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Redefining Co-Amorphous Solid Dispersions: The Role Of Flavonoids As Functional Carriers

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ABSTRACT
The advancement of co-amorphous solid dispersions (CSDs) is reshaping drug formulation and tackling the difficulties with poorly soluble drugs. The flavonoids are emerging as innovative functional carriers within this realm. Flavonoids stand out as superior carriers in CSDs compared to traditional excipients, due to their natural, eco-friendly, non-toxicity, and better pharmacokinetic profile. They are also known for their antioxidant, anti-inflammatory, and bio-enhancing properties, and offer dual functionality by stabilizing amorphous drug forms and potentially enhancing bioavailability (BA). Thus, this review explores the potential of flavonoids to redefine CSDs, focusing on their role in improving drug stability, solubility, and BA through π-π stacking, hydrogen bonding, and electrostatic interactions. Such interactions between flavonoids and active pharmaceutical ingredients (APIs) contribute to the suppression of drug recrystallization, a key challenge in the long-term stability of amorphous formulations. This article also explains recent cell lines/ animal studies indicate that incorporating flavonoids as carriers in CSDs can enhance therapeutic outcomes, predominantly for poorly soluble drugs. The unique properties of flavonoids open new avenues in CSD design, making them promising candidates for future drug delivery systems.

Keywords: *Flavonoids, Co-Amorphous Solid Dispersion, Functional Carrier, Bioavailability, Therapeutic Potential.*

1. INTRODUCTION

More than 85% of medications supplied worldwide are taken orally, making this the most popular method of drug delivery. The characteristics of a drug that controls oral absorption are crucial to its development in this context[1]. In 1961, *Sekiguchi and Obi* introduced the idea of solid dispersions (SD) to solve the widespread pharmaceutical problems of oral dose forms[2]. Amorphous solid dispersion (ASD) is a subtype of SD characterized by APIs' molecular and amorphous distribution within inert carriers[3]. Due to its inherently disordered structure and lack of crystalline lattices, the amorphous form of API improves solubility[4]. In addition, ASDs improve a drug's wettability, dissolution rate, and supersaturation, increasing the membrane flow and oral BA. However, thermodynamic instability and recrystallization tendencies during processing, storage, and dissolution limit their potential use[5]. In light of this, creating amorphous medications with sufficient stability is still very difficult, and formulation methods based on solid molecular dispersions are being used. As illustrated in Figure 1, co-amorphous systems (CAMs) are a novel formulation technique in which a low molecular co-former (such as an excipient, stabilizer, or functional carrier like flavonoids, represented by red spheres) stabilizes the amorphous drug or primary molecule (represented by blue spheres), through strong intermolecular interactions[6]. Co-amorphous solid dispersions combine two or more initially crystalline, low-molecular-weight components into a single-phase, homogeneous amorphous system. This formulation offers improved stability, enhanced solubility, better therapeutic efficacy, increased BA, and reduced adverse effects[7].

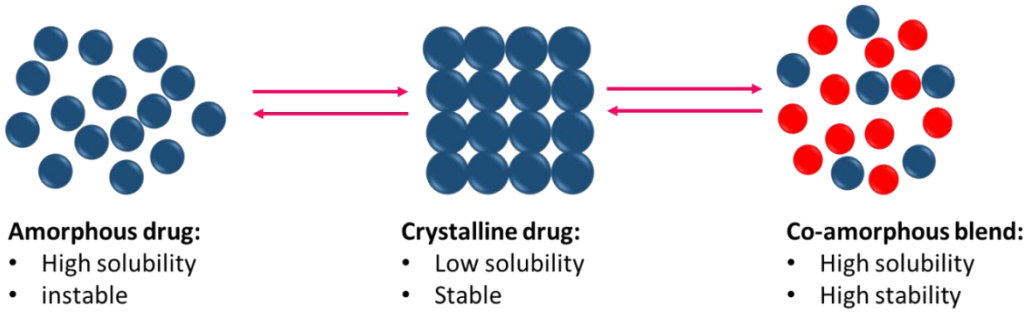

Figure 1: Advantages of CSD over crystalline and amorphous drug

Flavonoids can be used as co-formers in co-crystals and CSDs to improve their solubility, BA, and therapeutic efficacy. Their molecular structures contain multiple phenolic hydroxyl (OH) groups that can act as proton acceptors and donors, which allows them to form intermolecular hydrogen bonds with co-formers[8,9]. Thus flavonoids have gained significant attention for their potential as functional carriers, particularly in pharmaceutical and nutraceutical sectors. They also exhibit varied biological activities hence making them ideal candidates in enhancing drug delivery systems, including CSDs[10].

Thus this review explores the potential and advantages of flavonoids as functional carriers in CSDs. As eco-friendly and multifunctional agents, flavonoids offer promising opportunities to create more effective and sustainable CSDs in pharmaceutical development. The review further examines the challenges and future prospects of using flavonoid-based systems in both pharmaceuticals and neutraceuticals, with a focus on their applications for the prevention and management of issues related to CSDs.

2. THE COMPARATIVE ANALYSIS OF ASD AND CSD

2.1 Mechanisms of drug solubilization in ASD

The process of drug solubilization is necessary for the systemic absorption of drugs taken orally. Unfortunately, a substantial number of medications on the market (about 40%) and those in the research and development pipeline (about 90%) have low water solubility[11]. As a result, different formulation techniques have been used to address these issues[12]. It can be successfully improved by formulating them as ASDs[13–16]. Approximately 25 ASD formulations are currently approved by the Food and Drug Administration and commercially accessible on the market[17]. In ASDs, the drug's amorphous form is essential for boosting its solubility because the amorphous state represents a metastable, higher-energy state, which means it has greater potential to dissolve in a solvent like water. When the drug is amorphous, the drug crystal structure can be broken with no energy. It is also known that ASDs increase membrane flux because of increased supersaturation, which enhances BA[12]. The ASDs also exhibit higher wettability, attributed to the inclusion of hydrophilic polymers which increase the surface area for dissolution when exposed to aqueous environments. This helps in quicker solubilisation[18].

The ASDs can be either single-component or multi-component systems. A **single-component ASD** consists of an amorphous drug alone, without the addition of any polymers or coformers. In this type, the drug is converted to its amorphous form, taking advantage of the increased solubility and dissolution, compared to its crystalline counterpart. However, in practice, single-component ASDs are less popular due to stability concerns[19]. Without a polymer or stabilizer, the amorphous drug in single-component ASDs is highly prone to recrystallization over time, especially under moisture or temperature fluctuations. They are also more susceptible to processing challenges like phase separation, leading to heterogeneous products with varying drug release properties[20]. Thus they are often supplemented with polymers or other excipients in most pharmaceutical applications to maintain the amorphous state and prolong stability[17].

2.2 Brief overview of CSD

2.2.1 Benefits of CSD compared to ASD

A co-amorphous system consists of a drug and a co-former, typically another tiny molecule mixed at the molecular level in an amorphous state. It is different than co-crystal formulations (Figure 2). The CSDs utilize co-formers such as:

a. Organic acids (e.g. succinic acid, tartaric acid, fumaric acid, citric acid, maleic acid, malic acid, lactic acid, and benzoic acid.)

b. Amino acids (e.g., glycine, L-arginine, L-lysine, L-histidine, L-proline, and L-glutamine)

c. Saccharides (e.g., glucose, sucrose, lactose, trehalose, mannitol, and sorbitol)

d. Pharmaceutical excipients (e.g., caffeine, nicotinamide, urea, polyethylene glycol (PEG), cyclodextrins,

hypromellose)

e. Natural compounds, such as flavonoids (e.g., quercetin, naringenin), curcumin, resveratrol, catechins, gallic acid, and ellagic acid

f. Other small molecules like thiourea, 2-pyrrolidone, carbamazepine, theophylline, and isonicotinamide.

These co-formers ensures better molecular-level interactions and more efficient stabilization of the amorphous drug which can also provide bioactive benefits[21,22].

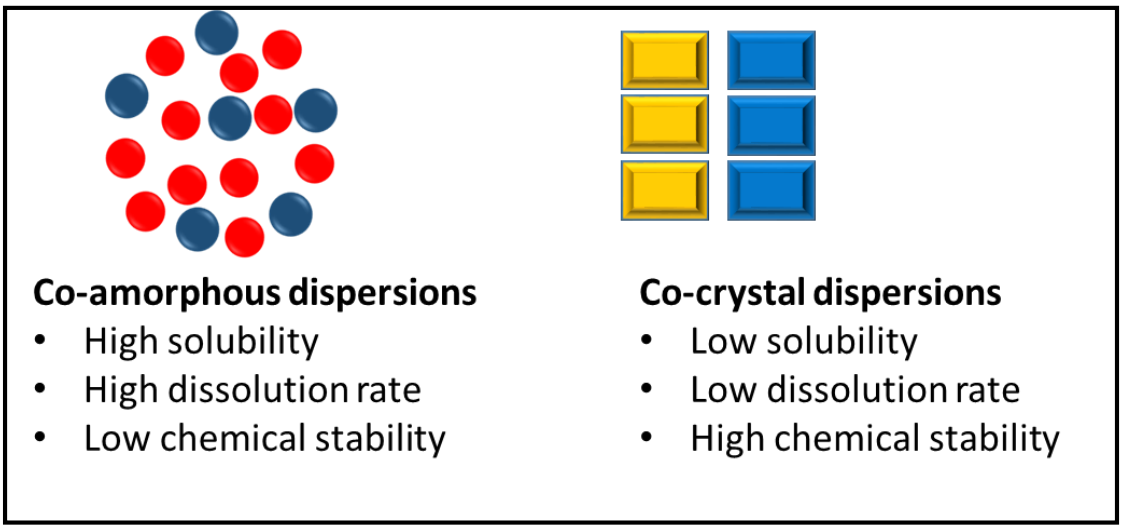

Figure 2: Difference between co-amorphous and co-crystal dispersions

CSDs are typically more stable than ASDs due to the stronger intermolecular interactions between the drug and co-former. These interactions make it less prone to recrystallization[6] and often demonstrate improved dissolution rates compared to ASDs[23]. CSDs do not face such viscosity-related limitations. This results in a faster and more uniform release of the drug from the CAM. Better maintenance of supersaturation in gastrointestinal fluids, improving absorption and BA[24].

2.2.2 Mechanism of action in CSD

In CAMs, strong non-covalent interactions between the drug and the co-former contribute to averting the conversion of the amorphous drug into the crystalline form[25]. Co-amorphous materials can alter the glass transition temperature (Tg), which impacts the thermodynamic stability of formulations throughout production and storage. They also play a key role in stabilizing the amorphous state by limiting molecular mobility and decreasing the propensity of drug molecules to reorganize into a crystalline lattice. These interactions are stronger and more consistent compared to the weak interactions between polymers and drugs in ASDs. *Budiman et al.* incorporated ritonavir (RTN)-saccharin (SAC) co-amorphous into mesoporous silica via solvent evaporation and examined the impact of SAC on RTN dissolution from the mesopores. The study highlighted that drug-co-former interactions within mesoporous silica can substantially enhance drug dissolution[26]. *Löbmann et al.* demonstrated that the solubility of the co-former and the strength of the drug-co-former interaction were critical factors in the dissolution test results of indomethacin/Amino Acid (AA) co-amorphous formulation[27]. But if the co-former dissolves too quickly and the interactions between the drug and co-former are weak, the co-former will dissolve more quickly than the drug, making the drug more prone to recrystallization[28]. The presence of a co-former often results in increased Tg of the system, which contributes to the stabilization by slowing molecular motion revealed by *Karagianni* and colleagues[7]. As per *Laitinen et al.* glibenclamide (GBC) was able to form CAM with both serine (receptor) and threonine (non-receptor) at a 1:1 molar ratio, as well as with glibenclamide-serine-threonine at a 1:1:1. Simvastatin (SVS) only formed CAM with LYS, aspartic acid, and serine (SER), the receptor-binding amino acids. For three and six months, co-amorphous systems demonstrated enhanced physical stability for SVC-LYS and GBC-SER. The AA's ability to stop the amide group from changing into the unstable tautomeric imide form may have contributed to the stabilization of GBC[29].

2.2.3 Challenges in carrier/co-former selection for CSD

In the development of CSDs, selecting the right carrier, or co-former is crucial but challenging. Thus there are some challenges which are mentioned below.

The biggest obstacle in drug-drug CAM design is the process of choosing potential medications that can combine to produce a glassy system. By identifying different molecule interactions in Fourier transform infrared spectroscopy and Raman spectra and offering insights into the near-range order of amorphous systems, quantum mechanics can help with this procedure[30] to

confirm the formation of CAM through molecular interactions. *Löbmann et al.* used quantum mechanics to study the synthesis of heterodimers in the indomethacin and naproxen CAM system[31]. *Russo* and colleagues investigated the H-bonding interactions between omeprazole and amoxicillin to further investigate the application of quantum mechanics in assessing intermolecular interactions between the medication and co-former of CAM[32]. *Gniado et al.* showed how the dissolving rate of sulfamerazine CAM is affected by three co-formers: sodium taurocholate, citric acid, and deoxycholic acid[33]. During milling, the drug may crystallize if the processing temperature exceeds its Tg. Additionally, elevated temperatures enhance the molecular mobility of the drug, potentially leading to phase separation. Therefore, this method is best suited for thermally stable drugs and co-formers with a higher Tg[34]. It is necessary to examine the impact of co-formers on nucleation and crystal growth inhibition to ascertain the physical stability of CAM since the advantages of this supersaturated system can only be understood if the co-former inhibits either of these two crystallization stages[35]. Based on these obstacles some approaches are useful to choose appropriate co-formers. They can be selected based following parameters (Figure 3).

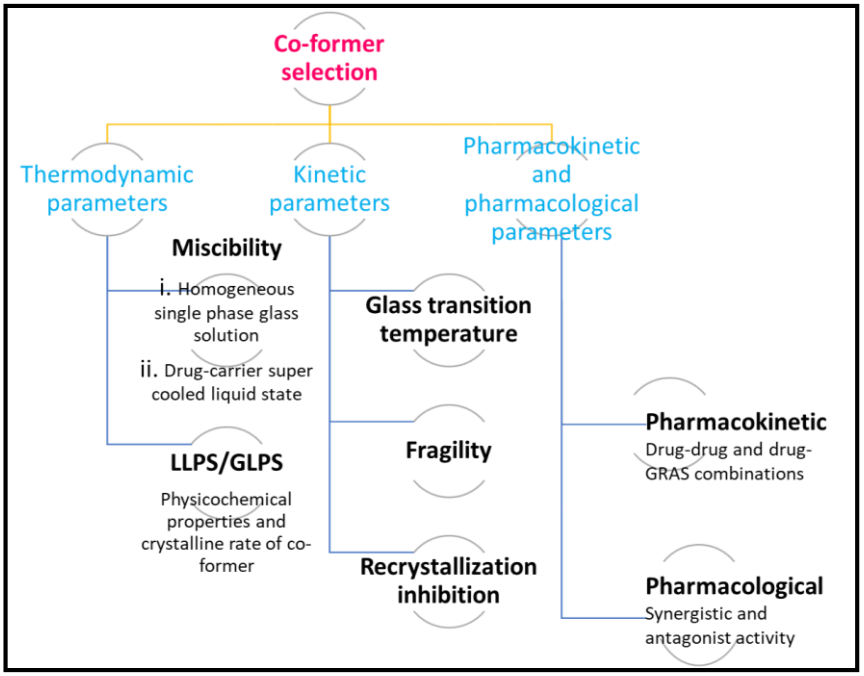

Figure 3: Overview of co-former selection approaches

LLPS: Liquid-Liquid Phase Separation, GLPS: Gas- Liquid Phase Separation

3. UNDERSTANDING THE CONCEPT AND ROLE OF FLAVONOIDS

3.1 Chemical structure and classification of flavonoids

A class of phenolic compounds known as flavonoids has an oxygenated heterocycle with two aromatic rings joined by a bridge made up of three carbon atoms. They are divided into six subclasses: isoflavones, flavones, flavan-3-ols, flavanols, anthocyanins, and flavanones (Figure 4)[36]. The hydroxylation pattern, conjugation between the aromatic rings, glycosidic moieties, methoxy groups, and other substituents all affect the chemical makeup of flavonoids[37]. The electronic spectra of flavonoids contain conjugated double bonds and groups (hydroxyl or other substituents) that can donate electrons through resonance to stabilize the free radicals[38].

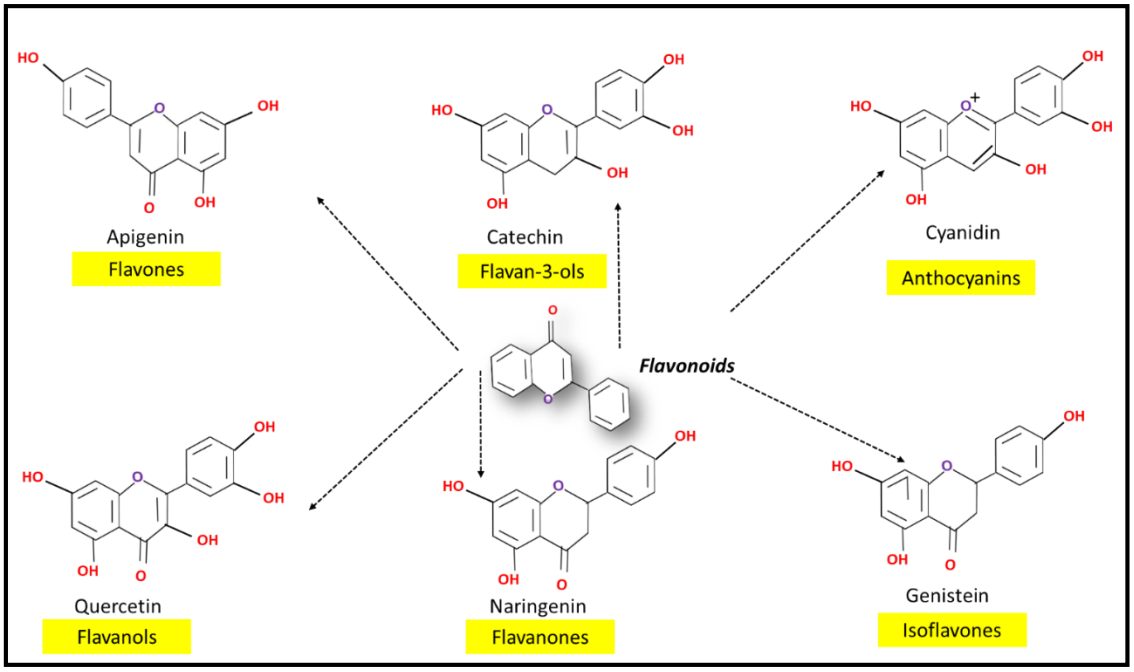

Figure 4: Basic structure of flavonoids along with their classes

3.2 Role of flavonoids as a therapeutic agent

Over 10,000 flavonoid compounds have been found and isolated thus far. The majority of flavonoids are commonly used as medicines[39]. It is well known that flavonoids serve as a tumor suppressors and slow down cell proliferation such as Hesperedin (Hsp), Aurone., quercetin has been effectively used for colorectal cancer[26,40]. Myricetin is a significant flavonoid that exhibits anti-inflammatory and anti-cancer activities. Female hop cones contain flavonoids that show anti-tumor and anti-microbial properties[41]. The flavonoids found in *Emblica officinalis* possess antitumor, anti-inflammatory, antioxidant, and immunomodulatory properties. Oesophageal carcinoma is prevented by berry flavonoids[42].

Additionally, flavonoids exhibit antioxidant properties. Examples are *Tamarix aphylla*, *Oryza sativa*, *Rosa damanscena*, *Bauhina variegate*, *Tinospora cardiofoli*. Numerous research has demonstrated the cardioprotective and neuroprotective properties of flavonoids. Tea and other flavonoids like proanthocyanidin and anthocyanidin treat cardiac conditions[43]. Flavonoids protect against Parkinson's, dementia, Alzheimer's, and other age-related neurodegenerative illnesses. Two flavonoids, hesperetin and hesperidin are recognized because of their neurological properties[39]. *Chalcones* are natural compounds of flavonoids and iso-flavonoids used for stroke prevention. Genistein, mulberries, *Acanthus syriacus*, etc. have protective benefits against sciatic nerve damage. Flavonoids also show potent antimalarial, antiviral, antibacterial, and antifungal activity[10,44].

3.3 Flavonoids as functional carriers in CSD

Flavonoids are being explored as potential carriers in CSDs due to their unique physicochemical properties. As mentioned earlier, flavonoids as a co-formers can form strong hydrogen bonds and other non-covalent interactions with poorly soluble drugs, dropping the risk of drug crystallization and boosting physical stability without requiring polymers. Additionally, flavonoids have inherent bioactive properties, such as antioxidant and anti-inflammatory effects, which may synergize with the drug's therapeutic effects, providing added health benefits. By serving as both stabilizers and permeability enhancers, flavonoids in CSDs hold promise for increasing drug BA, enhancing formulation stability, and offering a natural, multifunctional alternative to synthetic excipients (Table 1)[9,45].

Table 1: Role of flavonoids as a functional carrier in CSD

Drug	Co-former/ carrier	Outcomes
Neohesperidin (NE)	Naringin (NA)	The NE-NA co-amorphous binary system is enhancing the dissolution behaviour and stabilizing the amorphous state of NE. It also reduces cost and time[46].
Ceritinib	Naringin	Significant improvements in the solubility,

		dissolution, and permeability[47].
Ciprofloxacin	Quercetin	Increased aerosol performance and stability with the 1:1 M ratio [48].
Docetaxel (DOC)	Myricetin	Better oral absorption and dissolution of poorly soluble and permeable DOC due to its superior physical stability[49].
Raloxifene (RLX) HCl	Quercetin	The concentration of RLX was enhanced by the CAM[50].
Curcumin (CUR)	Naringin	The significant impact of the co-former- NA on the amorphous state of CUR, enhancing its solubility and oral BA[51].
Genistein	Lysine and arginine	Greatly improve genistein's solubility and biological activity[52].
Ceritinib	Rutin	Improvement in solubility, BA, and physical stability[47].

4. MECHANISTIC ROLE OF FLAVONOIDS IN CSD

4.1 Molecular-level interactions between flavonoids and APIs

Most flavonoids are classified as BCS Class II, which poses difficulties for their synthesis and development[53]. They interact with APIs at the molecular level through a range of non-covalent interactions that can influence drug pharmacokinetics and pharmacodynamics. Their interactions are primarily governed by their polyphenolic structure, allowing them to bind or interact with APIs[54]. The brief discussion is mentioned below.

a. ***Hydrogen bonding***: Flavonoids have -OH groups that might act as hydrogen donors or acceptors, forming hydrogen bonds with API molecules. This bonding is crucial for stabilizing the molecular complex and can improve the solubility and BA of the API[55].

b. ***π-π Stacking***: Many flavonoids have aromatic rings, which can engage in π-π stacking interactions with aromatic groups on the API. These interactions help stabilize the complex and influence the drug's binding affinity with its target[56].

c. ***Hydrophobic interactions***: The nonpolar segments of flavonoids can interact with hydrophobic regions of an API, promoting binding stability and potentially improving pharmacokinetics by shielding the API from degradation[57].

d. ***Electrostatic interactions***: Electrostatic interactions occur between charged groups, where oppositely charged entities attract each other. Flavonoids, which are polyphenolic compounds, can possess both acidic and basic functional groups, enabling them to interact with APIs that have complementary charges (Table 2)[58].

Table 2: Molecular interaction of flavonoids with API

Moiety name	Interactions	Outcomes
Analogs of flavonoids with distinct -OH groups	H-bonding	The findings show that the interactions between drugs and polymers strengthen with increasing OH group numbers, reducing drug crystallization in the CSD system. Lastly, the quantity of OH groups and the intensity of the interactions determine how medicines dissolve in CSDs *in vitro*[55].
Quinoa protein nanomicelles interact with quercetin,curcumin, luteolin and resveratrol	Hydrophobic interaction and H-bonding	Overall physicochemical properties are improved[59].
Flavonoids and 4,4′-	Heteromolecular H-	This work provides practical ideas for research on

Vinylenedipyridine (VDP)	bonding	similar or other cocrystals and aids in the design and prediction of the flavonoid and VDP cocrystals[60].
The hydrophobic core of the beta-casein micelles in bovine was loaded with NA.	Hydrophobic interactions	Increased aggregation numbers and lower critical micelle concentrations, which led to a notable rise in their concentrations in aqueous solutions[57].
Myricetin incorporated into a carrier of diblock polymeric nanoparticles (PNP)	Electrostatic interactions.	PNPs increase myricetin solubility >25-fold compared to myricetin alone[58].
The binding of eight classic flavonoids to γ –globulin	Hydrophobic interactions, H-bonding, and electrostatic forces	This research shedding light on BA factors such as absorption, biodistribution, and elimination of flavonoids *in vivo*[61].

4.2 In vivo/vitro studies of flavonoid-based CAMs

In vitro and *in-vivo* studies of flavonoid-based CAMs have shown that these systems can boost the solubility, dissolution rate, BA, and stability of APIs (Tables 3 and 4).

Table 3: *In vitro* studies of flavonoid-based CAMs

Flavonoids CAM	Cell lines/assay	Activity	Inference
Kaempferol, quercetin and myricetin	*S. aureus* and *E. coli*.	Antibacterial	All have excellent antibacterial qualities against *S. aureus* and *E. coli*, which can be used successfully in antibacterial products[56].
Myricetin Genistein hesperetin Pratensol	HCT-8 and CaCO-2 cancer cells.	Cancer	The outcomes displayed improved anti-tumor effects against cancer cells[60].
Fisetin	PAMPA	Neuroprotection	Improved solubility, antioxidant prowess, and microbiome intervention [62].
Genistein and amino acids	Antioxidant assay	Antioxidant, antidiabetic	Exhibited the most marked apparent solubility enhancement, and significant improvement in antioxidant activity [63].

PAMPA: Parallel Artificial Membrane Permeability Assay

Table 4: *In vivo* studies of flavonoid-based CAMs

Flavonoids CAM	Animal model	Activity	Inference
Quercetin	Healthy male Wistar rats	Anti-inflammatory	CAM-loaded pellets' strongest anti-inflammatory effects, as may the increase in dissolving rate[64].
Kaempferol with proline	18 male Sprague–Dawley (SD) rats	-	Altered the pharmacokinetic profile, demonstrating a shorter Tmax, increased Cmax, and enhanced AUC_{0-24} h compared with pure kaempferol[65].
Quercetin and amino acids	Wistar rats	Pain management	Improved its dissolution behavior and antioxidant capacity[9].
Naringenin and Fisetin	Diet-induced Obesity Murine Model	Obesity & related disorders.	Notable decreases in fat accumulation, better metabolism of cholesterol, and increased glucose tolerance[66].
Curcmin and	SD rats	Food industries,	Solubility, and oral bioavailability increased is

naringin		cosmetics	thereby evident from the study[1].

4.3 Advantages of using flavonoids as carriers in CDS over other traditional excipients

a. Flavonoids are naturally derived compounds found in many fruits, vegetables, and plants. They are generally recognized as safe (GRAS), making them biocompatible and reducing the risk of toxicity or adverse reactions. Whereas, many traditional excipients are synthetic one. E.g., Polyvinylpyrrolidone (PVP), **Hydroxypropyl Methylcellulose (HPMC),** Poloxamer 188 and 407.

b. Flavonoids can stabilize poorly soluble drugs in the amorphous state by forming strong H-bonds or π-π interactions with the drug molecules. This reduces the risk of recrystallization. Flavonoids can augment the physical and chemical stability of drugs, particularly those prone to degradation.

c. Flavonoids have shown a potential to enhance the solubility and dissolution rate of hydrophobic APIs by stabilizing their amorphous state, thereby improving BA

d. Flavonoids, unlike traditional excipients, have inherent bioactivity (e.g., antioxidant, anti-inflammatory, and anti-cancer properties) which can contribute to the therapeutic profile of the drug, adding potential health benefits beyond simple drug delivery.

e. Using flavonoids as carriers can reduce reliance on synthetic polymers, often resulting in a cost-effective formulation[8,26,68].

4.4 Challenges and limitations of flavonoid-based CAMs

Flavonoids can lower the risk of several diseases by increasing eating of fruits and vegetables and decreasing the consumption of meals high in fat. *Hesperetin*, however, has poor water solubility and insufficient stability in the gastrointestinal (GI) tract, which leads to minimal oral absorption, much like the majority of hydrophobic bioflavonoids[69]. Although flavonoids are effective against cancer in many literature, their pharmacological effectiveness may be restricted because of their insoluble nature in water[70]. Poor transport across the enterocyte and highly effective conjugation metabolism of these chemicals seem to be the limiting factors for the oral bioavailability of tea flavonoids in humans[71]. Flavonoids' sensitivity to moisture and temperature requires precise control over processing conditions, and making scale-up. Additionally, temperature has a significant impact on flavonoid extraction and shelf life. It is impossible to forecast the quantity and biological activity of flavonoids in plant extracts because environmental conditions are hard to regulate[72]. Due to the natural variability of flavonoids, achieving batch-to-batch consistency in commercial-scale production can be difficult. Quality control is essential, with mandates for detailed sourcing, extraction methods, and impurity profiling to ensure product consistency. Stability testing is crucial and additionally, flavonoids' potential interactions with APIs and metabolic enzymes must be assessed to prevent impacts on drug bioavailability and therapeutic outcomes[73]. While this guidance focuses on enhancing the research and reporting of flavonoid-related human studies, it is also critical to recognize how basic research in animal and *in vitro* models can be improved to align preclinical and mechanism-of-action studies better. Hence, researchers working in the field must keep working toward the standards[74].

5. CONCLUSION AND FUTURE DIRECTIONS

In conclusion, flavonoids hold significant promise as functional carriers in CSD, offering several. Their ability to prevent recrystallization, addresses a critical challenge in amorphous drug formulations. Additionally, the intrinsic therapeutic properties of flavonoids provide synergistic benefits, potentially improving overall treatment outcomes. Despite these advantages, further studies, particularly animal models, are needed to fully assess the safety, efficacy, and scalability of flavonoid-based CSDs. Also flavonoid-based CAM highlight promising advancements in drug delivery and personalized medicine to enable more tailored, patient-specific formulations. Collaborative efforts across pharmacology, materials science, and biotechnology will be essential to overcome existing challenges and fully harness flavonoids' potential in stabilizing CSD.

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Conflict of Interest: None

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