# Designer Solubility: Ionic Liquid-Mediated Cyclodextrin Inclusion Complexes Revolutionize Azithromycin Bioavailability.

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**Abstract**

This study investigates the development of a solid inclusion complex with azithromycin (AZM), β-cyclodextrin (β-CD), and a surface-active ionic liquid (SAIL) to enhance the solubility of this widely prescribed macrolide antibiotic. Using a co-evaporation technique with a 1:1 molar ratio, the researchers successfully prepared an inclusion complex that demonstrated significantly improved aqueous solubility compared to commercially available AZM. The formation of the complex was confirmed through multiple analytical techniques. FTIR spectroscopy revealed characteristic shifts in vibrational bands upon complexation, while $^{1}$H NMR spectroscopy showed changes in chemical shifts for the β-CD cavity protons, indicating successful inclusion of AZM. Field Emission Gun Scanning Electron Microscopy (FEG-SEM) further validated the complex formation through distinct morphological changes, showing the integration of AZM with β-CD and ionic liquid structures. Optimization studies determined that the most effective preparation conditions involved a 1:1 molar ratio at 45°C with 3 hours of stirring at 300 rpm. This novel formulation approach effectively addresses the poor aqueous solubility of AZM, potentially enhancing its bioavailability and therapeutic efficacy. The research demonstrates that combining cyclodextrins with ionic liquids offers a promising strategy for improving the pharmaceutical properties of poorly water-soluble drugs.

**Keywords:** Azithromycin, Cyclodextrin, Ionic Liquid, FTIR, SEM

**Abbreviation:** AZM: Azithromycin, IL: Ionic Liquid, β-CD: β-Cyclodextrin

## 1. Introduction

A team of Croatian pharmacists at PLIVA created the macrolide antibiotic AZM, which they named Sumamed, in light of one of Croatia's greatest successes. (1). In Pharmaceutical Chemistry, this antibiotic was also created under the name Zithromax. (2). Pfizer Central Research laboratories. Because of its antibacterial properties, AZM is prescribed to about 40 million individuals each year. (3). This well-known azalide antibiotic can be found in a range of bodily fluids and tissues and shares structural similarities with the macrolide family. (4). AZM prevents protein synthesis and impedes bacterial growth by reversibly severing the 50S bacterial ribosomal subunit. (3,5). Additionally, it can pass through the extracellular vesicles of bacteria, which are a form of secretory defense mechanism.

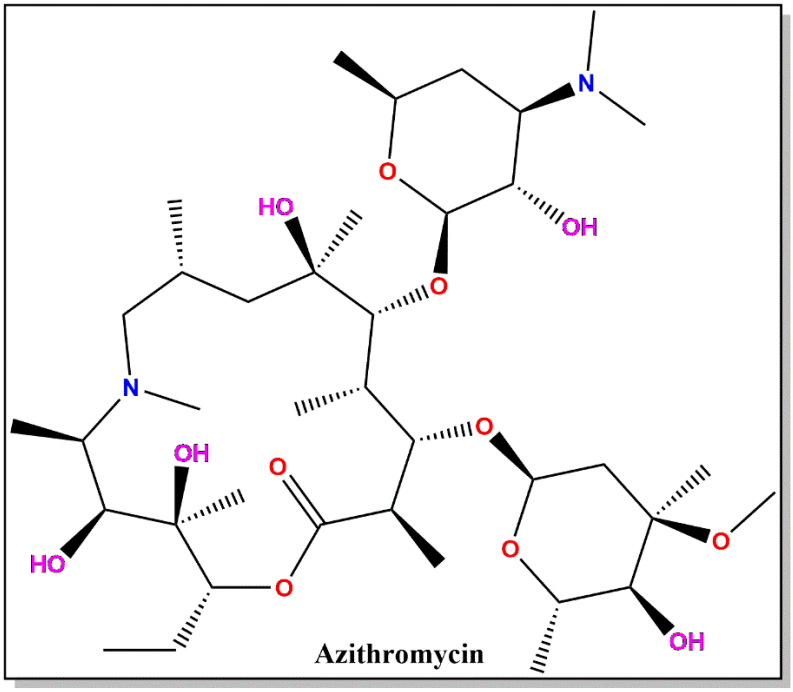


**Fig. 1**: Structure of Azithromycin

### 1.1. Pharmacodynamics of AZM

Because of its special properties, azithromycin is categorized as a macrolide antibiotic. Numerous cells, including fibroblasts and white blood cells, actively absorb AZM due to its dual-base composition(6). Numerous pyogenic bacteria, including Neisseria gonorrhoeae and Moraxella catarrhalis, as well as beta-lactam-resistant bacteria, including Legionella and Chlamydia spp., are inhibited by this antibiotic drug in vitro.(7). Because of its immunomodulatory, anti-inflammatory, and antibacterial modulatory properties, AZM helps patients with a variety of respiratory tract inflammatory illnesses. AZM has been used in

clinical trials to prevent bacterial infections in patients with COVID-19 and is also successful in these patients(8). Combining hydroxychloroquine (HCQ) with AZM has been shown to reduce the viral load of SARS-CoV-2.1. Additionally, AZM can alter the characteristics of the immune system, lowering the generation of cytokines, preserving the integrity of epithelial cells, and averting lung fibrosis.(8–10) The duration of AZM treatment is brief. Adults should take 1500 mg of immediate-release (IR) AZM, which is equivalent to 500 mg once day for three days or 500 mg on day one and 250 mg on days two through five(3). The highest oral dose approved for the treatment of gonococcal urethritis is 2.0 g of IR AZM(10–12).

### 1.2. Pharmacokinetics of AZM

Pharmacokinetic characteristics the primary metabolic pathway is demethylation, and the metabolites are thought to have negligible antibacterial action. Following oral treatment, AZM's bioavailability increased to 37%. AZM absorption can be reduced by as much as 50% when taken with a substantial meal(11,13). When AZM is taken with antacids that contain magnesium and aluminum, peak plasma concentrations may drop by 24%; nevertheless, the overall level of absorption remains unchanged. After a single 500 mg oral and intravenous dose, the average plasma clearance of AZM is 630 ml/min(14,15). Biliary excretion is the main method of AZM elimination, especially when the medication is intact, and the faces are a major elimination pathway. Urinary excretion of AZM appears to be a modest elimination pathway because, over the course of a week, around 6% of the administered dose is released as an unaltered substance in urine. In humans, AZM has a half-life of roughly 35–40 hours following a 500 mg dosage. The time needed for plasma/blood concentration to drop by 50% following the achievement of pseudo-equilibrium of distribution is known as the terminal half-life. AZM's elimination half-life, or the amount of time that drug removal alone causes the medication's plasma concentration to drop, is close to 68 hours. Long-term research has shown that AZM does not have the ability to cause cancer or mutagenesis in typical lab animals and testing. The most common side effects associated with AZM are headache, dizziness, hearing loss, cardiovascular arrhythmias, and upset stomach. Hepatotoxicity has been documented in rare instances. When administering AZM, care should be taken in individuals with a prolonged QT interval, impaired hepatic function, and renal GFR <10 ml/min(16).

All medications must have some degree of aqueous solubility in order to be pharmacologically active, and the majority of pharmaceuticals should be lipophilic in order to passively diffuse through biological membranes. Insufficient bioavailability is frequently

caused by poorly water soluble medicines' weak solubility and slow rate of dissolution in aqueous gastrointestinal fluids(17). The capacity of cyclodextrins and their derivatives to form molecular inclusion complexes with medications that are poorly soluble in water is one of their special qualities. These typically have an oligosaccharide-shaped bucket to retain the hydrophobic chamber, which has adequate room to hold "guest" molecules that are lipophilic in nature. As a result, the medications become enclosed in the cavity, improving their water solubility and speed of dissolution. NSAIDS and barbiturates are two examples of drugs with increased bioavailability(18).

Short-chain oligosaccharide molecules called cyclodextrins (CDs) are produced when starch breaks down. Three types of cyclodextrins—6 units (a), 7 units (b), and 8 units (c)—compose D-glucopyranose units connected by a glycosidic link between carbon 1 and carbon 4.

Its many benefits are that cyclodextrin is non-toxic, easily soluble in water, highly bioavailable, and easily modified. Moreover, it has broad accessibility and offers noteworthy advantages in a variety of research fields(19). They are widely used in pharmaceutical science and technologies for a variety of reasons, such as boosting the duration and dissolution of medications in liquids, boosting the effectiveness of drug absorption into the body, muffling tastes and odours, controlling the rate at which medications are released into the body, lowering systemic and localized toxicity, and facilitating the passage of medications through biological barriers. Cyclodextrins provide several advantages for anti-inflammatory medication performance and containment, as well as for better administration, release, and delivery. Further research in this field is necessary to advance the field of nanomedicine. They have shown to be the most effective in the production of bioactive medications and antibiotics, and new versions have been created to accept bigger molecules, such as proteins (18). This field continues to be very interesting in research(20,21).

### 1.1. Solid inclusion complex with cyclodextrin

Pharmaceutical excipients such as cyclodextrins are primarily utilized in aqueous formulations as solubilizing and stabilizing agents for lipophilic compounds. An inclusion complex forms in cyclodextrin solutions, which solubilizes a variety of compounds(22). When it comes to hydrophilic drug carriers, hydroxylalkylated derivatives like HPβCD are widely recognized due to their amorphous nature, high water solubility, solubilizing ability, low cost, and low toxicity(23,24).

The combination of benzimidazole with cyclodextrins has the potential to produce a valuable and effective compound with enhanced solubility and bioavailability, which could have applications in the pharmaceutical industry.

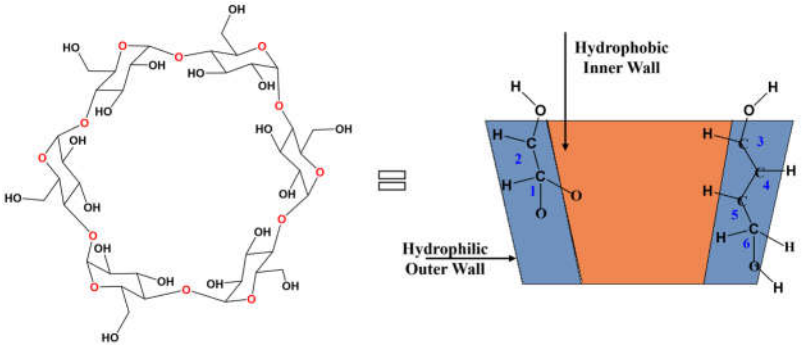


**Fig. 2:** Structure of Cyclodextrin

### 1.2. Ionic Liquids

Ionic liquids (ILs) have garnered considerable attention due to their potential as alternative media in many catalytic, separation, and electrochemical processes, attributed to their exclusive chemical and physical features. According to the widely recognized definition, these salts are in a liquid state below 100 °C and possess a negligible vapour pressure(25–28). The analysis of the structure-activity relationship (SAR) of a typical imidazolium IL suggests that ILs may exhibit surface-active qualities equivalent to surfactants, causing them to form micelles in aqueous solutions. The IL will have a charged hydrophilic head group and a hydrophobic tail domain, as seen in Fig. 1.

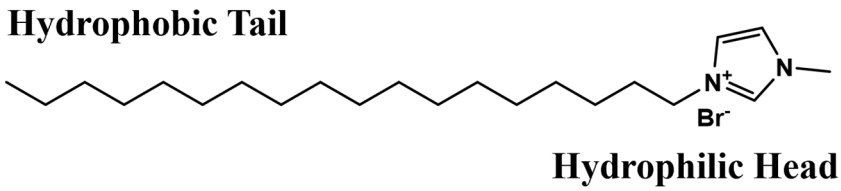


**Fig. 3.** SAIL, 1-methyl-3-octadecyl-imidazolium bromide.

This suggests that ILs may exhibit characteristics similar to amphiphiles and can behave like a surfactant, including micelle production and surface activity, potentially categorizing them as foaming agents, emulsifiers, or dispersants(29,30). These functions apply to the adsorption of surfactants at a surface, whether gas, liquid, or solid, with the hydrophilic ends of the molecules directed toward the aqueous phase. These ionic liquids could potentially constitute

a novel category of cationic surfactants(31). Surface-active ionic liquids (SAILs) are generally categorized as ILs possessing long alkyl chain substituents, typically exceeding eight carbon atoms(32). The most extensively studied SAILs are cationic, characterized by a positively charged head group, a long alkyl chain, and a changeable counter anion. Numerous scaffolds featuring imidazolium, pyridinium, pyrrolidinium, piperidinium, and phosphonium head groups with different alkyl chain lengths have been documented(33,34).

Numerous standard surfactant-based drug formulations and carriers, including micelles, vesicles, microemulsions, liposomes, hydrogels, polymer conjugates, and nanoparticles, are recognized for their ability to dissolve or encapsulate drugs, thereby enhancing bioavailability, stability, safety, and efficacy. The drug-binding capacity of SAIL [$C_{14}$mim][Br] with dopamine hydrochloride outperformed that of the standard cationic surfactant tetradecyltrimethylammonium bromide due to the interactions that occur between the π systems of the imidazolium ring of the SAIL and the drug(35).

Here, 1-methyl-3-octadecyl-imidazolium bromide, also known as SAIL [$C_{18}$mim] [Br] is used as shown in Fig. 3.

## 2. Material and methods

All the required drug (Azithromycin) and excipient (Cyclodexrins) used were of analytical grade. The ionic liquid is synthesized with the reported methods availables(36). The investigated solutions were formulated in double-distilled water and subsequently filtered through a nylon filter (pore diameter of approximately 0.45 mm) to eliminate any contaminants before to each measurement.

### 2.1. Preparation of AZM/ Cyclodextrin (β-CD) / Ionic liquid inclusion complex

Co-evaporation was used to create the 1:1 molar ratio Azithromycin Inclusion Complex (AZM-IC)(37). In summary, all of the BNZ and HP-β-CD and IL were fully dissolved in methanol and water, respectively(38). Additionally, the cyclodextrin and ionic liquid solutions were agitated in a beaker using a magnetic stirrer as methanol containing AZM was added dropwise. The mixture was then kept at room temperature for 30 minutes with gentle stirring. After that, the mixture's temperature was raised to 50 °C and held there for three hours while stirring at 300 rpm. The resulting solution was then dried by evaporating it in an oven until all of the solvent had vanished.(39,40).

### 2.2. Solubility Studies

For solubility analysis, we have taken the excess amount of commercially available AZM in one vial containing 10 ml of distilled water, and in another vial of the same volume, we have taken the excess amount of inclusion complex, which we have prepared of cyclodextrin, ionic liquid, and AZM. After that, it is left overnight to attain equilibrium. The next day, it is filtered through Whatmann filter paper, and the dilution of 0.1, 0.2, 0.3, 0.4, and 0.5 ml is prepared for both the Commercial AZM and the inclusion complex solutions separately. After that, it is checked for solubility at 547 nm range under UV-Spectrophotometer.

### 2.3. Fourier Transform Infrared Spectroscopy (FT-IR)

The Perkin Elmer FTIR Spectrum GX Range: 10000 cm-1 to 370 cm-1 was used to produce the FT-IR spectra of BNZ, HP-β-CD, physical mixture, and BNZ/HP-β-CD inclusion complex. The samples were scanned at 20 scans per second throughout a spectral range of 500–4000 cm–1, with a resolution of 0.15 cm–1. To perform the measurements, the samples were first compressed into pellets and diluted with KBr powder.

### 2.4. $^{1}$H NMR Analysis

With the Avance III 400MHz FT NMR Liquid, proton ($^{1}$H) spectra of individual compounds and the AZM/β-CD/IL inclusion complex were acquired with the maximum frequency resolution (0.005 Hz) and 25 ns event timing. Tetramethylsilane (TMS) was used as the internal standard to record chemical shifts (in ppm) after the test samples were dissolved in dimethyl sulfoxide (DMSO) at 298 ± 0.1 K.

### 2.5. Field Emission Gun Scanning Electron Microscopy (FEG-SEM)

FEI Ltd.'s Nova Nano SEM 450 Scanning Electron Microscope, which has an ultra-high brightness Schottky emitter, was used to investigate the morphology of the test samples. Before performing microscopic scans, the sample was fixed on a brass stub and then coated with a small layer of gold to ensure good electrical conductivity. Secondary electrons (SE) were used to record images at 1.0 KX magnification to get clear photographs.

## 3. Result and Discussion

### 3.1. Preparation of AZM/ Cyclodextrin (β-CD) / Ionic liquid inclusion complex

Using the co-evaporation approach, the AZM-ICs were created, and the effects of various variables on complexation efficiency were also looked into. The results demonstrated that the

preparation of the inclusion complex is greatly influenced by the molar ratio of AZM (guest) and IL and β-CD (host). An increase in the molar ratio of IL and β-CD to AZM up to 2:1 was shown to enhance the complexation efficiency, which might be explained by the increased number of host molecules available to accommodate the AZM molecules. However, taking the equimolar ratio is the best condition for preparation, so we conducted the studies using the 1:1 molar ratio. Up to 45 °C, the effect of reaction temperature on entrapment efficiency was found to be positive; however, no discernible increase was observed at higher temperatures. Although inclusion complexes have favorable effects at higher temperatures, normal body temperature is favored because our goal is not simply to promote solubility but also bioavailability. After optimization, the response time and stirring speed were determined to be 3 hours at 300 rpm, respectively.

### 3.2. Solubility Studies

The solubility study of the AZM drug and the prepared inclusion complex is analysed spectrophotometrically at 547nm and it shows the favourable outcomes the solubility of the prepared inclusion complex is much higher than the commercially available AZM which is depicted through graphical representation below.

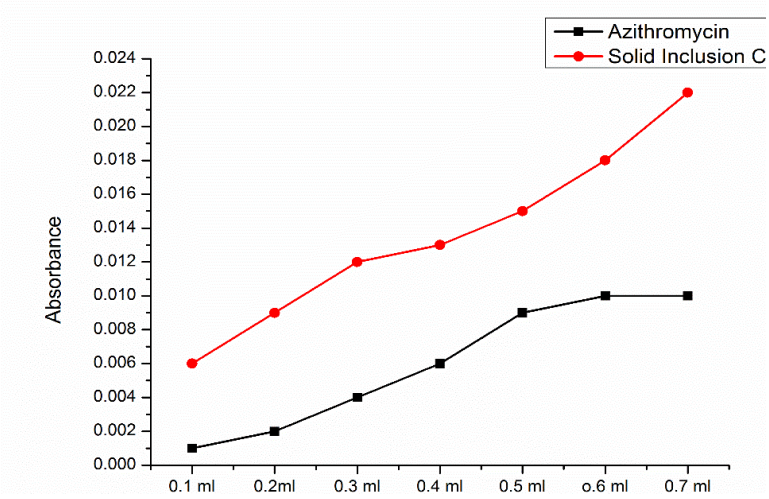


**Fig. 4**: Comparative solubility analysis of AZM and prepared Solid Inclusion Complex

### 3.4. Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR spectroscopy makes it simple to evaluate how well pharmaceutical inclusion complexes with cyclodextrins are formed. This method aids in figuring out how the individual moiety's vibrational bands alter during the complex creation process.

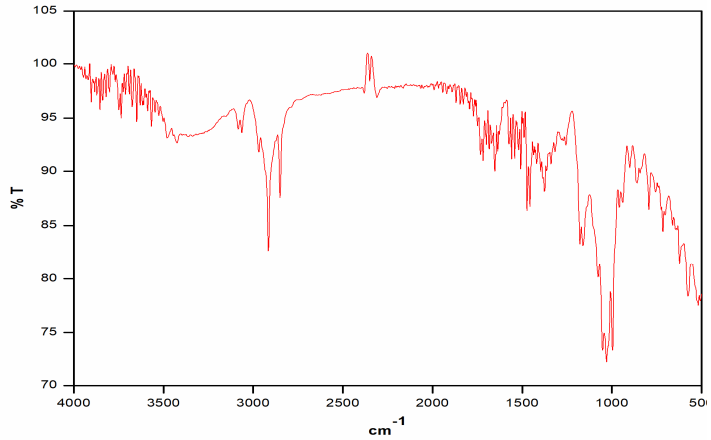


**Fig. 5:** FTIR analysis of AZM, ionic liquid, and β- Cyclodextrin inclusion complex

AZM has aromatic rings (e.g., benzene), and the C-H stretching vibration appears around **3019 cm⁻¹**. The amide group in AZM is showing a characteristic **C=O stretching vibration** in the **1636 cm⁻¹** region. The ether linkages in AZM show a **C-O stretching** vibration at around **1052 cm⁻¹**. The presence of an **amine** or **amide group** in AZM, an N-H stretching band, could appear around **3402 cm⁻¹**. Alkyl C-H stretching vibrations appear in the **2850 cm⁻¹** region. This would be observed for the alkyl chains present in the molecule. C-H bending (in-plane and out-of-plane bending) vibrations of the aromatic rings appear in the **600–900 cm⁻¹** region. For beta cyclodextrin, A **broad O-H stretching band** (3479cm⁻¹) was observed due to hydrogen-bonded hydroxyl groups. **Strong C-O stretching peaks** around **1052 cm⁻¹** from the glycosidic bonds and hydroxyl groups. A **C-H stretching band** in the **2968 cm⁻¹** range. **C-O-C stretching** related to the glycosidic bond in the **1030 cm⁻¹** region. **C-H bending vibrations** (in the **1456 cm⁻¹** range) due to the aliphatic $CH_2$/$CH_3$ groups.

### 3.5. $^1$H NMR Analysis

The two Images below show the $^1$H NMR spectroscopy of (a) Pure AZM and (b) the prepared solid inclusion complex (AZM/ β-CD/ Ionic liquid), respectively. AZM is a macrolide antibiotic with a complex molecular structure, leading to a diverse and intricate $^1$H NMR spectrum. The spectrum exhibits a broad range of proton environments, reflecting its multiple

functional groups and stereocenters. Aliphatic methyl protons (−$CH_3$) typically appear as triplets around 0.85–1.30 ppm. Methoxy groups (−$OCH_3$) resonating as singlets near 3.30–3.40 ppm. Protons attached to carbon atoms with two substituents (−$CH_2$−) often show up as multiplets in the 1.20–2.50 ppm region. Protons attached to chiral centers (−CH−) appear as multiplets between 1.50–3.50 ppm. Hydroxyl (−OH) and amine (−$NH_2$) protons can be identified by their broad, exchangeable signals, often found between 2.30–5.20 ppm. For the prepared inclusion complex β-CD, Protons in the inner cavity (H-3, H-5) typically appear around 3.0–4.0 ppm. The outer protons (H-1, H-2, H-4) show shifts in the 4.5–5.5 ppm region. For IL alkyl chains, showing signals from 0.8–1.5 ppm, and cationic parts around 3.5–4.5 ppm. The chemical shift change of β-CD and ionic liquid for H-3 and H-5 and broadening of the peaks of AZM is because of the inclusion of AZM in β-CD cavity and which can be the evidence of formation of inclusion complex(41,42).

### 3.6. Field Emission Gun Scanning Electron Microscopy (FEG-SEM)

Using FEG-SEM, the microscopic surface morphology was evaluated. Fig. 8 displays SEM images of β-CD and prepared AZM/IL and β-CD inclusion complex. The spherical shape of β-CD, along with the cavity inside, was disclosed by their surface morphology (41). Additionally, the irregular rectangular broken brick-shaped crystal structure was seen in the β-CD topography image, Furthermore, the fractured brick-like structure of β-CD and spherical bulky globule of ionic liquid were observed in the inclusion complex (Fig. 8-c), which was connected to AZM crystal particles. Therefore, the SEM analysis verifies the formation of the inclusion complex, and it also verifies that the cyclodextrins and ionic liquid morphological attachment to the AZM molecules is what causes their overall increased solubility.

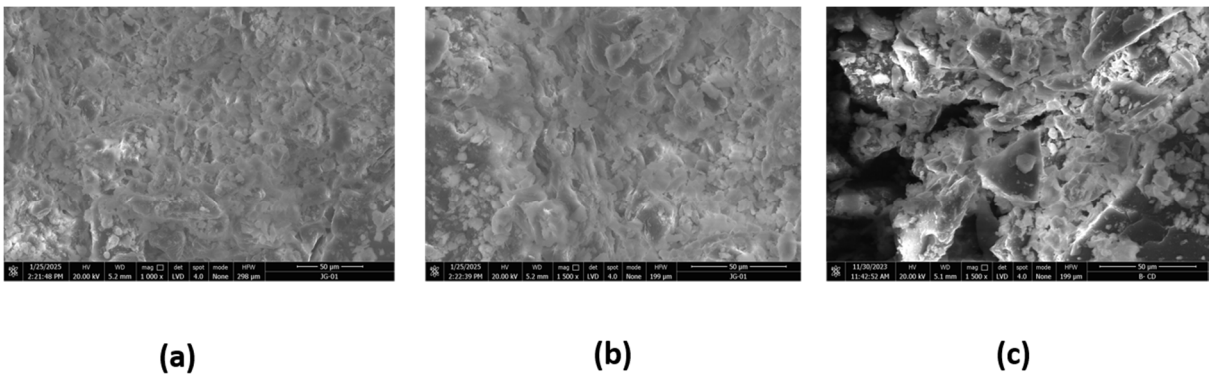


**Fig. 6:** FEG-SEM Images of **(a)** Solid inclusion complexes **(b)** Solid inclusion complexes **(c)** β-Cyclodextrin

## 4. Conclusion

The preparation of solid inclusion complexes of a drug with cyclodextrin and ionic liquid has proven to be an effective strategy to enhance drug solubility. This approach leverages the unique properties of cyclodextrins, such as their ability to form host-guest complexes and the solubilizing potential of ionic liquids. The resulting solid complexes exhibit improved dissolution rates, increased bioavailability, and better stability than pure drugs. This method offers a promising pathway for optimizing the solubility of poorly water-soluble drugs, thereby enhancing their therapeutic efficacy. Future studies focusing on these complexes' detailed characterization and in vivo evaluation will further validate their potential in pharmaceutical applications.

## 5. Acknowledgements

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