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Short communication

Importance of stabilizers of nanocrystals of poorly soluble drugs

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Introduction

Approximately 70-90% of the new active pharmaceutical ingredients/drugs are poorly soluble in water/biological fluids. Improvement of solubility, dissolution rate, bioavailability are the main characteristics of drug nanocrystals that are important for oral drug administration. High bioadhesive activity, depending on the type of stabilizer, is considered to be an essential feature of drug nanocrystals for oral, dermal, ocular dosage forms (Chang et al., 2015; Sheokand et al., 2018; Tuomela et al., 2016). Drug nanocrystals are solid nanosized particles of pharmacologically active substances, mainly BCS class IIa and IIb, 200 to 600 nm in diameter, homogeneously coated with 10-50% stabilizer/surfactants and/or polymers, forming ultrafine dispersion (Malamatari et al., 2018). Drug nanocrystals are usually in the crystalline state, but depending on the manufacturing method and process parameters, they may be in the amorphous state (Shete et al., 2014). Drug nanocrystals can be obtained by increasing their particle size by controlled precipitation/agglomeration from solution or by reducing drug particle size by milling to the desirable size. The two basic methods for obtaining drug nanocrystals are bottom up (e.g., precipitation) and top down (e.g., milling) methods, or drug nanocrystals can be made by a combination of these processes. By combining these two methods the desired particle size of drugs can be achieved and disadvantages of the individual methods are overcomed. These methods are intended for the preparation of liquid pharmaceutical nanosuspensions whose internal phase consists of drug nanocrystals particles, which can be converted into solid drug nanocrystals by post-production processes (spray drying, freeze drying or other process) in order to improve chemical, physical stability of drug during storage, when the selected stabilizer of drug nanocrystal could not provide long-term stability of the liquid nanosuspension (Sheokand et al., 2018).

Classification and role of stabilizers of drug nanocrystals

In order to obtain physically stable drug nanocrystals ionic surfactants, non-ionic surfactants, synthetic linear polymers, synthetic co-polymeric, semi-synthetic ionic polymers, semisynthetic non-ionic polymers, food proteins, amino acids and co-polymers are used as stabilizers (Chang et al., 2015; Shete et al., 2014). Stabilizers provide electrostatic (electrostatic repulsion) (ionic polymers/surfactants), steric (steric hindrance) (non-ionic polymers/surfactants) or electrosteric (mixture of ionic and non-ionic polymers/surfactants) stabilization of drug nanocrystals (Chang et al., 2015; Peltonen and Strachan, 2015; Sheokand et al.,

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2018). Stabilizers provide physical stability of drug nanocrystals by reducing their free surface energy, reducing their hydrophobicity, inhibiting the aggregation of their particles, Ostwald ripening, changing the crystalline shape of nanosized particles during preparation and storage (Chang et al., 2015).

Selection of stabilizers of drug nanocrystals

The selection of stabilizer depends on the properties of the active substance and the stabilizer, affinity and interaction between them, concentration of the drug and the stabilizer, the method of manufacture, the route of administration, the pH of the medium to which it is exposed. Drug nanocrystals who have minimal size differences are produced by the addition of a polymer that has surface energy similar to the drug. A combination of a drug and a stabilizer with a similar log P value (lipophilicity), having approximately equal hydrophobicity, form stable nanosuspensions. Drugs with high enthalpy of melting are preferred (Shete et al., 2014). Polymer stabilizers such as hydroxypropylcellulose and hydroxypropyl methylcellulose, polyvinylpyrrolidone K30 and Pluronic® (F68 and F127) with higher molar mass (50 kDa-100 kDa) are more effective steric stabilizers than those of lower molar masses (Malamatari et al., 2018). The affinity of the stabilizers for the drug particle surface influences absorption rate of the drug (Shete et al., 2014). The stabilizer concentration is usually low, but must be high enough to completely cover the surface of the drug nanocrystals and result in physical stability of drug. Higher stabilizer concentration leads to Ostwald ripening, while insufficient stabilizer concentration leads to the aggregation of the drug nanocrystals. Due to the low stabilizer concentration, drug nanocrystals are safe for parenteral administration (Chang et al., 2015; Malamatari et al., 2018; Shete et al., 2014).

Conclusion

The role of stabilizers is to physically stabilize drug nanocrystals. Ionic surfactants (e.g., sodium lauryl sulfate) below a critical micellar concentration have much better stabilization potential than non-ionic surfactants (e.g., Tween 80) because they provide surface charge to drug particles that provides their electrostatic repulsion. Ion stabilizers are very sensitive to changes in pH value. The length of the polymer chain should be of sufficient size to overcome the attraction Van der Waals forces between drug particles, to prevent their aggregation due to short or too long polymer chains (chain collapse). Most stabilizers bind for nanosized particles of pharmacologically active substances by hydrophilic-hydrophobic interactions and increase their wetting. The most commonly used steric stabilizers are: hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone K 30, Pluronic® F68, Pluronic® F127, D-α-tocopherol polyethylene glycol 1000 succinate, electrostatic stabilizers are: sodium lauryl sulphate, sodium docusate, and of electrostatic stabilizers: sodium carboxymethylcellulose. More efficient physical stability of drug nanocrystals is achieved by a combination of stabilizers (surfactants and polymers: sodium lauryl sulfate and hydroxypropyl methylcellulose, Pluronic® F68 and lecithin).

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