REVIEW ARTICLE

Vitamin-E TPGS Based Microemulsion: An Approach for Solubility Enhancement of Poorly Water-Soluble Drugs

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ABSTRACT

Poor aqueous solubility is the primary concern for dissolving new drug substances during early development. Several novel solubility enhancement techniques such as particle size reduction, salt formation, making solid dispersion, complex formation, use of cosolvent techniques, use of surfactants, physical and chemical modification, and PH adjustment using buffering agents have been explored extensively to resolve the issue of poor aqueous solubility of drug substances. Drug delivery in micro and nano-sized formulations is one of the ways to improve the solubility of these drug candidates over the physiological pH range. In recent years, combination methods have also been considered an interesting approach where more than one solubility enhancement technique is used. The present review focuses on the feasible approach for improving the solubility by forming Vitamin E TPGS-based suspension in micro or nano form by particle size reduction. Further, by granulation or spray drying techniques, these suspensions converted to a solid dosage form for oral drug delivery for patient compliance are being explored.

Keywords: Poor water-soluble drugs, Solubility enhancement, Top spray granulation, Vitamin E TPGS, Wet milling.

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INTRODUCTION

Recent discoveries lead to new chemical entities (NCEs), showing that more than 60% of drugs have poor aqueous solubility, attributed to lower bioavailability.[1] There are significant challenges in formulating such drug candidates.[2] Drugs with low aqueous solubility mainly belong to BCS class II and IV. Some strategies referenced in literature for the solubility improvement of such drug candidates, like using cosolvent, complexing agents, making solid drug dispersion, and using prodrug or salt form of drugs with more solubility than the parent molecule. There are certain limitations to these techniques. In the co-solvency approach, the toxicity of solvents should be considered, and there is also a risk of drug precipitation. A complex formation technique requires a large amount of complexing agent, and it has a safety concern. Preparation of solid dispersion of drugs involves complex manufacturing and scale-up procedures. Converting the amorphous drug form formed in solid dispersion into crystalline is possible. Making prodrugs have a limitation of toxicity and precipitation.[3] Drug delivery in micro and nanoformulations is one of the ways to improve the poor solubility of drug substances. Combination techniques are emerging as an exciting approach in recent years.[4]

The present review focuses on vitamin E TPGS properties, uses, its action mechanism, application of particle size reduction for solubility improvement of drugs, preparation of micro or nano-sized systems, and their conversion to form solid dosage form.

This review provides a feasible approach for improving drug solubility by forming vitamin E TPGS-based suspension in micro or nano form using the wet milling technique and further converting suspension into a solid dosage form for oral drug delivery.

Vitamin E TPGS

Vitamin E TPGS Figure 1.[5] succinate undergoes esterification with polyethylene glycol (PEG) 1000 to form Vitamin E TPGS. It is a non-ionic surfactant. It helps solubilize poorly soluble molecules by forming stable micelles in the aqueous system.[6] Chemically, it is (d-α tocopheryl polyethylene glycol 1000 succinate). It plays a vital role in enhancement of oral bioavailability permeability of drugs. It not only stabilizes amorphous drug forms but also acts as a surfactant to increase solubilization. By P-glycoprotein efflux inhibition it improves drug permeability.[1,7]

Absorption of the highly lipophilic drug, like cyclosporine, can be enhanced by vitamin E TPGS, which leads to dose reduction to some extent.[2,10] Vitamin E TPGS-based formulations have many benefits in bioavailability improvement for oral dosage forms.[10]

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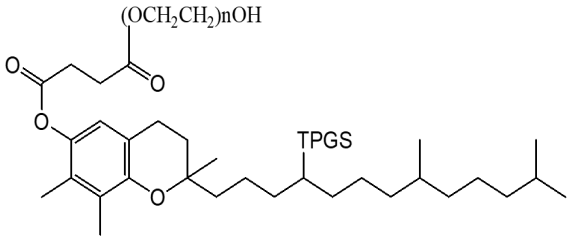

Figure 1: Vitamin E TPGS

Most BCS Class IV drugs[10] and anticancer drugs are p-glycoprotein (P-gp) substrates, for instance, paclitaxel, etoposide, doxorubicin, and vinblastine. It is accepted as a non-medicinal ingredient in Canadian List.[11] Paclitaxel bioavailability can be enhanced using vitamin E TPGS due to increased solubility and permeability.[8,9] In the case of anticancer drugs, vitamin E TPGS is used in treating MDR i.e. multidrug resistance effect by facilitating cellular uptake.[15] Literature references vitamin E TPGS as an adjuvant in formulations like solid dispersions, nanosuspensions, microemulsions, and prodrug vaccines.[2,7] For example, microemulsions for the development of novel anti-psoriatic formulations.[12,13]

It is GRAS listed and approved in the US FDA inactive ingredients database (IID) as an excipient ophthalmic preparations, capsules, solution, tablets, topical solution. As per IID-approved drug product search, the maximum tolerable potency per unit dose of vitamin E TPGS is 300 mg for oral administration (capsules), and the limit for maximum daily exposure (MDE) is 85 mg for oral administration (tablet).

Reduction in Particle Size

Particle size reduced by either dry or wet milling techniques, by reducing particle size improvement in solubility of low aqueous soluble drugs.[3] Reduction in size by milling is achieved by one of the mechanisms of crushing and grinding. These occur due to the principle of either shear, friction, pressure, attrition or impact. Jet mills, ball mills, and high-pressure homogenization used for this purpose.[16] By milling process reduction in the particle size of the drugs can be done, due to which specific surface area increases. Reduction of particle size from micron to nano-sized drug particles enhances the dissolution rate. This approach can overcome the issue of less aqueous solubility of drugs.[17] Obtained powder post-wet milling has poor flow properties. To improve the flow properties of milled drugs, fillers are used, for instance, calcium phosphate, lactose, mannitol, etc., These fillers are also used as carriers for granulation to enhance flow properties and content uniformity. They also modify of drug release, drug stability enhancement, and taste masking.[3]

Preparation of Micro or Nano-Sized Systems

Preparing microemulsions can be the best option for such drugs.[14] Vitamin E TPGS-based microemulsion for anti-psoriatic drug tacrolimus has been reported for enhanced anti-psoriatic efficacy.[18] Microemulsions can solubilize the drugs in the oil phase and increase the dissolution rate. Therefore, drugs having less solubility in water are chosen for this drug delivery systems.[19] Nanosuspension technology has also been used to enhance oral or parenteral dosage forms solubility enhancement.[15] Vitamin E TPGS-based nanosuspension of drugs with poor solubility can improve dissolution.[20] Skin permeation in transdermal drug delivery can be increased with vitamin E TPGS-based formulations.[21]

Formation of Solid Dosage Form

Here, in this case, mannitol or lactose-like excipients can be used. Conversion to a solid state can be termed a solidification process. It is reported in the literature that the physical characteristics of the drug particles are retained.[3] This powder, after solidification, is either forms capsules or tablets. It leads better patient compliance. One of the techniques used for this is Top spray granulation fluidized bed granulation.[22] Nano-formulations converted into oral products have many advantages in chronic disease treatment. It improved efficacy and patient compliance. It is beneficial in treating local intestinal diseases. It also leads to enhanced GI track dissolution of hydrophobic drugs. Improve drug formulation stability. For drying these suspensions and emulsions, spray drying is commonly used. Nanoparticle aggregation on drying may be the limitation of this process. One can use stabilizers such as trehalose and mannitol to overcome it.[23] Wet media milling followed by spray granulation is most widely used in this case.[24] Further, there is scope for research in this area of conversion of nanosuspension into solid dosage forms.[17]

Drug Candidates with Increased Solubility by this approach

In vitamin E TPGS-based formulations, it can be used as a solubilizing agent, penetration enhancer, stabilizer, emulsifing agent, antioxidant, and protection of drug in micelles. Formulations such as solid disperdions nanosuspensions, gels, microemulsions, nanoemulsions, are made by using vitamin E TPGS. In formulating novel formulations, it can be combined with other techniques.[25] When comparing

Table 1: Drug candidates with increased bioavailability by this approach

Approach using Vitamin E TPGS	*Drugs*	*References*
Microemulsion	Celecoxib	26
Microemulsion	Tacrolimus	18
Amorphous solid dispersion by hot-melt extrusion	Itraconazole	27
Solid dispersion	Nifedipine	28
Tablet dosage form melt dispersions method	Olmesartan, Medoxomil	29
Solid dispersions	Rosuvastatin Calcium	30
Nanosuspension	Fenofibrate	31
Nanosuspension	Rilpivirine	32
Nanocrystals	Ursolic acid	33
Nanocrystals	Ezetimibe	34

vitamin E TPGS-based formulation with formulation without vitamin E TPGS, the earlier one shows increased intestinal absorption and enhanced skin permeability in transdermal formulations. For instance, microemulsion of celecoxib[26] and microemulsion of tacrolimus.[18] Amorphous solid dispersion of itraconazole, nifedipine, and rosuvastatin using vitamin E TPGS showed improved dissolution and absorption and enhanced solubility and dissolution.[27,28,30] Olmesartan medoxomil tablet dosage with vitamin E TPGS leads to increased bioavailability.[29] Nanosuspension of fenofibrate,[31] rilpivirine[32] containing vitamin E TPGS shows improved bioavailability.[31] Ursolic acid nanocrystals and ezetimibeusing vitamin E TPGS as show enhancement in bioavailability[33] and superior pharmacodynamic activity upon oral administration, respectively.[34,35] All above mentioned example are summarized in (Table 1)

CONCLUSION

Reduction in particle size is commonly used approach to improve solubility of drug substances. Enhancement of solubility of a less soluble drug substance using vitamin E TPGS-based micro-suspension can be considered a new approach. Formulating nano or micro-sized formulations by reducing particle size increases surface area and enhances solubility. Solid dosage forms like tablets and capsules with vitamin E TPGS are reported more. Hence there is further scope for developing micro or nano-sized suspension using vitamin E TPGS and conversion to a dried solid state by a novel technique like top spray granulation to form solid dosages like tablets and capsules for better patient compliance.

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