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Application of surfactants in solid dispersion technology for improving solubility of poorly water soluble drugs

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ABSTRACT

Discovery of several poorly water soluble drugs in the past decade has led to the constant need of developing a novel dosage form which increases the solubility of these drug. They increase solubility of drug in gastrointestinal tract by increasing the dissolution rate which leads to enhanced absorption of drug and thereby increasing bioavailability. Solid dispersion is one of the most promising techniques to overcome the challenges faced by low aqueous solubility. However, there are several limitations associated with the development of solid dispersion, like miscibility of polymer and drug, the stability of the dispersion, etc. The use of surfactant(s) in the solid dispersion may overcome these limitations. Addition of surfactant(s) to solid dispersion not only increases drug-polymer miscibility but also reduces recrystallization. It also improves the wettability of solid dispersion, which leads to increase in dissolution and improved physical stability. However, caution must be employed in selecting the surfactant. The surfactant can interact with polymer and thereby increase the recrystallization of drugs. The variety of surfactant, aspects to consider and related parameters have been discussed in this review article.

Contents

1. Introduction

Over the past few decades, discovery pipeline of new chemical entities majorly has poorly water soluble drugs. Low aqueous solubility of these drugs is a limiting factor for oral bioavailability.

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Many techniques have been developed by the scientific community to overcome the challenges faced due to the poor water solubility of drug molecules, which includes, salt formation [1], micronization [2], prodrug [3], lipid formulations [4] and solid dispersion [5,6] and so on. These techniques increases the dissolution rate of drugs in the gastrointestinal tract which leads to increased absorption of drugs in systemic circulation and increasing bioavailability. Nevertheless, there are several limitations associated with all these techniques [7]. Among these methods, the solid dispersion was demonstrated to be the most promising approach [7]. Solid dispersion(s) is defined as a dispersion of one or more active pharmaceutical ingredients (APIs) in an inert carrier matrix. Recently more focus has been given to amorphous solid dispersions. The solid dispersion can be prepared using various techniques like spray drying [5], freeze drying [8], fusion method [9], hot melt extrusion [10] and supercritical fluid precipitation [11]. Solid dispersion of APIs demonstrates enhanced dissolution profile and thereby increasing the bioavailability. The dissolution profile of drug with solid dispersion is governed by the properties of the polymer and its concentration used in the formulation. Beyond a certain concentration of hydrophilic polymer(s) in the formulation could retard the solubility of the drug in solid dispersion [12,13]. Over the last few decades, the surface active agents, including surfactants have been used in solid dispersion alone or in combination with a polymeric material. The use of surfactants in solid dispersion not only improves the dissolution rate of the poorly water soluble compound but also improves the physical stability [14–16]. These surfactants aid in physical miscibility of hydrophobic drugs due to amphiphilic nature and reduce the drug recrystallization [14–16]. Furthermore, these surfactants improve wettability and prevent drug precipitation in the aqueous medium [15,17,18]. Various other reports have also shown improved dissolution profile of drugs with a solid dispersion containing surfactants compared to drugs without surfactants [19–22]. Surfactants reduce the interfacial energy barrier between the drug and dissolution medium and thereby increase the wettability. Moreover, the concentration of surfactants above the critical micelle concentration (CMC) increases the drug solubility due to solubilization and thereby increases the dissolution rate [23,24]. In this review, the use of surfactants in solid dispersions is discussed along with the classification and commonly used surfactants in solid dispersion and the mechanism by which surfactants increase the dissolution rate of drugs.

2. Surfactants

Surfactants are also commonly known as surface active agents, wetting agents, emulsifying agents or suspending agents based on their use and application. Surfactants exhibit some superficial or interfacial activity [25] and have characteristic structures possessing both hydrophobic(non-polar) and hydrophilic (polar) groups. The polar groups generally contain heteroatoms such as, O, S, P or N, as part of the functional groups such as alcohol, thiol, ester, acid, sulfate, sulfonate, phosphate, amides, amines etc. The polar groups of surfactants have a strong affinity for polar solvents, particularly water and are termed hydrophilic whereas the non-polar part of surfactant is called hydrophobic and the surfactant which has dual affinity are termed as amphiphilic.

The amphiphilic surfactants do not feel “at ease” in any solvent, be it polar or non-polar since there is always one of the groups that does not like the solvent environment [25]. Thus, these molecules do have strong tendency to migrate to interfaces or surfaces to orient themselves.

Surfactants can be classified into four categories based on their dissociation in water:

- Anionic Surfactants
- Cationic Surfactants
- Amphoteric/Zwitterionic surfactants
- Nonionic surfactants

2.1. Anionic surfactants

Anionic Surfactants on addition to water dissociate to form an amphiphilic anion and a cation. These are most commonly used surfactants. Examples include sodium lauryl sulfate (SLS), alkyl benzene sulfonates, etc.

2.2. Cationic surfactants

Cationic surfactants dissociate in water to form an amphiphilic cation and an anion. These are commonly used for their disinfectant and preservative properties since they have good bactericidal properties and belong to quaternary ammonium compounds. Examples include cetrimide, benzalkonium chloride, etc.

2.3. Nonionic surfactants

Nonionic surfactants do not dissociate in aqueous solution. These are less irritant than anionic and cationic surfactants. The hydrophilic region contains polyoxypropylene, polyoxyethylene or polyols derivatives and hydrophobic region contains saturated or unsaturated fatty acids or fatty alcohols. The most commonly used nonionic surfactants are poloxamers, polysorbates, etc.

2.4. Amphoteric/Zwitterionic surfactants

Amphoteric/Zwitterionic surfactants exhibit both cationic and anionic dissociations. These surfactants are mild in nature and they can be anionic or cationic or nonionic depending on the pH of the water. Alkyl betaine is an example of amphiphilic surfactant.

Most commonly used surfactants in the pharmaceutical industry are SLS, Poloxamers, and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS), commonly known as Vitamin E TPGS. The structures of SLS, poloxamer and Vitamin E TPGS are given in Fig. 1 and the structure of polysorbate is given in Fig. 2. SLS is an anionic surfactant with a hydrophilic-lipophilic balance (HLB) of 40. Poloxamers are non-ionic triblock copolymer of polyoxyethylene–polyoxypropylene–polyoxyethylene with surfactant properties. Various grades of poloxamer are available depending on the values of a and b, given in Table 1. Poloxamer 124 has HLB of 12–18 and poloxamer 407 had HLB of 18–23, whereas poloxamer 188, 237 and 338 has HLB of >24. TPGS is a mixture of succinate ester of natural vitamin E and polyethylene glycol 1000. TPGS has a hydrophilic head (polyethylene glycol chain) and a lipophilic tail (tocopheryl group). It is non-ionic surfactant with HLB of TPGS is 13. Polysorbates are nonionic surfactants with HLB of 14–18.

3. Use of surfactant in solid dispersion

Surfactants can be added as an extragranular excipient or can be incorporated during the solid dispersion manufacturing process internally. Studies shows that surfactants like SLS [26,27] and poloxamer [10], added extragranularly to the solid dispersion, have minimal effect on the drug release. However, when the surfactants are intimately mixed with solid dispersion i.e. when surfactant,-drug, and polymer are dissolved in common solvent and dried to yield solid dispersion, they have shown a positive effect on drug release [26–28]. It was shown that when surfactants are mixed physically with the solid dispersion, drug released immediately