

VITAMIN K2 DISSOLUTION IN SUNFLOWER OIL OR VITAMIN K2 DISSOLUTION IN MCC POWDER

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Abstract

Vitamin K2 belongs to the fat-soluble vitamin category and it cannot dissolve easily in water. Hence, the use of an appropriate carrier becomes important in its preparation and bioavailability. The present article discusses two types of carriers used to formulate Vitamin K2; which include sunflower oil and microcrystalline cellulose (MCC). Sunflower oil provides a lipid medium where Vitamin K2 may be dissolved and uniformly dispersed in addition to improving its intestinal bioavailability with the help of lipid digestion and construction of micelles. But the high amount of fatty acids makes the oil vulnerable to oxidation that necessitates its protection with antioxidants and proper packaging. In comparison to sunflower oil, MCC is typically used as a solid carrier. MCC is used for the incorporation of Vitamin K2 through use of adsorption, dry blending, liquid loading and granulation while the release of the vitamin is affected by such factors like the size of the carrier and its porosity, wetting and properties of the mixture. The evaluation emphasizes the pros and cons of the two systems regarding solubilization, incorporation, dissolution behaviour, stability and manufacturing convenience. Generally speaking, the sunflower oil seems to be a better option for lipid-based solubilization, whereas MCC has some advantages in terms of solid dosage formulations. In future studies, other aspects of Vitamin K2 launch, including optimization of its loading, stability, dissolution, and bioaccessibility should be analyzed which includes the creation of hybrid lipid-MCC delivery systems.

Keywords

Vitamin K2; Sunflower Oil; Microcrystalline Cellulose; Solubilisation; Dissolution Behaviour

1. Introduction

Vitamin K2, which is known as menaquinone, is a fat-soluble vitamin that exists in various forms including MK-4, MK-7, and MK-9. The compound's highly lipophilic nature combined with its poor solubility in water creates significant issues in formulation as well as oral delivery (6; 4). To solve the problem, it is vital to use a proper carrier that will help to enhance its dispersion, dissolution, stability, and bioavailability. Sunflower oil provides the needed lipid-rich environment able to absorb hydrophobic substances like vitamin K2. Due to the triglyceride structure, sunflower oil seems to be ideal for producing liquid formulations and ensures reverse intestinal micelle formation during digestion (1). Nevertheless, high levels of unsaturated fat make sunflower oil oxidized which negatively impacts the stability of vitamin K2 for storage purposes (7).

Conversely, microcrystalline cellulose (MCC) is an extensively utilized pharmaceutical excipient for solid dosage forms owing to its excellent binding, flow and compression characteristics (42). Vitamin K2 does not dissolve in MCC, rather it gets incorporated in it via the modes of adsorption, mixing, liquid loading or granulation. Thus, the delivery of vitamin K2 may depend on the characteristics of the particles being used, porosity, wetting and formulation of the product. This article thus evaluates the different mechanisms of vitamin K2 solubilisation via the use of oils and MCC and its dissolution behaviour in combination with discussing its advantages and limitations.

2. Physicochemical and Formulation Characteristics of Vitamin K2

Vitamin K2 or menaquinone is classified under lipophilic compounds and is a fat-soluble compound, having a structure characterized by a ring of 2-methyl-1,4-naphthoquinone connected to an ever-changing chain of isoprenoid units (6). Due to its highly sophisticated structure especially in longer isoprenological chains which create menaquinone-7 (MK-7) which leads to the absence of water solubility while it shows high solubility in other organic solvents and oils including sunflower oil (5). In the oil of sunflower, the structure of the active compound is undissolvable which leads to its inability to crystallize thus attaining a more uniform distribution (1). Also, during the formation of the mixed micelle, the dissolution of K2 leads to its high bioavailability via the digestive system, resulting in its effects on human health and aging-related diseases (4).

On the contrary, the use of Vitamin K2 in solid dosage forms and through the use of carrier powders such as microcrystalline cellulose (MCC) is based on the principle of physical adsorption or dry dispersion as opposed to molecular dissolution (5). Since Vitamin K2 does not dissolve within the solid crystal structure of MCC, the even distribution of the form is dependent on high shear mixing or spraying a solution of the pre-dissolved concentration on high surface area porous MCC granules. The MCC acts as an effective binder-diluent with high compressibility in direct compression tablet making, but solid adsorption of lipophilic menaquinones without any fat carrier may result in low dissolution rates and variable bioavailability (4). Furthermore, Vitamin K2 is chemically unstable when exposed to light, heat, atmospheric oxygen, and alkaline media, thus requiring stabilization methods despite the substrate of the carrier chosen (5).

Considering the stability and production aspects, the mode of delivery influences the path of degradation and

consumer-friendly characteristics. The use of oil-based formulation in sunflower oil isolates menaquinone molecules from air humidity and mechanical pressure; however, it makes use of oil-soluble antioxidants (like tocopherols) to avoid the autoxidation of unsaturated fatty acids and subsequent degradation of active substances (5). On the contrary, the methods of dry powder formulation using MCC should pay attention to particle size distribution and micro-encapsulation in order to keep trans-isomers safe from oxidative damage during the use and storage of products (2). Pure Vitamin K2 obtained by fermentation from wild-type or engineered microorganisms, should be carefully processed in order to reach the desirable level of isomer purity before adding to sunflower oil or dry MCC formulation (3).

3. Vitamin K2 in Sunflower Oil: Solubilisation and Stability

Vitamin K2 (or menaquinone) is classified as a fat-soluble substance and is comprised of a structure that includes a lipophilic isoprenoid side chain of an undetermined length, which is connected to a core 2-methyl-1,4-naphthoquinone ring (6). The non-polar nature of vitamin K2 makes it extremely hydrophobic and practically insoluble in water-based solutions and thus requires either a non-polar solvent system or lipid bases to be incorporated in stable forms of liquid formulations (5). The availability of high levels of unsaturated triglycerides when applying sunflower oil as a delivery system helps create the perfect hydrophobic environment for menaquinone molecules by solubilizing them completely; therefore, it allows avoiding phase separation and active recrystallization over long periods of time (8).

The complete solubilization of the molecules in a lipids' matrix is one of the factors that play an important role in enhancing the bioavailability through the human body; when the compound passes through the gastrointestinal tract, Vitamin K2 is dissolved and forms mixed micelles

with the bile salts, helping the compound to be absorbed through the epithelial cells and transferred into any organs that need it (8). Also, there are derivatives of sunflower processing such as certain hydrolysates, which have surface activity during the interaction with hydrophilic and lipophilic phases (9); however, it is still the whole molecule of sunflower lipid triglycerides that plays the main role and provides possibility for achieving high efficiencies and provides possibility to deliver the active components (7).

Though the dissolution of Vitamin K2 in sunflower oil does indeed guard the active component against its moisture-facilitated hydrolytic degradation, the lipophilic menaquinones are still susceptible to the effects of light, high temperature, oxygen, and free radicals (2). Also, the stability of Vitamin K2 in sunflower oil is closely linked to the oxidation status of the carrier lipid (8). In the course of autoxidation of the unsaturated fats present in sunflower oil, the primary products of lipid oxidation (hydroperoxides and secondary volatile radicals) appear that lead to the chemical degradation and isomerization of active trans-menaquinone (7).

In order to tackle lipid rancidity and preserve the active ingredient, it is necessary to enhance the oil vehicle with lipophilic antioxidants (9). The introduction of natural bioactive substances such as carotenoids, tocopherols, and plant-derived polyphenolic extracts proves to be an efficient way to break the free radical chain reaction, enhance peroxide formation, and preserve structural integrity during processing and storage (7). Safeguarding the lipid vehicle allows to achieve significant retention of pure trans-isomers developed by means of either wild-type or genetically modified bacterial fermentation (2), which leads to the development of effective, stable liquid droplet and soft gel products that are appropriate for functional foods and pharmaceutical uses (8).

3.1 Solubilisation of Vitamin K2 in Sunflower Oil

Vitamin K2 (menaquinone) is a fat-soluble compound that possesses a unique structure with a 2-methyl-1,4-naphthoquinone nucleus and a variable length hydrophobic isoprenoid side chain (6). Due to its non-polar molecular structure, Vitamin K2 is a quintessential hydrophobic compound and has almost no solubility in water, thus requiring non-polar lipid solvents for proper formulation (10). The use of sunflower oil as a medium provides favorable conditions for complete dissolving of Vitamin K2 molecule due to its high content of unsaturated fatty acids, especially oleic and linoleic acid (9). Sunflower oil composition enables greater solubility of lipophilic vitamin when compared to other lipid carriers (12).

Molecular solubility in sunflower oil is essential for in vivo activity. The vitamin is incorporated into mixed micelles with bile salts and pancreatic enzymes during gastrointestinal digestion, thus making trans-mucosa transport possible and increasing systemic bioavailability as compared to undissolved dry powders or non-lipid carriers (11). Modern techniques of processing, such as ultrasound treatment, can also play a role in oil properties and retention of phenolic compounds, as well as in soluble vitamins during formulation (15). In addition, employing nanoemulsion delivery systems for fat-soluble vitamins shows that decrease in lipid droplet size and oil encapsulation is beneficial for thermodynamic stability, intestinal release and cell uptake (13). Trans-menaquinone-7 (MK-7) can be produced efficiently via microbial fermentation using native strains, such as *Bacillus subtilis*, and subsequently dissolved in stabilized sunflower oil to produce effective functional foods (14).

3.2 Factors Affecting Vitamin K2 Solubility and Stability

Vitamin K2 (menaquinone) is characterized by its lipophilic naphthoquinone structure featuring an isoprenoid side chain, which implies that the aqueous behavior of Vitamin K2 varies significantly in conditions of nonpolar solvent (17). Long-chain isoprenoid derivatives, for example, MK-7, possess poor solubility in polar solvents and hence require the use of nonpolar lipids to ensure successful solubilization process (18). Moreover, the viscosity, length, and structure of the lipids used as carriers determine the solubility capacity and saturation limits of Vitamin K2 in oil-like formulations (16). The isomeric purity profile comes to play great importance when considering the behavior of MK-7 in regard to its crystallinity and dissolution rates because all-trans MK-7 in comparison with its cis-isomers and degradation products has different crystallinity (16). When mixed with complex matrices or nanoparticles, the interaction of MK-7 molecules with inorganic substances (such as gold nanoparticles or porous surfaces) influences its adsorption, solubility, and dispersion (19).

Vitamin K2's chemical stability is affected by environmental variations during the fermentation, production, and storage at room temperature (20). When exposed to UV light, heat, oxygen, and alkaline pH conditions, active menaquinones are more likely to undergo photodegradation (17). To keep the proper level of trans-isomer, all sorts of environmental parameters should be controlled (20). The compatibility of the formulation is one of the keys in the dosage form stability; if the product contains reactive mineral salts or alkaline excipients, these substances should be encapsulated into liposomes or contained inside light-proof packaging, in order to maintain their biological effectiveness (16).

3.3 Advantages and Limitations of Sunflower Oil as a Carrier

Sunflower oil is an extremely capable lipid carrier for administering poorly soluble active ingredients because it is a very dense source of the unsaturated triglycerides and in addition it is a economical, and aesthetically pleasing oil (21). The main fatty acids, linoleic acid and oleic acid, form a very low polarity matrix which can dissolve lipophilic compounds such as the highly lipophilic compound Vit K2. Active components are prevented from being recrystallized or precipitated out of the solution over time (18). Moreover, unrefined, cold-pressed sunflower oils also contain native lipophilic antioxidants like, in particular, α -tocopherol which naturally boosts the final formulation's nutritional content and baseline capacity against oxidative degradation (24). Different types of agricultural breeding and esterification can adjust the characteristics of sunflower oil according to specific formulation requirements through a combination of these processes. Such manipulations would enable manufacturers to produce specialized lipid bases suited for advanced use in pharmacy and industry (23).

Despite these improved formulations, one of the most significant challenges that arise with the use of sunflower oil is its high susceptibility to oil oxidation, which consequently leads to the degradation of the active ingredient contained in the formulation (25). The high quantity of polyunsaturated fatty acid-containing linoleic acid makes the oil more susceptible to exposure to heat, oxygen in the atmosphere, and UV light which results in the fast accumulation of the lipid hydroperoxides (22). This susceptibility increases during the industrial refining process (e.g. bleaching and deodorization) where various lipid-soluble components including tocopherols and phenolic compounds that provide protection from oxidation are removed (25). As it was already mentioned, the presence of oxidatively degraded products in the carrier leads to the changes in biomolecules, particularly

in the physiological instability of biologically active substances such as Vit K2 (27). In this regard, the use of sunflower oil as an industrial carrier requires additional antioxidants to be used in the formulation besides careful selection of the conditions for storage and packaging of the product (26).

4. Vitamin K2 in MCC Powder: Incorporation and Dissolution Behaviour

The physical techniques of adsorption, dry blending, or wet granulation produce solid dosage forms containing Vitamin K2 (menaquinone) mixed with microcrystalline cellulose (MCC) (27). Due to the insolubility of lipophilic menaquinones in solid aqueous and crystalline matrices, MCC serves as a porous, high-surface-area binder that encapsulates the active agent in solid formulations (27). In order to achieve uniform vitamin distribution in batches, Vitamin K2 is delivered to the porous MCC particles in an aqueous environment (26). The remarkable compressibility and binding properties of MCC allow for direct tableting and stable powder flow for homogenous active ingredient content across the production line (27).

The characteristics of the release and dissolution of Vitamin K2 from an MCC matrix create unique challenges in comparison to liquid lipid vehicles (25). Following disintegration of a solid dosage form in the gastrointestinal tract, the non-polar Vitamin K2 molecules have to desorb from the insoluble MCC fibers and disperse in the surrounding fluids without the aid of dissolved lipid carrier (28). The dependency on endogenous bile salts for in situ emulsification may result in varying release patterns and lower dissolution rates vis-à-vis oil-based formulations (26).

Moreover, stability in a solid state is an important quality characteristic since menaquinones adsorbed on powder carriers could be subject to degradation from environmental factors such as atmospheric oxygen, light, and some excipients unless protected by

microencapsulation or special coating (27). It is necessary to maintain the integrity of the isomer during the production process for the active all-trans form of the menaquinone to be kept intact after incorporation into solid MCC matrices, either made of bacteria obtained via wild-type fermentation or engineered organisms (28).

4.1 Incorporation of Vitamin K2 into MCC Powder

The formulation of Vitamin K2 (menaquinone) into a solid dosage form with microcrystalline cellulose (MCC) powder raises certain technical challenges because of its highly lipophilic nature (30). Utilization of the latter occurs due to the inability of the vitamin to dissolve molecularly in the solid MCC structure; therefore physical adsorption, high-shear drying blending, or introducing a liquid solubilized phase on the porous material is necessary (27). MCC functions as a convenient binder-diluent offering excellent compactibility and adequate specific surface area for uniform dispersion of menaquinone particles throughout solid powders (29). The accomplishment of homogenous combination during the manufacturing process makes it possible to ensure proper dose distribution of the product.

When solid dosage forms containing MCC enter the gastrointestinal environment and disintegrate, the released Vitamin K2 will have to undergo intestinal micellization (30). Only by doing this, Vitamin K2 can become absorbable by the body and be taken up systemically. Vitamin K2 has to undergo absorption efficiently in order to realize its systemic metabolic functions. These include suppressing NF- κ B activation so as to promote osteoblastogenesis without the suppression of osteoclastogenesis in bone tissue (31).

Besides that, at both the hepatic and cellular levels, available Vitamin K2 affects intracellular lipid pathways, controlling metabolic activity of fatty acids as well as lipid precursors of inflammatory reactions (29). Therefore,

fine-tuning the loading of Vitamin K2 onto porous MCC frameworks with the simultaneous prevention of oxidative degradation during processing is fundamental for conserving the integrity of the active *trans*-isomers which are prerequisite for subsequent cellular physiological activity (30).

4.2 Factors Affecting Dissolution and Dispersion of Vitamin K2

The behavior of Vitamin K2 (menaquinone) regarding dissolution and dispersion is primarily determined by its lipophilicity and hydrophobic structure (35). Vitamin K2 has very low solubility in water, depending on the polarity of its naphthoquinone structure, consisting of a naphthalene core plus many isoprenoid units, thus requiring the improvement of solution conditions and the selection of suitable solvents or carriers (32). Supersaturation has a great importance in the process of crystallization and the generation of vitamin K2 solutions; by influencing the process of nucleation and crystal formation in the course of crystallization, it influences the morphology of particles, their size, and dissolution proportions (36). The primary necessity of maintaining supersaturation at the correct level is the opportunity to optimize the process of crystal-forming particles creation and achieve a lower degree of flocculation in the dispersion process (32). In addition, the structural purity of the menaquinone preparations produced with the help of the wild type or optimized *Bacillus subtilis* has an important place in understanding how well the vitamin would disperse (33).

The inclusion of Vitamin K2 in solid dosage forms is heavily influenced by the selection of excipients and methods of processing, which determine the rate of dispersion (34). The use of microcrystalline cellulose (MCC) to create the carrier matrix yields high surface area and mechanical stability, but the solid-state processing methods, such as extrusion and compression, influence the

interaction between the hydrophobic active compounds and the porous fiber materials (37). Various engineering methods, including wet extrusion-spheronization and fluid-bed coating, can be utilized to enhance the wetting of liquids and to avoid agglomeration of active substances that may have occurred locally while ensuring the even distribution of the drug throughout the solid pellets or granules (36). Due to the fact that Vitamin K2 does not dissolve in the solid MCC structure, the consistent release of the active ingredient depends on achieving the right porosity of the carrier, the right binding material, and the appropriate amount of disintegrate so that the compound can be dispersed rapidly in the gastrointestinal fluids and can get into micelles (36).

4.3 Advantages and Limitations of MCC as a Carrier

Microcrystalline cellulose (MCC) is a commonly used important excipient in solid dosage forms. It is utilized in tablet making because of three major properties, superior compactibility, high binding capacity, and good flow properties (38). As a result of its unique porous structures and high specific surface area, MCC has a significant ability to serve as a carrier matrix for physical adsorption in direct compression tableting, wet granulation, and solid dispersion applications (40). In addition, it has a strong fibrous structure which makes it effective in carrying liquid adsorbent active amounts of MCC to lyophilized compact formulations (39). Furthermore, the porous and structural versatility of MCC makes it an excellent choice for a wide range of industries from environmental separation matrices (43) to other solid-state pharmaceutical formulations (39).

MCC, while advantageous in tablet preparation, has limitations in the delivery of highly lipophilic drugs like Vitamin K2 (39). MCC is a solid polymer of crystalline cellulose, and hydrophobic drugs do not get dissolved in its structure, meaning that all the absorption of the drug comes from either surface adsorption or mechanical

entrapment (40). This means that drugs will not get released properly and that the dissolution rate in gastrointestinal fluid will be slow, and efficacy as opposed to the use of liquid lipid carriers will be low unless surfactants or co-processed lipids are employed (41). Moreover, MCC has moisture sensitivity and can absorb moisture from the air which may lead to unstable behavior of drugs that are moisture or oxygen sensitive for a long time (37). Maintaining the same properties of particles in every batch is also very important to ensure the same behavior of tablets as for tablet disintegration and active release (38).

5. Comparative Review of Sunflower Oil and MCC-Based Vitamin K2 Formulations

In terms of using sunflower oil and microcrystalline cellulose (MCC) as carrier vehicles, significant differences can be observed in the process of incorporating and releasing Vitamin K2 (menaquinone) into the system. Sunflower oil is characterized by its unsaturation in the lipid profile and impressive nutritional content making it a non-polar solvent that allows complete dissolution of Vitamin K2 (45). The liquid nature of the oil aids in allowing the active ingredient to not become agglomerated and quickly create mixed micelles in the gastrointestinal tract helping with the delivery of the Vitamin K2 (44). MCC is, however, limited to being a solid adsorbent whereby the Vitamin K2 cannot be dissolved within its porous crystalline structure (43). The mechanisms of release from an MCC matrix only rely on the breaking down of the structure and gradual emulsification using the fluid present in the gut and leads to a slower release rate and variability of bioaccessibility among different patients compared to the lipid-based vehicles (44).

Both systems of delivery provide various advantages and disadvantages from the standpoint of their production and storage. Sunflower oil vehicles are good for the production of liquid oral drops and softgels; however, their lipid

matrix may undergo oxidation, leading to the destruction of sensitive trans-menaquinones unless natural antioxidants or herbal extracts are applied (47). Meanwhile, MCC has higher mechanical strength, binding and compressibility, which transform it into an ideal carrier for dry solid tablet and capsule technologies as well as dry functional foods, including fortified bread and complex food matrices (46). In addition, the application of agricultural byproducts like sunflower seed hulls from oil production creates a bigger picture of sustainability and efficiency of processing in the supply chain of plants used for technology (48). Therefore, the choice of sunflower oil or MCC may depend on the form of the ultimate product, length of storage it needs, and the aim of using the Vitamin K2 nutraceutical (44).

6. Research Gaps and Future Perspectives

Vitamin K2 has been researched quite thoroughly as far as its biological functions, production and stability are concerned, yet the comparative studies on vitamin K2 in its formulation with sunflower oil and MCC powder are still lacking. It is important to conduct the studies for more research in order to establish the real solubility, loading capacity and stability of various forms of vitamin K2 especially MK-7 in sunflower oil. In case of MCC-based products, research has to be conducted to find out how efficient the process of loading vitamin K2 is, what the uniformity of loading is and how vitamin K2 behaves during the release and dissolution process when different MCC grades and sizes are used.

The main direction of the research in the future will be the direct comparison between sunflower oil and MCC systems produced under the same conditions. Research must measure vitamin K2 content, solvent efficacy, chemical stability, isomer purity and bioaccessibility. Hybrid systems of lipid solutions using MCC-based dry systems can prove useful in solving the issues associated with the use of each system separately. Approaches such

as microencapsulation, nanoemulsion, spray drying and lipid solid dispersions can greatly increase the stability and availability of vitamin K2. Further research must also take into account antioxidant protection, packaging, storage conditions and industrial production possibilities.

7. Conclusion

Vitamin K2 is characterized by its lipophilicity and low water solubility, necessitating carrier choosing while formulating it. Sunflower oil seems to be appropriate for lipid medium in which K2 can be solubilised. At the same time, the disadvantages of the oil may include oxidation, which can influence the stability of the formulation. While MCC is beneficial for solid dose forms due to its binding and compressibility properties, it is also true that vitamin K2 should not be molecularly dissolved in MCC and require special techniques to achieve good dispersion. To sum up, sunflower oil is the best option for lipid technology, while the advantages of MCC are considered in solid dosage forms. Further research in this area of study should deal with comparative studies and the creation of hybrid systems that would integrate advantages of oil-based technology with manufacturing benefits of MCC.

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