
12	APX20	25	10	PVP K30	36.17±0.48
13	APX21	25	25	PVP K30	43.16±0.25
14	APX22	25	25	PVP K30	44.01±0.75
15	APX23	10	25	PVP K30	28.95±0.44
16	APX24	40	40	PVP K30	56.27±0.63

Table 7: ANOVA for I-Optimal model

Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	1344.53	6	224.09	104.31	< 0.0001	significant
A-weight of Sylysia 350	557.99	1	557.99	259.74	< 0.0001	
B-weight of carrier	290.19	1	290.19	135.08	< 0.0001	
C-Carrier Type	310.08	1	310.08	144.34	< 0.0001	
AC	56.03	1	56.03	26.08	0.0006	
A^2	22.50	1	22.50	10.47	0.0102	
B^2	10.74	1	10.74	5.00	0.0522	
Residual	19.33	9	2.15			
Lack of Fit	18.03	6	3.00	6.89	0.0709	Not significant
Pure Error	1.31	3	0.4362			
Cor Total	1363.87	15				
Std. Dev.	1.47		R^2			0.9858
Mean	42.76		Adjusted R^2			0.9764
C.V. %	3.43		Predicted R^2			0.9563
			Adeq Precision			37.8946

Table 8: Drug content and particle size estimation of optimized APX 15

Parameters	Specification	Resus
Drug content	90-110	$98.12 \pm 0.36\%$ (N=3)
Particle size	For information	298 ± 2 nm
Polydispersity index	For information	0.319

Table 9: Comparative *in vitro* drug release Study in pH 6.8 phosphate buffer

Time (min)	% drug release	
	Batch no. APX (Plain Drug), N=3	Batch no. APX 15 (Mesoporous Nanomatrix), N=3
5	9.30 ± 1.24	65.88 ± 0.96
10	16.66 ± 1.18	95.27 ± 0.82
15	19.00 ± 0.93	100.12 ± 0.76
30	21.62 ± 0.66	101.02 ± 0.55
45	21.12 ± 0.55	100.58 ± 0.48
60	21.96 ± 0.42	100.39 ± 0.36
90	21.55 ± 0.32	100.66 ± 0.25

Table 10: Composition Formula Immediate Release Tablet

Ingredients	Batch no. APX (mg/tab)	Batch no. APX 15 (mg/tab)
Apixaban Nanomatrix	-	85
Apixaban	10	-
Lactose monohydrate	75	-
Micocrystalline cellulose	5	5
Sodium starch Glycolate.	9	9
Magnesium Stearate	1	1
Tablet weight	100	100

Table 11: Comparative in vitro drug release study of immediate-release Tablet in pH 6.8 phosphate buffer

Time in minute	% drug release	
	Batch no. APX (Plain Drug), N=3	Batch no. APX15, N=3
5	6.33 ± 2.34	18.27 ± 1.53
10	9.14 ± 1.87	34.15 ± 1.43
15	14.65 ± 2.45	48.78 ± 1.12
30	18.11 ± 1.52	72.12 ± 0.98
45	18.99 ± 0.95	86.18 ± 0.77
60	19.01 ± 0.32	98.66 ± 0.54
90	18.91 ± 0.45	99.89 ± 0.36

Table 12: Assay of tablet Formulation

Batch no.	Assay in % (N=3)
APX (Tablet with Plain drug)	97.00 ± 0.53
APX15 (Tablet with Mesoporous Nanomatrix)	96.75 ± 0.63

Coded Equation

47.5053 + 8.22232 * A + 5.67955 * B + 4.71477 * C + -2.5522 * AC + -2.61794 * A^2 + -1.82021 * B^2

From the above DoE trial, the maximum solubility was found $58.19\pm0.38\mu$g/mL in run no.7 (batch no. APX 15) with a combination of Apixaban (10 mg), Sylysia 350 (37 mg) and HPMC K15M (38 mg). However, the other evaluated polymer run no.16 (batch no. APX 24) with a combination of Apixaban (10 mg), Sylysia 350 (40 mg) and PVP K30 (40 mg) showing solubility $56.27\pm0.63\mu$g/mL. Hence, HPMC K15M polymer was selected for further formulation trials.

Evaluation of Optimized Apixaban Nanomatrix

Drug content, Particle size measurement and Polydispersity index

The DoE trial run no.7 (batch no. APX 15) with combination of Apixaban 10 mg, Sylysia 350, 37 mg and HPMC K15M, 38 mg mesoporous Nanomatrix is showing highest solubility and was further evaluated for Drug content, particle size estimation and Polydispersity index and is presented in Table 8 and Figure 4, respectively. The observed mean Particle size of batch no. APX 15 (DoE run no.7) Nanomatrix was around 298 ± 2 nm and has a uniform controlled distribution.

DSC of Apixaban mesoporous Nanomatrix

The optimized trial batch APX 15 and API was evaluated for DSC and is presented in Figure 5 and Figure 6, respectively. The batch APX 15 shows sharp endothermic peak onset from to be in 231.56 ºC. This corresponds to the melting point of Apixaban which shows the crystalline nature of Apixaban Nanomatrix.

In vitro drug release

The comparative *in vitro* dissolution of Apixaban plain 10 mg drug and optimized Apixaban Mesoporous Nanomatrix (APX 15) 10 mg blend in pH 6.8 phosphate buffer is shown in Table 9 and Figure 7. From the dissolution study, it was clear that the batch APX 15 (Mesoporous Nanomatrix) shows a greater rate of drug release as compared to the APX (plain drug).

Formulation of Immediate Release Tablet

Based on the above-mentioned evaluation parameters, the optimized Apixaban Nanomatrix batch no. APX 15 and plain drug batch no. API (was further selected to formulate the immediate-release tablets as per the formula composition is shown in Table 10. The tablets were prepared by direct compression method using the different composition of diluents, binders and lubricants and were evaluated for in vitro drug release and an assay of the formulation.

Evaluation of compressed Tablet

In vitro drug release Study of an immediate-release tablet

The evaluated comparative dissolution profile of test batches in pH 6.8 phosphate buffer is presented in Table 11 and Figure 8.

From the dissolution study, it is evident that the immediate-release tablet manufactured with the Mesoporous Nanomatrix (batch no. APX 15) shows gradual and complete drug release within 1h. However, the tablet manufactured with a plain drug does not showed complete drug release for evaluated till 1 hr.

Assay of Formulation

The evaluated Assay for test formulations is presented in Table 12. On the basis of the assay result, it was concluded that the tablets contain the potency within the specification of 90-110 %.

CONCLUSIONS

From the present study, we can concluded that the optimized Apixaban mesoporous Nanomatrix is a suitable potential option for solubility enhancement, increased *in-vitro* drug release and can be used for effective delivery of BCS class IV drugs.

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