

Available online on 15.12.2025 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

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Research Article

Solubility and Dissolution Enhancement of Poorly Soluble Drug Apixaban by Solid Dispersion

Akanksha Chaurasiya , Neha Jain *

Faculty of Pharmaceutical Sciences, Ram Krishna Dharmarth Foundation University, Bhopal, (M.P.) India

Article Info:



Article History:

Received 13 Sep 2025
Reviewed 07 Nov 2025
Accepted 25 Nov 2025
Published 15 Dec 2025

Cite this article as:

Chaurasiya A, Jain N, Solubility and Dissolution Enhancement of Poorly Soluble Drug Apixaban by Solid Dispersion, Journal of Drug Delivery and Therapeutics. 2025; 15(12):69-73
DOI: <http://dx.doi.org/10.22270/jddt.v15i12.7499>

*For Correspondence:

Dr. Neha Jain, Professor, Faculty of Pharmaceutical Sciences, Ram Krishna Dharmarth Foundation University, Bhopal, M.P.

Abstract

Apixaban is an anticoagulant used for the prophylaxis of stroke and systemic embolism in nonvalvular atrial fibrillation, and deep vein thrombosis (DVT) leading to pulmonary embolism (PE), including in patients after a hip or knee replacement surgery. Apixaban has low water solubility, but more soluble in organic solvents like dimethyl sulfoxide (DMSO) and dimethylformamide. Various formulation strategies, such as solid dispersions and cocrystals, are being explored to enhance its solubility and bioavailability. Present work is primarily focused on the development of solid dispersions of apixaban through solvent evaporation technique utilizing a blend of lactose and MCC as a carrier. The dissolution test results showed that the increasing amount of lactose gave a significantly higher percentage of drug release profile. The present study introduced a new APX SD that potentially exhibits better solubility and permeability, thus increasing APX's bioavailability.

Keywords: Solid dispersion; Apixaban; lactose; MCC; Solvent evaporation; Solubility; Dissolution; Bioavailability

INTRODUCTION

Solubility is an important physico-chemical factor affecting absorption of drug and its therapeutic effectiveness. One of the major problems responsible for the low turnout in the development of new molecular entities as drug formulations is poor solubility and poor permeability of the lead compounds ¹. Formulating a poorly water-soluble drug for oral route is always a challenge for scientists. There are many techniques such as particle size reduction (micronization and nanonization) modification of crystal habit can be done by manipulating crystalline state of the drug, drug dispersion can be made by formulating a eutectic mixture, using complexing agents complexation can be done, solid solution or solid dispersion, self-emulsifying drug delivery system and surfactants are used for the solubilization for formation of nano/micro-emulsion ²⁻⁴. 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 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 ⁵.

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 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. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water-soluble compounds ⁶. 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 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 outcomes⁷⁻⁸.

Solid dispersion consists of at least one active pharmaceutical ingredient as a carrier in solid state. Various methods for preparing solid dispersions includes melt extrusion, fusion lyophilization, spray drying, solvent evaporation, and super critical fluid (SCF) technology. Solvent evaporation technique is used among various solid dispersion methods. Apixaban (AP) is a factor X inhibitor, an orally active drug that inhibits blood coagulation for better prevention of venous thromboembolism. It has poor solubility, dissolution rate and low bioavailability⁹. The present invention relates to a Factor Xa inhibitor dosage form comprising Apixaban in a solubility-improved form wherein the dosage form provides controlled release of Apixaban and methods for preventing or treating venous thromboembolisms, deep vein thrombosis and acute coronary syndrome with said dosage form. Activated Factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation¹⁰. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (Factor Xa, Factor V, Ca²⁺ and phospholipid). Since it is calculated that one molecule of Factor Xa can generate 138 molecules of thrombin inhibition, Factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system. Accordingly, Factor Xa inhibitors are a class of compounds that are

efficacious for the treatment of thromboembolic disorders. The aim of this study was to improve the aqueous solubility and dissolution rate of oral AP as a step to enhance its bioavailability. A solubility-improved formulation solid dosage form provides controlled release of apixaban¹¹.

MATERIALS AND METHODS

Drug Apixaban was received as a gift sample from Intas Pharm. Pvt. Ltd; lactose, MCC, Sodium hydroxide and Anhydrous potassium dihydrogen orthophosphate were procured from Loba Chemie, Mumbai, Yarrow Chem, Mumbai and Central drug house, New Delhi respectively. Solvents like methanol and hydrochloric acid were supplied by Renkem, New Delhi.

Solubility study of Apixaban in water:

Diclofenac solubility was measured in water by UV visible spectrophotometric method. Excess amount of apixaban was added in beaker containing fixed volume of water and is placed in magnetic stirrer for 24hrs. After 24hrs the solution was filtered, dilution of filtrate was done using water and was analyzed by spectrophotometer at 276 nm¹².

Preparation of solid dispersion by solvent evaporation method:

A blend of lactose and MCC in given ratio was mixed with the solution of rivaroxaban in chloroform (2mL). The solvent was allowed to evaporate at room temperature with substantially stirring. The solid wet mass was passed through a #40 mesh sieve; upto granules were prepared and subsequently dried at 60°C using a vacuum until a constant weight was obtained for enhancement of solubility at the simulated gastric fluid pH1.2 buffer. The granules were filled into 0-size hard gelatine capsules by own hand manually¹³⁻¹⁵.

Table 1: Composition of solid dispersion of apixaban by solvent evaporation method

F. Code	Drug	Lactose (mg)	Microcrystalline cellulose (mg)	Solvent (ml) Chloroform
ASDSE1	Apixaban (20mg)	10	70	2
ASDSE2	Apixaban (20mg)	20	60	2
ASDSE3	Apixaban (20mg)	30	50	2
ASDSE4	Apixaban (20mg)	40	40	2
ASDSE5	Apixaban (20mg)	50	30	2

Evaluation of prepared solid dispersion

Organoleptic properties: The organoleptic properties of Rivaroxaban such as color, odor and taste were noted by sensory organs.

Density: The drug complex & SD was exactly weighed and poured gently through a glass funnel into graduated cylinder and the volume was noted and bulk density was determined.

Particle size: The average particle size (d_{avg}) of drug complex was determined by using a microscope (66172/Olympus, 100 X, Olympus (India) Pvt. Ltd., New Delhi) fitted with ocular micrometer and stage micrometer.

Flow properties: The flow properties of drug complex were characterized in terms of Carr's index (%), Hausner's ratio and angle of repose (θ). The Carr's index

((I_c)) and Hausner's ratio (H_R) of drug powders were calculating according to previous discuss equations ¹⁶.

Solubility determination: The solubility of drug complex was determined in various dissolution media (Water, 0.1 N HCl, pH 7.4 phosphate buffer and pH 6.8 phosphate buffer was discussed in earlier. The solubility value of drug in different medium was determined by UV spectrophotometric method described in earlier. The samples were filtered by using Whatmann filter paper (0.45µm pore size). The solubility assessment of drug was determined by UV spectrophotometric method at 249 nm of Rivaroxaban and 276 nm of Apixaban ¹⁷.

Wettability study: The various formulations i.e. physical mixture complexes or solid dispersion (1 g) was placed in a sintered glass funnel (55 mm i.d.). The funnel was plunged into beaker containing water so that the surface of the water in the beaker remained at the same level as the powder in the funnel. Methylene blue powder (100 mg) was poured onto the surface of the test sample. The time required for wetting the methylene blue powder was measured. The average of three observations was calculated.

Percent (%) Drug content: The various formulations solid dispersion (1 g) were taken randomly and crushed in pestle-mortar. The weight equivalent to one tablet was taken in volumetric flask (100ml) and dissolved in 0.1 N HCL and filtered. This solution was analyzed in UV spectrophotometer at λ_{max} at 276 nm of Apixaban.

Kinetics modelling of drug release: For evaluating the mechanism of drug release from the solid dispersion the

dissolution data was fitted in kinetic models. The release kinetics were analyzed via linear regression analysis using mathematical models of zero- order kinetics, Higuchi diffusion model and Korsmeyer Peppas kinetic model ¹⁸.

RESULT AND DISCUSSION:

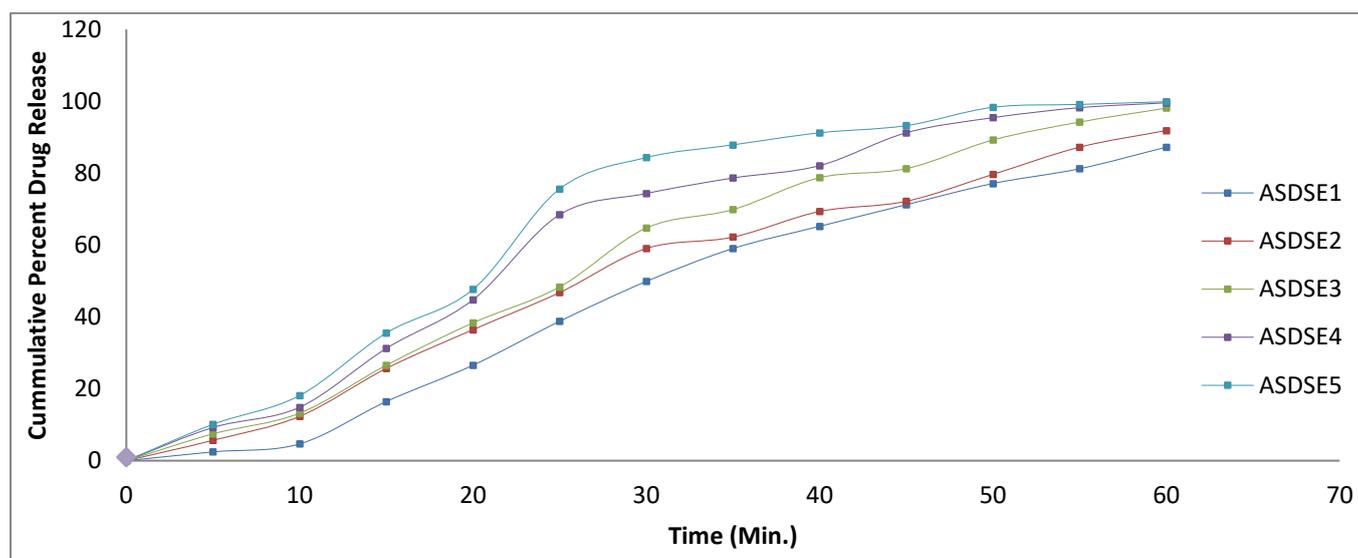
Apixaban solubility solid dispersion results show that solid dispersions significantly increase apixaban's solubility and bioavailability. Solid dispersions can increase apixaban's saturation solubility several-fold compared to its raw form. Different polymers have varying degrees of effectiveness. The enhanced solubility and permeability translate to better oral bioavailability. Solid dispersions can be a suitable method for formulating drugs that have low water solubility, such as apixaban, to improve their effectiveness. The solvent evaporation method, which is one of the most used methods in the pharmaceutical industry for the preparation of SDs, was applied to prepare the final APX SDs samples. Table 3 also shows the enhancement of solubility profile of the formed APX SDs by the solvent evaporation method in various solvent. All SDs with different hydrophilic carriers and different APX-to-carrier ratios showed a higher increase in saturation solubility as compared to APX (Figure1). This can be explained by the improvement of wetting of drug particles and localized solubilization by the hydrophilic carriers. The formulation ASDSE5 containing 50:30 ratio of lactose and MCC able to reduce the particle size and enhance the solubility profile of drug at desired solvent system.

Table 2: Physicochemical evaluation of apixaban solid dispersion

F. Code	Properties			Density (gm/ cm ³)		Particle size (µm)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
	Color	Odor	Taste	Bulk density	Tapped density				
ASDSE1	White to pale Yellow	Odorless	Slight bitter	0.296	0.317	114	13.11±0.011	1.16±0.01	22.02±0.11
ASDSE2	White to pale Yellow	Odorless	Slight bitter	0.299	0.318	113	13.17±0.011	1.18±0.01	22.12±0.11
ASDSE3	White to pale Yellow	Odorless	Slight bitter	0.295	0.315	115	13.18±0.011	1.17±0.01	20.11±0.14
ASDSE4	White to pale Yellow	Odorless	Slight bitter	0.298	0.316	112	13.18±0.012	1.16±0.01	21.12±0.09
ASDSE5	White to pale Yellow	Odorless	Slight bitter	0.298	0.318	109	12.79±0.05	1.15±0.11	21.02±0.08

Table 3: Solubility profile and other evaluation of apixaban solid dispersion

F. Code	Solubility (mg/ml)				Wetting time (Min.)	Drug content (%)
	Water	0.1 N HCl	Phosphate buffer pH 6.8	Phosphate buffer pH 7.4		
ASDSE1	17.101±1.21	2.982±1.01	2.711±1.18	3.111±1.12	5.24	96.44
ASDSE2	18.103±1.11	2.123±1.11	2.722±1.21	3.213±1.11	5.54	96.64
ASDSE3	18.102±1.12	2.211±1.21	2.732±1.23	3.161±1.02	5.32	96.52
ASDSE4	18.111±1.14	2.112±1.21	2.341±1.22	3.321±1.11	5.71	96.66
ASDSE5	18.113±1.11	2.311±1.13	2.261±1.21	3.241±1.01	5.18	97.35

**Figure 1: In-vitro drug release study of apixaban solid dispersion complex (ASDSE1-ASDSE5)**

CONCLUSION

The success of the solubility enhancement and in vitro drug release studies recommends that the method can be further used for formulation design by controlling the drug release from the final dosage form. From the present study, it can be concluded that the optimised Apixaban solid dispersion by solvent evaporation is a suitable option for enhancing solubility and increasing in-vitro drug release, and can be used for the effective delivery of BCS class II drugs.

Acknowledgement: The authors highly acknowledge the RKDF University for providing the facility to conduct the present work.

Author Contributions: All authors have equal contributions in the preparation of the manuscript and compilation.

Conflict of interest: There is no conflict of interest among all authors.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Ethical approval: Not applicable.

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