World Journal of Pharmaceutical and Life Sciences

www.wjpls.org

Impact Factor: 8.21 Coden USA: WJPLA7

TECHNIQUES FOR BIOAVAILABILITY ENHANCEMENT OF BCS CLASS II DRUGS: A REVIEW

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DOI: https://doi.org/10.5281/zenodo.18803407

How to cite this Article: *Sakshi Khot, Samiksha Dadas, Om Pandekar, Ravi Barkade, Dr. G. H. Wadkar. (2026). Techniques For Bioavailability Enhancement of Bcs Class Ii Drugs: A Review. World Journal of Pharmaceutical and Life Sciences, 12(3), 24–29.

Article Received on 29/01/2026 **Article Revised on 19/02/2026** **Article Published on 01/03/2026**

ABSTRACT

Drugs have different degrees of solubility which has an impact on the bioavailability of the drug in the body. Low solubility drugs in water have the greatest solubility problems. The effectiveness of drug formulations and therapies is limited for Class II BCS drugs, which exhibit high permeability but poor solubility. This review focuses on various techniques Employed to improve the solubility of BCS Class II drugs. A number of traditional and contemporary methods are employed. These include solid dispersions, complexation with cyclodextrins, nanosizing, surfactant formulations, and lipid-based drugs. The review covers in detail the mechanism of molecular dispersion, complexation with cyclodextrins, nano-crystallization, surfactant formulations, and lipid-based drugs, discussing the pros and cons of each method. The review also covers the recent innovations in the formulation BCS Class II like amorphous drug formulations, supercritical fluid technology, and nanocrystals.

KEYWORDS: Bioavailability, Solubility, Nanosuspension, Dispersion, Lipophilicity.

INTRODUCTION

Hydrophilic carriers are mixed with the active pharmaceutical ingredients (APIs). Amorphous carriers such as sugars, as well as semicrystalline carriers like polyethylene glycol (PEG), can be utilized for the preparation of solid dispersions. Just as APIs can exist in crystalline, amorphous, or partially crystalline forms, hydrophilic carriers may also possess both crystalline and amorphous domains.[1] One term for a medication's ability to form crystals into a variety of shapes is "crystallinity." A number of physiological factors influence how well oral medications are absorbed.[2] Excipients may impact drug absorption in one of three ways: (1) by altering the dosage formulation's stability, disintegration, or stability; (2) by altering the physiological processes that take place in the gastrointestinal tract; or (3) by altering all three.[3] As the solubility increase bioavailability increases. Solubility defines as:

Table 1: Definition of Solubility.[4]

Descriptive term	Part of the solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

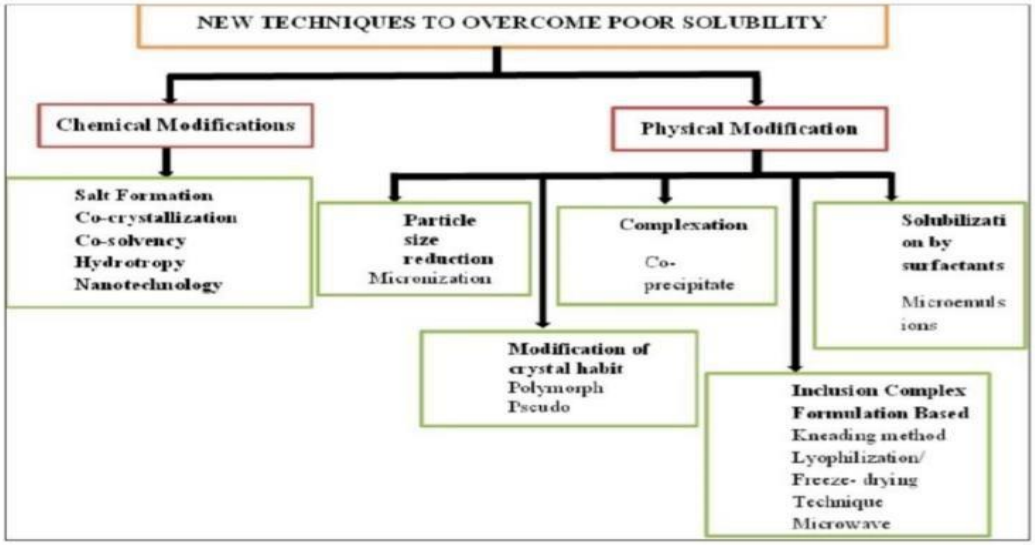
BCS (Biopharmaceutics classification system) classify the drug in to four classes according to their solubility and permeability. Solubility challenges are faced in the low solubility, high permeability drugs, low solubility, low permeability drugs of the BCS system (where dissolution becomes the rate limiting step for the absorption of drug) which comprises of newer generation of NSAIDs like Zaltoprofen, Cyclofenil, Flurbiprofen, their older congeners like Indomethacin, Ibuprofen, Ketoprofen and Diclofenac; anti-diabetics Gliclazide, Glipizide; newer calcium channel blockers (CCBs) like Nimodipine, Felodipine. The BCS was first devised in 1995 by Amidon et al.[5]

Table 2: BCS Classification of Drug.[6]

Sr. No.	BCS Class	Solubility	Permeability	Example
1.	Class I	High	High	Metoprolol, Amlodipine
2.	Class II	Low	High	Ibuprofen, Naproxen
3.	Class III	High	Low	Cimetidine, Ranitidine
4.	Class IV	Low	Low	Furosemide, Nelfinavir

Techniques for solubility Enhancement

Increasing a drug's solubility and, thus, its oral bioavailability can be extremely challenging when creating new drugs, particularly for oral drug delivery systems. To increase the solubility of medications with low water solubility, a number of techniques have been reported in the literature. The attribute of the chosen excipients, the kind of the intended dosage form, and the characteristics of the medication under consideration are some of the specific aspects that influence the processes that are chosen. Only when oral drugs have good bioavailability and are sufficiently soluble in the stomach can they be fully absorbed.[7]



The approaches for improving solubility may be classified into physical changes, chemical changes of the medicinal ingredient, and additional ways shown in figure 1. Fig. 1: Solubility enhancement techniques

1. CHEMICAL MODIFICATION

The solubility of a compound can be increased by incorporating polar functional groups, such as carboxylic acids, ketones, and amines. By strengthening hydrogen bonds and enhancing the contact with water, this is accomplished. The chemical alteration of is at the forefront of advancements in biological imaging and biopharmaceutics. There are different methods for chemical modifications which include Salt Formation, Co-crystallization, Co- solvency, Hydrotropic, Use of novel solubilizer and Nanotechnology.[8]

A. Salt formation

A variety of instability issues frequently prevent the development of a therapeutic agent in its original form. This causes them to change into solid forms such hydrates, solvates, salts, cocrystals, and polymorphs. Each of these characteristics improves the medication's overall performance attributes by having a unique effect on its stability, bioavailability, purity, and manufacturability. For many years, the process of creating salts from weak acids and bases has used to enhance the solubility of the drug candidates that are not very soluble. Ionization of a chemical in a solution is the

process that creates salts. This technique is efficient for injectable and liquid preparation as well as solid dosage forms. A salt version that is more soluble than the original medication is created from an ionizable drug. Progesterone is a steroid that is not hydrophilic but can dissolve in peanut oil, serving as an illustration of this approach. Barbiturates, theophylline, and aspirin are a few more examples.[9]

B. Co-crystallization

An API's many physical, chemical, or physiological constraints are lessened via co- crystallization. Co-crystallization is an excellent technique for maximizing therapeutic properties since it changes the molecular structure and interaction of medicinal compounds. Regardless of an API's ionizable, basic, or acidic properties, co-crystals offer an alternate pathway for co-crystallization.[10]

Different techniques for co crystallization

Solvent Evaporation

Solvent removal method is widely used in the drug industry for microencapsulation.[11]

Various Methods of Solvent Evaporation

Single emulsion method

The inherent issue of water-soluble and slightly water-soluble drugs being inadequately encapsulated makes this drug entrapment approach reasonably effective. an inventory of the nanoparticles made with the single emulsion process and solvent evaporation.

Multiple emulsion method

Usually as double or multiple emulsions, this approach is frequently employed to create microspheres containing water-soluble medications, proteins, peptides, and vaccines.[12]

Slurry Co Crystallization

When the conformers have differing solubilities, slurry co-crystallization is an alternate technique that can be utilized to create cocrystals. A slurry is created at the beginning of the process by suspending one or a mixture of the conformer crystals in minimal solvent. Similar to solution mediated polymorphic transformation, the separate crystals of the single substance dissolve during the onset and propagation of the stable cocrystal. Only when the intended cocrystal has the highest energy-stable shape in relation to other crystal forms is this method appropriate for cocrystal creation. Consequently, the technique can also be applied to assess the crystal's most durable arrangement.[13]

Solvent drop grinding

The application of the dropwise solvent grinding has several noteworthy advantages, such as change of obtaining pure co-crystals, the use of compatible components in an equimolar ratio for the cocrystal, the avoidance of excessive solvent evaporation, the use of a minor quantity of solvent (an environmentally friendly approach), and a significantly shorter time for the synthesis of cocrystal phases.[14]

Sono crystallization Method

In contrast to crystallizations that take place without any agitation, Sono crystallization speeds up the nuclei's creation and produces finer crystal a more constrained size range. Although there are studies indicating the potential participation of other factors, the exact mechanism by which ultrasonography causes nucleation is still not entirely understood. shock waves and heterogeneous nucleation promotion. Additionally, a new phenomenon in the disciplines of Sono crystallization and nucleation is the breakdown of molecular crystals caused by ultrasonic waves. To confirm that the interaction between shockwaves and crystals is the main cause of crystal breaking, decoupling investigations were carried out.[15]

C. Co-solvency/ Solvent Blending

Cosolvents are widely used as cosolvents in the drug industry. There are three types of co-solvency models: analytical, partly-empirical, and practical. While the empirical models are ideal for examining solubility connections, the theoretical models offer essential insights into the solution. A fundamental co-solvency model, the Yankowski logarithmic model calculates a drug's solubility in water-cosolvent combinations by taking into account the drug's solubility in water.[16]

D. Hydrotropic

"Salting out" agents are salts that decrease a solute's solubility, while "salting in" agents are substances or compounds that increase a solute's capacity to disperse in a given solvent. Hydrotropic salts, which dissolve in water, are present and produce the solubilization of non-electrolytes by salt due to their large ion. The term "hydrotropism" refers to this process. Hydrotropic solutions are defined by a weak contact between the hydrotropic agent and the solute and lack colloidal properties. Enhanced aqueous solubility brought on by the presence of a sizable number of additives is known as hydrotropic. The main cause of the solubility improvement is complexation, which occurs when hydrotropic agents such sodium salt, and urea have weak contact with low-solubility drugs. Hydrotropic is a novel and unmatched technique that uses particular chemical components known as hydrotropic to increase the solubility of low-solubility compounds.[17]

E. Nanotechnology

By modifying the properties of nanoparticles and applying them to the creation of nano formulations, dietary supplements, and the food industry, nanotechnology has established a new paradigm. Nanomaterials are well suited for use in the food and nutraceuticals industries because of their distinctive properties, which include their low volume and high surface-to-volume ratio.[18]

2. PHYSICAL MODIFICATION

A. Particle size reduction

The size of a medicine's particles is frequently intrinsically related to its solubility. The specific surface area enhanced as particle size decreases. Increased solubility is the outcome of improved relationship with the solvent made possible by a larger surface area.[26] Drug micronation has long been thought to be the predominantly effective way to accomplish these advancements. However, the already extremely poor solubility of several novel chemical compounds within this range is not greatly impacted by their shrinkage. It is necessary to reduce the size to the nanometric scale.[19]

Micronation

In order to overcome issues with dissolving and bioavailability, the usage of medicine powders made of micronized drug particles has increased in a range of pharmaceutical dosage forms. Most newly developed drugs are sparingly soluble drug, which limits their ability to dissolve rapidly and be absorbed by the body. Features of the micronized pharmaceutical material, including particle size, size distribution, shape, surface characteristics, agglomeration behavior, and powder flow, are influenced by the specific micronation technique that is employed.[20]

B. Modification of crystal Habit Changes in the polymorphic form and the crystal morphology can be caused by different solvents and processing parameters. Furthermore, as crystals grow over time, behavioral changes may result. Consequently, it is essential to understand the factors influencing crystal habit and to carefully evaluate how it affects the efficacy of dose forms.[21]

The modification of the habit was attributed to PSA's specific adsorption onto the needle-like crystal structure's fastest-growing crystal face, which prevented the structure from forming. Scanning electron microscopy (SEM) was used to characterize the griseofulvin and PSA particles, yielding results consistent with a selective growth suppression technique.[22]

Polymorph

Polymorphism commonly occurs in medications, potentially compromising their quality by modifying their physical and chemical properties, such as solubility, hence reducing their bioavailability. The phenomenon known as polymorphism occurs when a material can exist in many crystal forms. Materials that differ in the arrangement of their molecules in the crystalline form but share the same chemical composition are known as polymorphs.[23]

Pseudo polymorphs

The material can take on multiple polymorphs, each of which is distinguished by unique internal crystal lattices and solid crystalline phases. The presence of polymorphism and pseudo polymorphism in the pharmaceutical industry may affect the bioavailability and therapeutic efficacy of the medicine.[24]

C. Complexation

The morphology of protein aggregates plays a crucial role in the electrostatic complexation of proteins and polysaccharides, as well as in defining the functional properties of the resultant complexes. These interactions are very important for the development of new dietary components.[25]

Co-precipitate method

Co-processing is the process of directly co-precipitating amorphous solid dispersions (ASDs) in the last stage of chemical processing.[26] Co-precipitation was a novel method for improving the functional properties of proteins in their unadulterated state.[27] Titanium with nanotubular structures was anodized and then loaded with antibiotics based on penicillin to provide targeted drug delivery. Using a co-precipitation technique, the drug molecules and simulated physiological fluid were mixed together to cause calcium phosphate crystals to form as a group.[28] The process also depends on the active ingredient co-precipitating with glycinin, a biodegradable protein matrix made from edible soybean protein, which is made possible by carbon dioxide. Under isoelectric conditions, glycinin precipitates easily and serves as the framework for capturing the active ingredient throughout the precipitation process. To illustrate the fundamental idea, the lipase enzyme that was extracted from Candida rugosa successfully co-precipitated with the protein pellet.[29]

D. Inclusion Complex Formulation Based

Kneading method

High-performance materials (HPs) and a polyethyleneimine (PEI) polymer solution are quickly combined during kneading to create a "dough" that facilitates the formation of stable suspensions in water-based solutions.[30]

Depending on the amount and characteristics of the salt-kneading material, the final measurements may be changed. This method reduces the likelihood of unpleasant needle-like forms while allowing pharmaceutical researchers to employ a size-reduction process that creates tiny, spherical, and readily flowing particles of the poorly soluble API.[31]

The kneading process is influenced by a number of variables, such as the water's temperature, the dough's temperature, the pace at which the dough is kneaded, the dough's aeration, and the total water content. The rheology of dough and the ensuing characteristics of bread can be significantly improved by employing enhancement techniques and carefully controlling the kneading process.[32]

Lyophilization/ Freeze- drying Technique

Despite having only a few steps, the process of freeze-drying is complex. This is because the final product's quality is impacted by the freezing, sublimation, desorption, and reconstitution procedures, which may subject it to varying pressures at each stage.[33]

Different types of lipid and polymeric nanoparticles were made and examined. The samples were then sprayed into a stream of cold air that contained different cryoprotectants to undergo spray freeze drying. After that, the frozen spherules were gathered for additional freeze drying.[34]

Microwave irradiation method

Reaction time is shortened and product purity is increased when microwave irradiation is used in solid phase peptide synthesis. Through increased product recovery, decreased by-product formation, and decreased energy consumption, the use of procedure intensification techniques such as ultrasound and microwave irradiation may enhance reaction efficiency.[35]

E. Solubilization by surfactants

Low levels of surface tension can be reduced by surfactants, which can result in emulsification, foaming, wetting, and solubilization By converting phospholipids into mixed micelles, surfactants that generate micelles in water-based solutions are highly efficient at dissolving them. Numerous parameters, including the number of aggregations (Nagg), binding constant (K1), micelle-water partition coefficient, molar solubilization ratio (MSR), critical micellar concentration (CMC), and Stern- Volmer constant, were evaluated as part of the solubilization capability assessment.[36]

Microemulsions

By introducing a suitable concentration of an amphiphilic material, like soap or detergent, aqueous phase can become completely miscible. Because of its historical significance, well dispersed stable solutions are referred to as "microemulsions"[37]

CONCLUSION

We have examined a broad range of solubility augmentation strategies in this thorough analysis, which are essential for resolving the challenges presented by poorly soluble drugs. Pharmaceutical researchers have a broad range of tactics at their disposal, from traditional techniques like particle size decrease and solid solution to innovative nanotechnological approaches like nanosuspensions and lipid-based nanocarriers. Furthermore, a key component of contemporary drug development is the incorporation of computational techniques for forecasting and refining solubility enhancement strategies. Pharmaceutical formulation decisions could be made more effectively and intelligently if experimental and computational methods work together. We can see that solubility enhancement is still a dynamic and developing topic as we investigate new approaches like co-crystal formation, liquid electrolytes, and supercritical medium technologies.

REFERENCES

1. Van Duong T., Van den Mooter G. The role of the carrier in the formulation of pharmaceutical solid dispersions. Part I: Crystalline and semi-crystalline carriers. Expert Opine. Drug Deliv., 2016; 13: 1583–1594. doi:10.1080/17425247.2016.1198768.
2. Sugano K. Biopharmaceutics modeling and simulations: theory, practice, methods, and applications. New Jersey: Wiley, 2012.
3. Flanagan T. Potential for pharmaceutical excipients to impact absorption: a mechanistic review for BCS Class 1 and 3 drugs. Eura J Pharm BioPharma: Official Journal of Arbeit gemeinschaft fur Pharmaceutics Verhaeren stotinki Ev, 2019; 141: 130–138. Doi: 10.1016/j.ejpb.2019.05.020.
4. Vaidhyanathan S, Haidar SH, Zhang X, Jiang W, Avon C, Dowling TC, Shao C, Kane M, Hoag SW, Falser MH, Ting TY, Polli JE. Effect of common excipients on the oral drug absorption of Biopharmaceutics Classification System class 3 Drugs cimetidine and acyclovir. J Pharm Sci., 2016; 105(2): 996–1005. Doi: 10.1002/jps.24643.
5. Yadav, A. N., Verma, P., Kumar, R., Kumar, V., & Kumar, K. (2017). Current applications and future prospects of eco-friendly microbes. EU Voice, 3(1): 21-22.
6. Awadhi, C. G., Magagula, I. O., Priya, P., Kumar, R., Yazdani, U., & Khan, M. G. (2020). Aflatoxins in foods and feeds: A review on health implications, detection, and control. Bull. Environ. Pharmocol. Life Sci, 9: 149- 155.
7. Kumar, R., Saha, P., Lok are, P., Datta, K., Selvakumar, P., & Chourasia, A. (2022). A Systemic Review of Ocimum sanctum (Tulsi): Morphological Characteristics, Phytoconstituents and Therapeutic Applications. International Journal for Research in Applied Sciences and Biotechnology, 9(2): 221-226.
8. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP), EMA/CHMP/ICH/493213/2018. ICH M9 guideline on biopharmaceutics classification system-based biowaivers (Step 5). 2020.
9. Bind, A., Das, S., Singh, V. D., Kumar, R., Chourasia, A., &Saha, P. Natural Bioactive for the Potential Management of Gastric Ulceration. Turkish Journal of Physiotherapy and Rehabilitation, 32(3).
10. Indian pharmacopoeia, Government of India ministry of health and family welfare, published by the government of publication, Delhi, 1996; 1: 7.
11. Aggarwal S., Gupta G.D., and Chaudhary S., Solid dispersion as an eminent strategic approach in solubility enhancement of poorly soluble drugs. International Journal of Pharmaceutical Sciences and Research, 2010; 1: 1-13.
12. Wu C.Y., Benet L.S., Predicting drug disposition via application of BCS: Transport /Absorption

elimination interplay & development of a biopharmaceutical drug disposition classification system. Pharmaceutical research, 2005; 22(1): 23-27.
13. Kumar A, Sahoo SK, Pade K. Prithi Pal Singh Kochar, Ajit Satapathy and Naveen Pathak Department of Formulation Research & Development. Jaspal Pharmaceuticals Limited. 2010,
14. Dehere L, Kore PK. A recent review on bioavailability and solubility enhancement of poorly soluble drugs by physical and chemical modifications. Research chronicle in health sciences. 2016; 2: 299–308.
15. Rajesh Jagtap1 Sneha Jagtap et al. Sneha Jagtap*1, Chandrakant Magdum2, Dhanraj Jadge1. 2018; 10: 2205–11.
16. Patole T, Deshpande A. SVKM's NMIMS, School of Pharmacy & Technology Management. In: Shivpuri- 425 405 Dist. Dhulia, Maharashtra, India Received on 06 March. Bauble, Banks of Tapi River, Mumbai-Agra Road, 2014.
17. Li M, Ruud O, Poncelet D, Curs G-. U. UMR CNRS 6144, Rue de la Gaudier, BP 82225, 44322 Nantes codex 3. Nantes codex. 2008; 6144.
18. Pawar N, Saha A, Nandan N, Par Ambil J. Solution crystallization: A scalable approach for cocrystal production. Crystals (Basel) [Internet]. 2021; 11(3): 303.
19. Yatish Rajendra Rajderkar1, Anjali Baburao tajanpure2, Jaiprakash Navnath Sangshetti3, Dabashi Ka Mahapatra 4, Sanjay Jayaprakash chiragra 5, submission date 19-24
20. John RG, Sander BW, Kenneth S. Sus lick Department of Chemistry, University of Illinois at Urbana-Champaign, 600 S. 600 S Mathews Av. 2013.
21. Faculty of Pharmacy and Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. 2007.
22. v. Sampathkumar, c. raja, Jayakumar Department of Chemical Engineering, A.C. College of Technology, Anna University, Chennai, India 600025. Email: c_jayakumar71@yahoo.com Received: 27 Jan 2013 Revised and Accepted: 25 May 2013.
23. Singh AR, Deus PK, Nakala RK, Kondi V, Devi S, Alam MS, et al. Nanotechnology-based approaches applied to nutraceuticals. Drug Deliv Trans Res [Internet]. 2022; 12(3): 485–99.
24. Leleux J, Williams RO. Recent advancements in mechanical reduction methods: particulate systems. Drug Devin Pharm [Internet]. 2014; 40(3): 289–300.
25. Vidal BC Jr, Dien BS, Ting KC, Singh V. Influence of feedstock particle size on lignocellulose conversion—A review. Appl Biochemistry Biotechnology [Internet]. 2011; 164(8): 1405–21.
26. Tiwary AK. Modification of crystal habit and its role in dosage form performance. Drug Devid Pharm [Internet]. 2001; 27(7): 699–709.
27. Jarmer DJ, Langfield CS, Anseth KS, Randolph TW. Supercritical fluid crystallization of griseofulvin: crystal habit modification with a selective growth inhibitor. J Pharm Sci [Internet]. 2005; 94(12): 2688–702.
28. Li Y, Yao F, Shang C, Ren F, Zhang J, Li Yet al, preparation characterization and in vivo evaluation of pharmacological activity of different crystal forms of ibuprofen. Pak J Pharmacy 2019; 32(5): 2139-47.
29. Rusti Chelli C, Gamberini G, Ferioli V, Gamberini MC, Ficarra R, Tommasini S. Solid-state study of polymorphic drugs: carbamazepine. J Pharm Biomed Anal [Internet]. 2000; 23(1): 41–54.
30. Zhao M, Hu J, Zhang H, Nishinari K, Fang Y. Electrostatic complexation of β-lactoglobulin aggregates with carrageenan and the resulting emulsifying and foaming properties. J Dairy Sci [Internet]. 2020; 103(10): 8709– 20.
31. Loftsson T. Drug solubilization by complexation. Int J Pharm [Internet]. 2017; 531(1): 276–80.
32. Tian T, Ren K, Tong X, Peng X, Lian Z, Lyu B, et al. Co-precipitates proteins prepared by soy and wheat: Structural characterization and functional properties. Int J Biomacromolecule [Internet]. 2022; 212: 536–46.
33. Yao C, Webster TJ. Prolonged antibiotic delivery from anodized nanotubular titanium using a co -precipitation drug loading method. J Biomed Mater Res B Appl Biomatter [Internet]. 2009; 91(2): 587–95.
34. Golubovic M, van Haltere SH, Ottens M, Wittkamp GJ, van der Wilen LAM. A method for lipase co-precipitation in a biodegradable protein matrix. Biotechnology Biogen [Internet]. 2007; 98(6): 1209–18.
35. Kasa Matsu Y, Taymour K, Haba H, Yoko Kita T, Shige Kawa Y, Kino A, et al. Co-precipitation behavior of single atoms of rutherfordium in basic solutions. Nat Chem [Internet]. 2021; 13(3): 226–30.
36. Šimek M, Nuchal J, Tarasova L. Salt-kneading: alternative sizing of active pharmaceutical ingredients? Pharm Dev Technol [Internet]. 2016; 21(8): 972–9.
37. Anuragi A, Chori S, Azhari MA, Sahagian CR, Suyadi BB, Pri apsara F, et al. Improvement of meloxicam solubility using a β-cyclodextrin complex prepared via the kneading method and incorporated into an orally disintegrating tablet. Adv Pharm Bull [Internet]. 2016; 6(3): 399–406.