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# Review: Mesoporous Silica Formulation in Biopharmaceutical Classification System (BCS) Class II Drug Development

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## ABSTRACT

About 40% of approved drugs and nearly 90% of drug candidates have low aqueous solubility which limits their bioavailability resulting in suboptimal pharmacological activity. According to the Biopharmaceutical Classification System (BCS), drugs with low solubility and high permeability are categorized as BCS Class II, where the dissolution rate becomes a key factor in gastrointestinal absorption. One approach to increasing its solubility is the formation of an amorphous state, which lowers lattice energy and enhances dissolution. However, the amorphous form tends to be unstable and prone to recrystallization. Mesoporous silica has been developed as a drug delivery system capable of maintaining the stability of the amorphous form through molecular interactions with silanol groups and the nano-confinement effect that suppresses crystal growth. With a high surface area and tunable pore structure, mesoporous silica enhances the dissolution rate and bioavailability of BCS Class II drugs, ultimately contributing to improved pharmacological activity. This review summarizes the development of mesoporous silica formulations in drug delivery systems for BCS Class II drugs to enhance their pharmacological efficacy.

**Keywords:** Biopharmaceutical Classification System class II, amorphous drugs, mesoporous silica, pharmacology activity

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## 1. Introduction

Solubility is a crucial physicochemical property in the development of pharmaceutical preparations, especially for the oral route, as it affects bioavailability. Low bioavailability of the formulation results in suboptimal therapeutic effects (1,2). The composition of the formulation, which includes active pharmaceutical ingredients (APIs) with poor water solubility, is one of the most significant issues in pharmaceutical formulation development (3,4). Based on the biopharmaceutical classification system, drugs with low solubility and high permeability are classified into category class II (5). The dissolution phase limits the process of drug absorption in the gastrointestinal tract. Increasing the dissolution rate of this class II drugs will enhance its bioavailability in the plasma (6).

One way to increase solubility is through the formation of amorphous (7,8). The formation of amorphous can be defined as a process that can transform crystalline materials into an amorphous state characterized by an irregular arrangement of drug molecules in a solid state (9). Drugs in amorphous form are considered to have better thermodynamic properties in terms of solubility and vapor pressure, due to the amorphous form having higher internal energy, specific volume, and molecular mobility compared to their crystalline form (10–12). However, the increased molecular movement leads to low drug stability, which often results in the recrystallization of the active ingredient in the formulation over time (13). Therefore, the addition of excipients is necessary to maintain amorphous stability, one of which is the use of porous drug carriers (14,15).

Mesoporous silica (MS) formulations as drug carriers in the pharmaceutical field are widely developed due to their unique porous structure with pore sizes ranging from 2-50 nm, large pore volume (>0.9 $cm^3/g$), and high surface area (>700 $m^2/g$); the presence of silanol groups allows for selective functionalization, thereby regulating drug release; and the biocompatibility of MS, which is stable in biological environments, non-toxic, and biodegradable (16–19). MS is thermodynamically stable and can maintain the drug in an amorphous form within its pores through two mechanisms of crystallization inhibition: (1) molecular interactions between the functional groups of the drug molecule and the MSN surface, namely hydrogen bonds, and (2) the nano-confinement effect of MS, which suppresses nucleation and crystal growth as the pore size is smaller than the critical crystal nucleus (20,21).

Several literature studies have investigated the effectiveness of drug loading into MS to produce stable amorphous drugs with improved solubility and bioavailability (22–24). The pore characteristics of SM, such as pore size, pore volume, and geometry, affect the drug loading efficiency as well as its release. Drug molecules that have entered into a closed pore space, cannot undergo recrystallization so that they are able to maintain their amorphous state. The process of dissolving amorphous drugs from mesoporous silica results in supersaturated solutions, which can be an effective way to improve the bioavailability of low-solubility drugs (19). Poorly water-soluble drugs will experience enhanced absorption only when in a supersaturated state (21).

Therefore, by utilizing solubility and bioavailability enhancement mechanisms, mesoporous silica has the potential to improve the therapeutic

effectiveness of BCS class II drugs that have low solubility. Given the significant challenges posed by poorly soluble drugs and the promising role of mesoporous silica in overcoming these limitations, a timely and comprehensive review of its formulation strategies and impact on drug efficacy is urgently needed to accelerate advancements in drug delivery systems. This study summarizes the development of mesoporous silica formulations in improving the dissolution profile and its impact on the efficacy of BCS class II drugs, to provide insights into drug delivery systems.

## 2. Method

The research method was carried out with a literature study on several published research journals. Primary sources used are research journals that have been published online on national and international journal websites. Data search keywords are "mesoporous silica nanoparticles", "BCS Class II", and "Efficacy Enhancement Mesoporous Silica". Inclusion criteria include articles in the form of original research, published in the range of 2015-2025, and articles that discuss the formulation of BCS class II drug loading into certain types of mesoporous silica accompanied by preparation methods, dissolution studies, or testing of pharmacological effectiveness or drug safety. Exclusion criteria included review articles or literature studies and articles that were not available in full text. The flowchart of methodology can be seen in Figure 1.

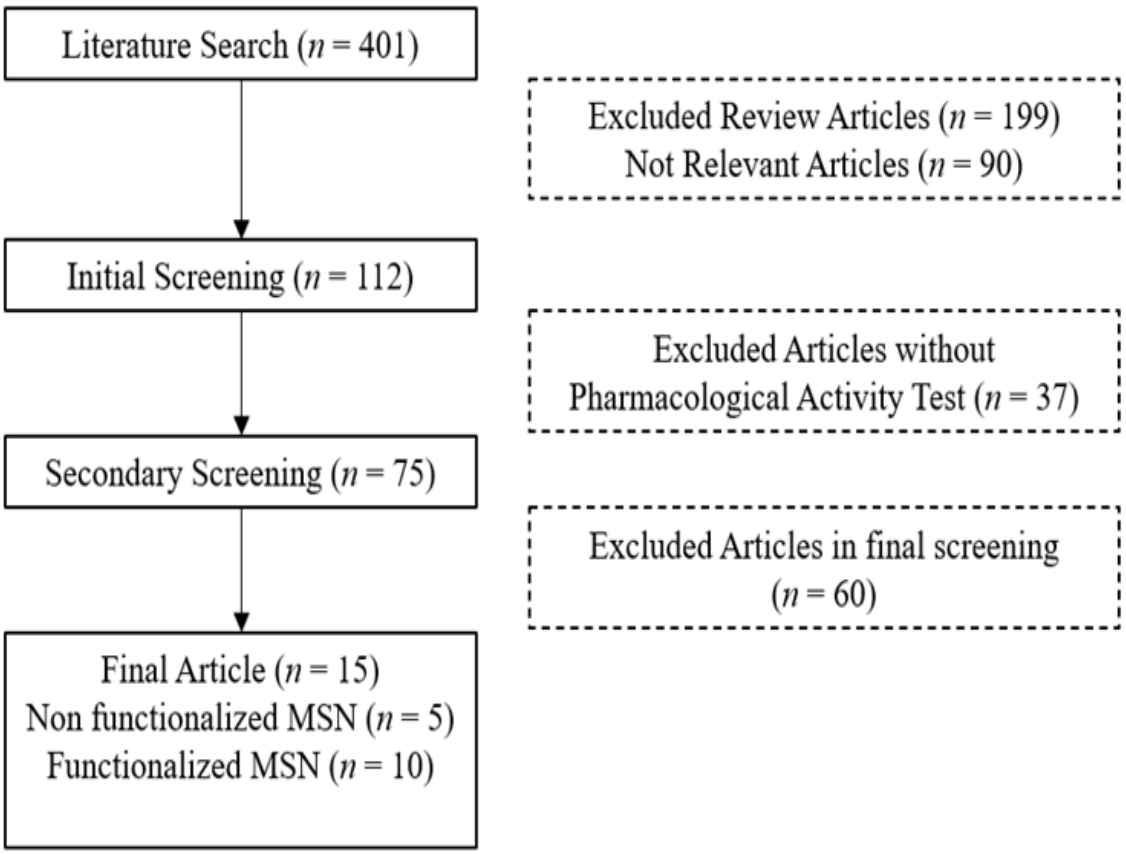


**Figure 1.** Flowchart of methodology

## 3. Result

Data were gathered from several journals and are summarized in Table 1.

**Table 1.** Enhancement of Dissolution and Pharmacological Activity of BCS Class II Drugs Encapsulated with Mesoporous Silica

| BCS Class II Drugs | Preparation Method | Silica Mesoporous Type | Dissolution Study | Pharmacological Activities | Reference |
|---|---|---|---|---|---|
| **Rifampicin (Rif)** | Passive diffusion | Mesoporous silica nanoparticle (MSN) | - | Increased absorption leads to higher antibacterial efficacy of MSN-Rif | (25) |
| **Indomethacin (IND)** | Sol-gel | Mesoporous silica nanoparticle (MSN) | - | MSN/IND treatments reduced the frequency of mitosis in tumour tissues by up to 37.95% and prevented tumour development by up to 70.09% compared to the IND groups | (26) |
| **Ibuprofen (IBU)** | Organic solvent drying | Amino functionalized mesoporous silica (Amino-MSN) | IBU release rate and amount were significantly improved and showed controlled drug release behaviour | IBU/Amino-MSN exhibited better anti-inflammatory effect and higher relative bioavailability (203%) | (27) |

| | | | | | |
|---|---|---|---|---|---|
| **Ketoconazole (KET)** | Sol-gel | Mesoporous silica nanoparticle (MSN) | - | Salicylic Acid/Ketoconazole (SA-KET) loaded in MSN has a higher zone of *Candida albicans* inhibition. SA-KET/MSN treated rabbit culture assay has rapid recovery & negative results | (28) |
| **Ketoprofen (KP)** | Immersion-rotavapor | SBA-15 | The dissolution of KP/SBA-15 was faster than crystalline KP. In the first 5 minutes, the release of KP/SBA-15 is very high (50%) while KP requires 120 minutes to reach 45%. | After 1 hour, KP/SBA-15 showed 82% inhibition in edema, while the standard showed 52%. | (29) |
| **Resveratrol (RES)** | Rotary evaporation | $PO_3$-MSN and $NH_2$-MSN | The dissolution of $NH_2$-MSN-RES is faster than RES crystals. $NH_2$-MSN-RES only needs 4 hours to reach 100% while regular RES needs 24 hours to reach 100%. | $PO_3$-MSN-RES showed higher anti-proliferative activity compared to plain RES dissolved in DMSO first (RES encapsulated in $PO_3$-MSN reversed hypoxia-induced resistance to Doc in $PC_3$ cells | (30) |
| **Breviscapine (BRE)** | Solution impregnation evaporation (SIV) | Mesoporous silica nanoparticles (MSN) | During the first 30 minutes, the release of pure BRE was about 26%, while BRE-MSNs was more than 80%. | The survival rate of BRE-MSN-SIV cells is higher than pure BRE so that BRE-MSN-SIV is biocompatible with Caco-2 cells and well tolerated in the digestive tract. | (31) |
| **Famotidine (FMT)** | Solvent evaporation | *Biomimetic synthesized mesoporous silica nanoparticles* (B-MSN) | The release of B-MSN encapsulated FMT occurred 80% during the first 5 minutes compared to pure FMT which was 100% release in 15 minutes. | The percentage of gastric mucoadhesiveness of mice given FMT encapsulated with B-MSN orally was 45.8% compared to mice given pure FMT orally. | (32) |

| | | | | | |
|---|---|---|---|---|---|
| **Pioglitazone (PIO)** | Simple adsorption | Mesoporous silica nanoparticles (MSN) | The release of pioglitazone encapsulated into mesoporous silica (MSN-PIO) was higher, namely 1.39 ppm than leptin/pioglitazone encapsulated into mesoporous silica (MSN-LEP-PIO), namely 1.19 ppm in the first 24 hours. | There was a significant improvement in motor performance, shown by TDP-43 mice treated with MSN-LEP-PIO. | (33) |
| **Cilostazol (CLT)** | Solvent evaporation, adsorption equilibrium, and fusion | MCM-48 and MCM-41 | The amount of CLT-MCM-48 that dissolved within 60 minutes was 85.78%, the amount of CLT-MCM-41 that dissolved within 60 minutes reached 63.41%, while pure CLT dissolved 13.56% within 60 minutes. | - | (34) |
| **Niclosamide** | Solvent evaporation | SBA-15 and MCM-41 | Pure niclosamide released 37% at 420 minutes. Meanwhile, at the same time, niclosamide-SBA 15 and niclosamide-MCM-41 released 75% and 60% | Niclosamide is effective in breast (MDA-MB-231) and prostate (PC-3) cancer cells; the drug containing SBA-15 significantly enhances its cytotoxic effect | (35) |
| **Mirtazapine (MRT)** | Incipient wetness, solvent evaporation, and impregnation | SBA-15, MCM-41, and Aluminate-MCM-41 | The solubility of MRT increases when loaded into MSNs in the order MCM-41< Alu-MCM41< SBA-15 | In vivo studies showed a 2.14-fold increase in oral bioavailability of MRT optimized by loading into SBA-15 compared to pure MRT in rabbit plasma | (36) |

| | | | | | |
|---|---|---|---|---|---|
| **Ritonavir (RTV)** | Solvent evaporation | MCM-41NPs and MCM-48NPs | The dissolution rate was significantly increased in RTV-MCM-41NPs and RTV-MCM-48NPs as compared to pure RTV. RTV-MCM-48NPs showed more than 95% drug release in dissolution media within 45 min, whereas pure RTV and R-MCM-41NPs showed almost 39% and 72% drug release in 0.1 N HCl respectively | The maximum RTV concentration in plasma was achieved by the RMCM-48NPs formulation, increasing approximately 1.67-fold more than the R-MCM41NPs formulation | (37) |
| **Ivermectin (IVM)** | Incipient wetness | MCM-41 | There was an increase in the dissolution rate in IVM-MCM 41 compared to pure IVM by 2.22-fold. | - | (38) |
| **Glimepiride (Gli)** | Solvent incubation | MCM-41 and *hexagonal mesoporous silica* (HMS) | Tablets formulated with glimepiride encapsulated in mesoporous silica MCM-41 dissolved 100% in 2 hours. This was an increase compared to tablets made with non-encapsulated glimepiride, which dissolved 30% in 2 hours. | - | (39) |

## 4. Discussion

Solubility plays an important role in determining drug efficacy because it affects the overall therapeutic potential, especially in oral formulations. BCS Class II drugs with low solubility are often excreted before optimal absorption in the gastrointestinal tract, resulting in low bioavailability and low dose proportionality (40). To achieve therapeutic levels, dose escalation is often required, but these risks cause local toxicity in certain tracts and reduce patient compliance (41). Therefore, strategies are needed to improve the solubility and bioavailability of this class of drugs.

Mesoporous silica (MSN) has been developed as a carrier capable of increasing the solubility of BCS class II drugs. The enhancement occurs through the mechanism of drug conversion from crystalline to amorphous form. The

spatial confinement effect of poorly soluble drug molecules in the mesopores lowers the lattice energy and prevents recrystallization. As a result, the bioavailability and dissolution rate of the drug are increased compared to the crystalline form. In addition, the high surface area of MSN and its hydrophilic nature increase the drug release rate (41). Thus, MSN-based formulations have the potential to increase the bioavailability and pharmacological effectiveness of BCS Class II drugs. However, despite the significant advantages of mesoporous silica in enhancing the solubility and bioavailability of BCS class II drugs, the limitations of using mesoporous silica, such as less compatibility and poor drug degradation, which will result in poor efficacy, also need to be considered for further drug development (42).

The ability of mesoporous silica to enhance the efficacy of BCS Class II drugs has been evaluated in various studies, including the formulation of rifampicin (Rif) for tuberculosis therapy. Subramaniam et al. (2019) studied the encapsulation of Rif into mesoporous silica nanoparticles (MSN) using the passive diffusion method. The results of the study indicated that the MSN-Rif complex had higher antibacterial activity against *Staphylococcus aureus* compared to free Rif. This increase was associated with increased particle uptake by macrophages, which optimized drug delivery to target cells. This formulation has the potential to reduce the need for high doses, reduce the risk of toxicity, and help prevent antibacterial resistance (30).

Ferreira et al. (2020) studied the encapsulation of indomethacin (IND), a non-steroidal anti-inflammatory drug (NSAID), into MSN using the sol-gel method, in which drug is loaded during mesoporous sol-gel synthesis using inert surfactant micelle (23). This study revealed that only MSN-IND showed anti-tumor activity, while free IND did not have similar effects. MSN-IND was able to inhibit tumor growth by 70.09% and reduce the frequency of tumor tissue mitosis by 37.95% compared to the IND group. These effects were attributed to the gradual release of IND from MSN, which inhibited COX-2 and blocked tumor cell proliferation. In addition, MSN-IND did not show significant systemic toxicity, making it a potential candidate for future cancer therapy (26).

The encapsulation strategy was also applied to ibuprofen (IBU), a BCS Class II NSAID drug, by loading it into mesoporous silica (SM) and SM functionalized with amino groups (Amino-SM) via a solvent evaporation method (31). This study showed that the conversion of IBU from the crystalline phase to the amorphous phase, as evidenced by DSC and XRD analysis, as well as the reduction of the molecular size in the confined space of the mesoporous material, enhanced the cumulative release of IBU/SM and IBU/Amino-SM. The drug release from the mesoporous material occurred gradually through a diffusion mechanism, with the highest loading efficiency and release ratio found in IBU/Amino-SM due to the hydrogen interaction between IBU and the amino groups in SM. This amino functionalization also improved the oral bioavailability and prolonged the elimination half-life. As a result, the anti-inflammatory effect of IBU/Amino-SM was more optimal, which was evaluated based on the decrease in the maximum swelling rate. Thus, amino functionalization of SM has been shown to be an effective strategy to improve the solubility and oral bioavailability of BCS Class II drugs.

The effect of SM surface functionalization was also studied in a

study by Chaudhary et al. (2019), who encapsulated resveratrol into PO3-MSN and NH2-MSN. PO3 functionalization (phosphonate group) increased the release of resveratrol by 40% in the first 8 hours, followed by a release of 65% at 24 hours. NH2 functionalization (amine group) increased the release of resveratrol by 85% in the first 8 hours, followed by a release of 100% at 24 hours (30).

Musallam et al. (2022), in their study, discussed mirtazapine (MRT) encapsulated into mesoporous silica SBA-15, MCM-41, and aluminate-MCM-41. The encapsulation methods used were solvent impregnation, solvent evaporation, and incipient wetness. The solubility of MRT increased when loaded into mesoporous silica in the order MCM 41<Alu-MCM 41<SBA-15. The results of this study also revealed that the encapsulation method used affected its solubility. Drugs loaded with the incipient wetness method will produce higher solubility compared to the other two methods. In this method, MRT molecules are found in the mesopore walls and in the micropores, which can strongly inhibit crystal growth. In addition, in vivo studies showed an increase in the oral bioavailability of MRT encapsulated into SBA-15, as much as 2.14-fold compared to regular drugs in rabbit plasma. Therefore, these findings can be a basis for selecting a formula with good bioavailability when used orally in humans at lower therapeutic doses to obtain equivalent clinical effects with fewer side effects (36).

Encapsulation of breviscapine into mesoporous silica was demonstrated in a study conducted by Yang et al. (2020). In the study, breviscapine was encapsulated with mesoporous silica using the solution impregnation evaporation (SIV) method. During the first 30 min, the release of pure BRE was about 26%, while BRE-MSNs was more than 80%. The survival rate of BRE-MSN-SIV cells is higher than pure BRE so that BRE-MSN-SIV is biocompatible with Caco-2 cells and well tolerated in the digestive tract (31). Li et al. (2016) studied the encapsulation of famotidine (FMT) into biomimetic synthesized mesoporous silica nanoparticles (B-MSN) using the solvent evaporation method (32). FMT is one of the H2 receptor antagonist drugs used in the management of gastric ulcers (43). The release of FMT encapsulated in B-MSN took place 80% during the first 5 minutes compared to pure FMT, which was 100% release in 15 minutes. Encapsulation of FMT into B-MSN also improved the drug release profile in describing the consistency of the drug released in the gastric environment. The percentage of gastric mucoadhesiveness of mice given FMT encapsulated with B-MSN orally was 45.8% compared to mice given pure FMT orally.

Pioglitazone encapsulated into MSN was shown by research by Díaz-García et al. (2022). Pioglitazone is one of the oral antihyperglycemic drugs that is included in the second class BCS with the Thiazolidinedione group (44). The release of pioglitazone encapsulated into mesoporous silica (MSN-PIO) was higher, namely 1.39 ppm than leptin/pioglitazone encapsulated into mesoporous silica (MSN-LEP-PIO), namely 1.19 ppm in the first 24 hours. In addition, there was a significant improvement in motor performance, shown by TDP-43 mice treated with MSN-LEP-PIO (33). Wang et al. (2014) encapsulated cilostazol into two types of MSN, namely MCM-48 and MCM-41. Encapsulation was carried out by three methods, namely solvent evaporation, adsorption equilibrium, and fusion methods. The dissolution profile showed that the amount of CLT-MCM-48

dissolved within 60 minutes was 85.78%, the amount of CLT-MCM-41 dissolved within 60 minutes reached 63.41%, while pure CLT dissolved 13.56% within 60 minutes (34).

Mesoporous silica formulation has been applied to the combination of two drugs. Masood et al. (2021) developed a mesoporous silica nanoparticle (MSN) formulation containing salicylic acid (SA) and ketoconazole (KCZ) using an in-situ sol-gel method. MSN-SA/KCZ showed higher efficacy than the free drug form, with faster elimination of fungal infections and accelerated wound healing. In vivo studies showed that all animals receiving MSN-SA/KCZ were free from infection, while the control group still showed active infections. This advantage is attributed to the bioadhesive and occlusive properties of MSN which allow controlled drug release in the wound area. In addition, this formulation has lower toxicity and better tolerability, as evidenced by a zero erythema score on day 14 (28). MSN acts as an ideal matrix in accelerating wound healing by increasing wound contraction and faster tissue closure (45). Hence, mesoporous silica-based combination therapies have the potential to improve patient compliance by synergistically enhancing antifungal efficacy at lower doses, reducing therapeutic agent toxicity, and accelerating the healing of fungal infections. This potential opens up opportunities for further development in other combination therapies.

Samples encapsulated in SM can be formulated in hard gelatin capsules such as the study of Abd-Elrahman et al. (2016), who encapsulated ketoprofen (KP) into mesoporous silica SBA-15 (SBA-15-KP) and then formulated it into capsule form (F#1). The presence of KP in amorphous form in the pores of SBA-15 significantly increased dissolution, with almost 50% of the drug released in five minutes, compared to pure KP which required 120 minutes to reach 45%. The dissolution rate of F#1 was proven to be equivalent to SBA-15-KP, indicating that drug release was not affected by the use of excipients and was only influenced by the change in the KP structure to amorphous. This increased dissolution contributed to faster anti-inflammatory and analgesic effects, with F#1 reaching maximum effectiveness in 30 minutes, compared to the reference drug, which required 120 minutes. Thus, the utilization of mesoporous silica in hard gelatin capsule formula has been shown to increase the dissolution of BCS class II drugs, thus potentially increasing their bioavailability and pharmacological effects (29).

Encapsulation of niclosamide into mesoporous silica has been studied by Pardhi et al. (2017). Niclosamide is a drug classified as BCS class II, which shows poor solubility. The method used to encapsulate niclosamide into mesoporous silica SBA-15 and MCM-41 is the solvent evaporation method. The drug encapsulated into mesoporous silica experienced an increase in dissolution rate. In pure drug, 37% of the drug was released within 420 minutes, while in the drug encapsulated in SBA-15 and MCM-15, 75% and 60% were released, respectively, within the same time period. In addition, the impact of niclosamide encapsulation into mesoporous silica was also seen in the results of in vitro cytotoxicity tests, which revealed that niclosamide was effective on breast (MDA-MB-231) and prostate (PC-3) cancer cells, where the drug containing SBA-15 significantly increased its cytotoxic effect (35).

Mahajan and Rajput (2018) in their study, discussed the encapsulation of ritonavir (RTV) into mesoporous silica

MCM-41NPs and MCM-48NPs using the solvent evaporation method. The results showed a significant increase in the dissolution rate in RTV-MCM-41NPs and RTV-MCM-48NPs compared to pure RTV. RTV-MCM-48NPs showed more than 95% drug release in the dissolution medium at 45 minutes and R-MCM-41NPs showed a release of 72%, while pure RTV showed almost 39% of the drug in 0.1 N HCl. In addition, the effect of encapsulation on the results of in vivo studies by administering drug suspensions orally to Wistar rats is also explained. RTV is a typical BCS II drug, namely, its absorption will be limited by its dissolution rate. In this study, the results showed an increase in the bioavailability of RTV-MSN compared to the pure drug. The maximum plasma concentration of RTV was achieved by the RTV-MCM-48NPs formulation, about 1.67 times more than the R-MCM41NPs formulation. When compared to pure RTV, the Cmax and AUC0-t values of RTV MCM-48NPs increased by 2.48-fold and 1.94-fold, respectively. Meanwhile, the Cmax and AUC0-t values of RTV-MCM-41NPs increased by 1.45-fold and 1.34-fold, respectively (37).

Ivermectin (IVM) is a drug used for parasitic infections. Velho *et al*. (2024) examined the effect of IVM encapsulated into mesoporous silica MCM-41 by incipient wetness method. The results showed an increase in the dissolution profile of the IVM-MSN sample of 78 ± 3% after 48 hours, while in the pure IVM the release only reached 35 ± 7% due to low solubility (38).

Drugs encapsulated into mesoporous silica can also be made into tablet preparations. As in the research conducted by Voycheva et al. (2019) who made tablet from MCM-41-loaded glimepiride (Gli/MCM-41) and hexagonal mesoporous silica (HMS)-loaded glimepiride (Gli/HMS). Based on the tests conducted, tablets formulated with Gli/MCM-41 dissolved 100% in two hours and Gli/HMS dissolved 93% in two hours, an improvement when compared to pure glimepiride tablets, which dissolved only 30% in 2 hours. Gli/HMS tablets had a slower release rate; this could be attributed to higher recrystallization compared to those encapsulated with MCM-41(39).

## 5. Conclusion

Based on the results obtained from various studies, the use of mesoporous silica as a nanocarrier to maintain the stability of amorphous materials is effective for improving the dissolution profile and bioavailability of BCS class II drugs that have low solubility. In the development of this method, it is necessary to pay attention to the encapsulation method and the type of mesoporous silica used. Thus, improved solubility and bioavailability of the drug will be achieved and a lower therapeutic dose will be obtained to obtain equivalent clinical effects with fewer side effects.

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