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Review

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Alternative Technologies to Improve Solubility of Poorly Water Soluble Drugs

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SUMMARY. The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. Solid dispersions (SD) and inclusion complexes (IC) are two of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved. The basis for this popularity from a pharmaceutical standpoint, is the ability of these materials to interact with poorly water-soluble drugs and drug candidates resulting in an increase in their apparent water solubility. This review is intended to give a general background to the use of cyclodextrins (CD) and solid dispersions as alternative technologies in the study of drug solubilization.

INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs [1,2]. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities under development these days are intended to be used as a solid dosage form that originate an effective and reproducible *in vivo* plasma concentration after oral administration [3,4]. In fact, most drugs are poorly water soluble drugs, not well-absorbed after oral administration [4,5] which can detract from the drug's inherent efficacy [6-8]. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs [9], there are practical limitations of these techniques.

Various techniques have been used to improve the solubility/dissolution rate of poorly water soluble drugs. Among them, the solid dispersion technique and the complexation with cyclodextrins are most frequently used. This review is intended to give a general background to the use of cyclodextrins and solid dispersions as technologies alternatives in the study of drug solubilization.

SOLID DISPERSIONS SYSTEMS

The term 'solid dispersion' has been utilized to describe a family of dosage forms where by the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability [10]. In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs just mentioned can be overcome [11]. This method, which was later termed solid dispersion [12], involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures. Sekiguchi and Obi suggested that the drug was present in a eutectic mixture in a microcrystalline state [13]. Later, Goldberg *et al.* [14] demonstrated that all the drug in a solid

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dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high. Soon after the experiments of Sekiguchi and Obi, had been used instead of eutetic mixtures, solid solutions contend molecular dispersions for Levy, preceded by Kaning [14-16].

One of the main factors that hindered its commercialization was the high cost due to technology and the instability of the amorphous form produced by the SD. However with the reduction in price and improvement in the technologies of SD attainment making possible itself its commercial use its studies with appearance of commercial formulations as the SD of griseofulvin in polyethylene. One of these improvements was the use of polyvinylpirrolydone (PVP) and polyethyleneglycol (PEG) as carriers, therefore they are polymers of low cost and favor the formation of amorphous salts of Rosiglitazone, that has as advantage to the stability of SD in conditions of humidity for high periods of time. It's evident that the choice of polymer or substance for the preparation of solid dispersions (beyond the drug nature) will go to determine the dissolution dynamics. Thus the hidrophilic polymer association with poorly water soluble drugs will determine increase of the solubility and consequence dissolution. Water soluble drugs with poorly soluble or water insoluble polymers will determine delayed release [17].

The increase in dissolution rate and solubility provided by solid dispersions can be explained by the mechanisms described by the Noyes–Whitney equation [**1**] [18,19]:

$$\frac{\mathrm{D}m}{\mathrm{d}t\,\mathrm{h}} = AD(Cs\text{-}Ct) \qquad [\mathbf{1}]$$

where $\mathrm{d}m/\mathrm{d}t$ is the dissolution rate, A is the specific surface area of the drug particle, D is the diffusion coefficient, h is the diffusion layer thickness, Cs is the saturation solubility, and Ct is the drug concentration at time t.

As there are already effective expressions [10] available to model carrier-controlled drug dissolution, it would clearly be desirable to derive an expression whereby the intact particle release mechanism could be described. Outlined below is a suggested basis for such an analysis. This approach has been developed on the idea of the solid polymer receding to a distance such that a single particle is released, as indicated in Figure 1.

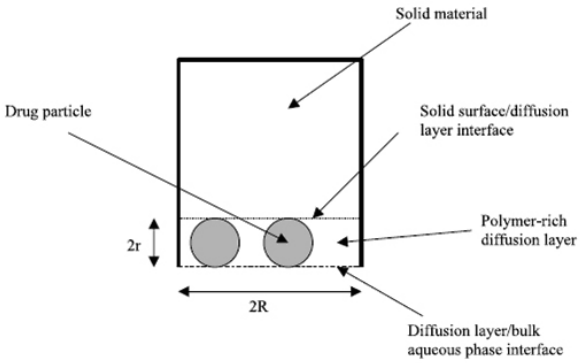

Figure 1. Schematic representation of the structure of solid dispersions with reference to the model derived for drug-controlled dissolution [10].

Advantages of solid dispersions over other strategies to improve bioavailability of poorly water soluble drugs

Improving drug bioavaliability by changing their water solubility has been possible by chemical or formulation approaches [20-22].

Chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a prodrug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral. Furthermore, it is common that salt formation does not achieve better bioavailability because of its *in vivo* conversion into acidic or basic forms [23,24]. Moreover, these type of approaches have the major disadvantage that the sponsoring company is obliged to perform clinical trials on these forms, since the product represents a new chemical entities (NCE) [4].

Formulation approaches include solubilization, particle size reduction techniques and solid dispersions, among others. Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do [23,24]. Milling or micronize-

tion for particle size reduction are commonly performed as approaches to improve solubility, on the basis of the increase in surface area [7,10]. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2-5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine [7,24,25] and, consequently, to improve the bioavailability [23,24,26]. Moreover, solid powders with such a low particle size have poor mechanical properties, such as low flow and high adhesion, and are extremely difficult to handle [24,25].

Solid dispersions disadvantages

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization [27-30]. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization [30-33]. Another factor that limits the success of this technology is on to the nature of carrier, that they are: the size of the polymeric chain and the relation of ratio with the drug [31,34].

It was demonstrated with the PVP that the chain size acts negative in its success, therefore the increase of polymer viscosity in dissolution process dicreases as well as its rate of release [35,36]. The more used PVP in solid dispersions is the PVP K-30 for better characteristics that others variations [33,37,38].

MANUFACTURING PROCESS

Solvent evaporation method

The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated [39-41]. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature [42].

A basic process of preparing solid dispersions of this type consists of dissolving the drug and the polymeric carrier in a common solvent, such as ethanol [21,24,25], chloroform [27,43] or a mixture of ethanol and dichloromethane [44]. Normally, the resulting films are pulverized and milled [21,40,45,46].

Van Drooge *et al.* [5] prepared an alternative solid dispersion by spraying a povidone and diazepam solution into liquid nitrogen, forming a suspension that was then lyophilized. The basic freeze-drying process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen.

Another common process is the co-precipitation method, in which a non-solvent is added dropwise to the drug and carrier solution, under constant stirring. In the course of the non-solvent addition, the drug and carrier are co-precipitated to form microparticles. At the end, the resulted microparticle suspension is filtered and dried [47].

Spin-coated films is a new process to prepare solid dispersions by the solvent evaporation method, which consists of dissolving drug and carrier in a common solvent that is dropped onto a clean substrate highly spinned [48]. Solvent is evaporated during spinning. This process is indicated to moisture sensitive drugs since it is performed under dry conditions [48]. The use of organic solvents, the high preparation cost and the difficulties in completely removing the solvent are some of the disadvantages associated with solvent evaporation methods [7,42]. Moreover, it is also possible that slight alterations in the conditions used for solvent evaporation may lead to large changes in product performance [49].

Melting method

Sekiguchi *et al.* were the first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. In the melting process, the molecular mobility of carrier is high enough to change the drug's incorporation [5]. A common adaptation to the melting phase consists of suspending the active drug in a previously melted carrier, instead of using both drug and carrier in the melted state, reducing, therefore, the process temperature [6,50,51]. To cool and solidify the melted mixture, several processes such as ice bath agitation [13,27], stainless steel thin layer spreading followed by a cold draught [12], solidification on petri dishes at room temperature inside a dessicator [51,52], spreading on plates placed over dry ice [53], immersion in liquid nitrogen [54] or stored in a dessicator [6,55] were used. After cooling, the mixture must be pulverized regarding its handling [52,55]. However, the use of high temperatures and the fact that several drugs can be degraded by the melting process, can be a limitation of this method [23].

CHARACTERIZATION OF SOLID DISPERSIONS

The methods that have been used to characterize solid dispersions are summarized in Table 1. Among these, the most important methods are thermoanalytical, X-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug [56].

Thermoanalythical methods

Include all that examine a characteristic of the system as a function of temperature. Of these, differential scanning calorimetry (DSC) is the most highly regarded method. DSC enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic phase transformations). The usual method of measurement is to heat the reference and test samples in such a way that the temperature of the two is kept identical. If an energy-requiring phase transition occurs in the test sample, extra heat is applied to this sample so that its temperature climbs at the same rate as in the reference. The additional heat required is recorded and used to quantitate the energy of the phase transition. Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can also be detected. Lack of a melting peak in the DSC of a solid dispersion indicates that the drug is present in an amorphous rather than a crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline. However, crystallinities of under 2% cannot generally be detected with DSC [57].

X-Ray Diffraction

The principle behind X-ray diffraction is that when an X-ray beam is applied to the sample, interference bands can be detected. The angle at which the interference bands can be detected depends on the wavelength applied and the geometry of the sample with respect to periodicities in the structure. Crystallinity in the sample is reflected by a characteristic fingerprint region in the diffraction pattern. Owing to the specificity of the fingerprint, crystallinity in the drug can be separately identified from crystallinity in the carrier. Therefore, it is possible with X-ray diffraction to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, crystallinities of under 5-10% cannot generally be detected with X-ray diffraction. Verheyen *et al.* used two types of X-ray diffraction in characterization of solid dispersion of diazepam and temazepam with PEG 6000: Guinier Camera Method and Bragg-Brentano powder diffractometry [58].

Infra red spectroscopy

Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not [49].

Dissolution testing

Release rate experiments cannot be used on a stand-alone basis to determine whether a solid solution has been formed or not. However, in conjunction with other physicochemical data, they provide strong evidence for the formation of a molecularly dispersed or nearly molecularly dispersed system. When the goal of preparing a solid dispersion is to improve the dissolution characteristics of the drug in question, the results of the release rate experiments are obviously of prime importance in assessing the success of the approach. A well-designed release experiment will show whether the solubility of the drug and its dissolution rate has been enhanced, and also whether the resulting supersaturated solution is stable or tends to precipitate quickly.

Comparison of results with those for pure drug powder and physical mixtures of the drug

Microscoping methods: Scanning electron microscopy (SEM) and transmission electron microscopy (TEM)
Thermoanalytical methods: Differential scanning calorimetry (DSC)
Spectroscopy methods: Infra red spectroscopy
X-ray difraction
Dissolution testing

Table 1. Methods for characterization of solid dispersions.

and carrier can help to indicate the mechanism by which the carrier improves dissolution: via solubilization and wetting effects which could be affected by a simple mixture of the components, or by formation of a solid dispersion/solution [58].

INCLUSION COMPLEXES - CYCLODEXTRINS

Cyclodextrins (CDs)are natural cyclic oligosaccharides that were discovered just over 100 years ago. They were called "cellulosine" when first described by A. Villiers in 1891 [59]. Soon after, F. Schardinger identified the three naturally occurring cyclodextrins -α, -β and -γ (illustrated in Fig. 4b). These compounds were therefore referred to as "Schardinger sugars" [59]. For 25 years, between 1911 and 1935, Pringsheim in Germany was the leading researcher in this area, demonstrating that CDs formed stable aqueous complexes with many other chemicals. By the mid 1970's, each of the natural CDs had been structurally and chemically characterized and many more complexes had been studied. Since the 1970s, extensive work has been conducted by Szejtli and others exploring encapsulation by CDs and their derivatives for industrial and pharmacologic applications [59,60].

CDs make up a family of cyclic oligosaccharides, composed of 5 or more α-D-glucopyranoside units linked 1-4, as in amylose (a fragment of starch). The 5-membered macrocycle is not natural. Recently, the largest well-characterized cyclodextrin contains 32 1,4-anhydroglucopyranoside units, while as a poorly characterized mixture, even at least 150-membered cyclic oligosaccharides are also known. The typical CDs obtained with larger income, known as natural, it contains six, seven eight units of glucose, being denominated α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin (six, seven and eight membered sugar ring molecule, respectively).

CDs are produced from starch by means of enzymatic conversion. Over the last few years they have found a wide range of applications in food, pharmaceutical and chemical industries as well as agriculture and environmental engineering. The conical space structure and the orientation of the groups hydroxyl for the exterior give to these sugars cyclical properties only physical-chemistry being capable of solubylizate in aqueous medium and at the same time to encapsulate inside her cavity hydrophobic molecules [61-63]. CDs can be also use for enhancement drug permeation in drug poor soluble drugs and drugs with permeation problems approached in Másson (1999) [64]. That can be possible through the double characteristic of the CD [64]. They present character much lipophilic as hydrophilic and that probable mechanism is shown in the Figure 2.

INCLUSION COMPLEXES PREPARATION

Kneading

It consists of forming a paste starting from the addition of the low amount of liquid (water or hydroalcoholic solutions) enough to moisten the powdered mixture of drug and CD. In laboratory scale it is accomplished in a mortar/pistil [65-67]. In industry scale can be use extruders and other machines it is the most common method to obtain inclusions. This method presents very low cost of production.

Atomization (spray drying)

It represents one of the most employed methods to produce the inclusion complex start-

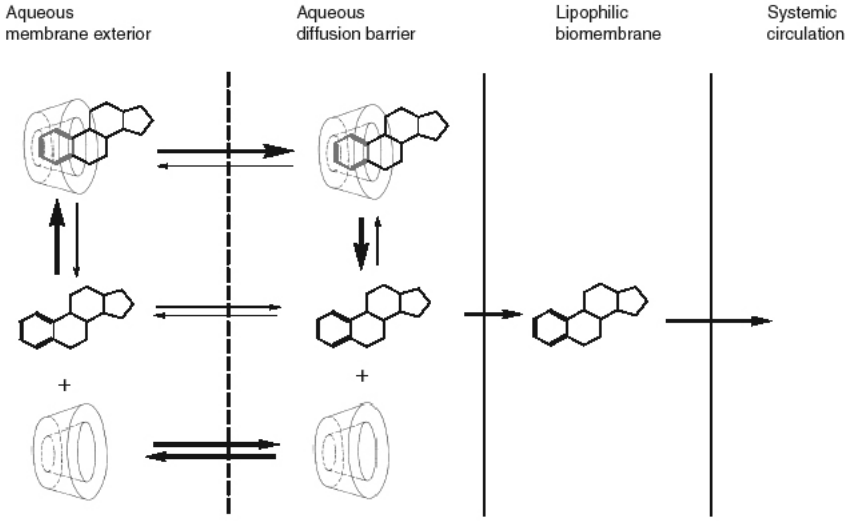

Figure 2. The effect of cyclodextrin complexation on drug bioavailability after non-parenteral administration [64].

ing from a solution. The mixture pass to a fast elimination system propitiate solvent and shows high efficiency in forming complex. Besides, this technique allows controlling the size of particles obtained this is one of explains about the good improvement in dissolution rate [68]. The low yield and the thermal stress are some of the limitations of this technique [65].

Lyophilization (freeze drying)

It consists in eliminating solvent systems of the solution, through a previous freezing and subsequent drying to reduced pressures. This technique allows the obtaining inclusion complex with high income and a low thermal stress. They are usually obtained powders dry, amorphous and with high degree of interaction drug-cyclodextrin (D-CD) [69,70]. It presents as disadvantages the long time in process and the bad characteristics of flow to obtain the powder.

Co-precipitation method

This technique leaves a drug-CD solution in very close conditions to the saturation and through abrupt changes of temperature with addition of organic solvents it is obtained to the precipitation of the material forming inclusion complex. The powders are obtained by rotation or filtration with heat while stirring the solution [71].

This method is quite used in laboratory scale, being frequently used to obtaining crystalline inclusion compounds with to CD. However, the low yield gotten in larger scales the risk of formation inclusion complex with organic solvents and the long time in the processing (one to three days) it turns little attractive in industrial scale [72].

Supercritical fluids

It constitutes one of the most innovators methods to obtaining complex in solid state. The drawing particles using carbon dioxide in state supercritical checks to the materials obtained by this technique, it is only characteristics for the interaction [73]. In spite of being a non-toxic method (organic solvents are not used), fast, chemically stable of low maintenance cost and with promising results are described in the literature. It is still an experimental technique and presents a quite high initial cost [74].

CHARACTERIZATION OF INCLUSION COMPLEXES

The methods that have been used to characterize the inclusion complexes are summarized in Table 1. The are the same methods used in characterization of solid dispersions, including the nuclear magnetic resonance (NMR), analytical method more specific than inclusion complexes.

Phase solubility studies

These studies are based in theorical methods developed by Higuchi & Connors [75] and consist in the most approach technique to evaluate the inclusions complex in solution medium. These studies can shows the effects on solubility improvements in inclusions stability and stoichimiometrical evaluation about the inclusions. This test can be use to estimate a constant according stability grade of the inclusions complexes. Figure 3 shows how to classify type A profiles. Linear solubility is representing in profile AL. This a first order drug in relationship of CD. AN and A_F have require more carefully interpretation because they present also multiples phenomenon. Profiles type B appears when poor solubility inclusion complex in some cases this compound can be inferior in compare with the hostage molecule [76,77].

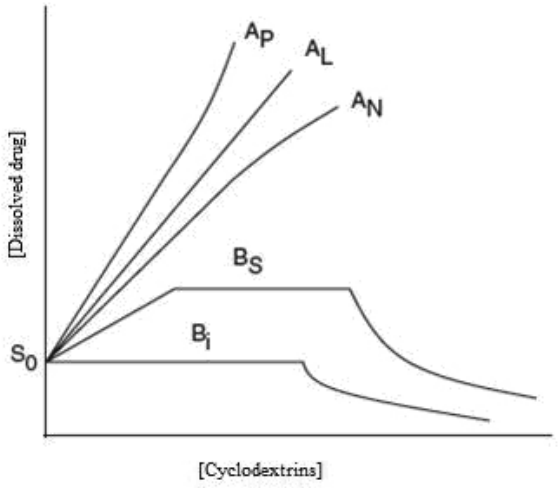

Figure 3. Solubility profiles by Higuchi and Connors theory. So is the drug intrinsic solubility in cyclodextrin absence [76].

MULTI-COMPONENTS SYSTEMS: POLYMERS WITH CYCLODEXTRINS

Though CDs had long been known to form both soluble and crystalline inclusion compounds (ICs) with a variety of small-molecule guests, Harada & Kamachi first demonstrated in 1990, using low molecular weight liquid polyethylene oxide (PEO) oligomers, that non-covalent bonded crystalline ICs could be formed

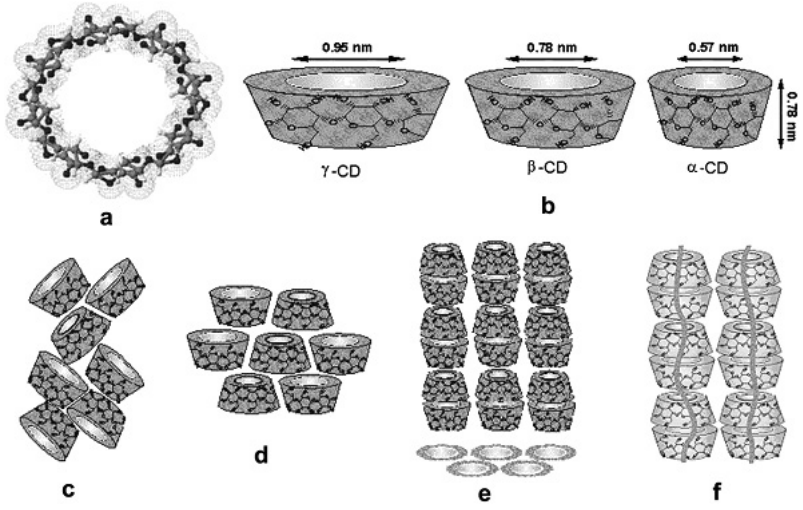

Figure 4. (**a**) γ-CD chemical structure; (**b**) approximate dimensions of α-, β-, and γ-CDs; schematic representation of packing structures of (**c**) cage-type, (**d**) layer type, and (**e**) head-to-tail channel-type CD crystals; and (**f**) CD-IC channels containing included polymer guests [79].

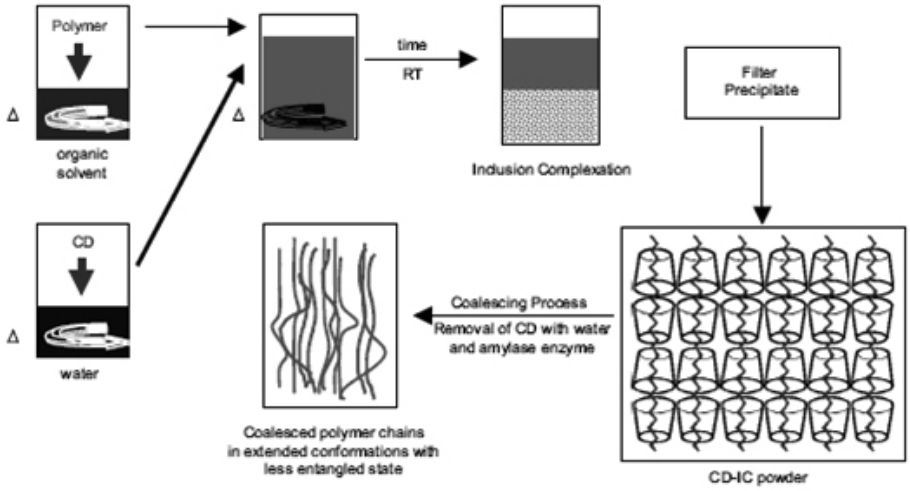

Figure 5. Schematic representation of polymer-CD-ICs formation, the coalescence process, and the coalesced polymer [79].

between guest polymers and host CDs as well [78]. This is accomplished by threading of the guest polymers through the CD cavities to form polymer threaded crystalline stacks, as illustrated in Figure 4. Polymer chains included in CD-ICs are necessarily both highly extended and isolated from neighboring chains, because they are threaded through and confined in the narrow CD channel cavities (Fig. 4f)

If the host CDs in polymer-CD-ICs are carefully removed and the guest polymer chains are permitted to coalesce into a bulk solid sample, then it can be reasonably expected that the arrangement of chains or their packing, might be significantly different from those normally produced from their randomly coiling and entangled solutions or melts, as suggested in Figure 5.

CDs may also be covalently bonded to polymers to alter their functionalities through incorporation of CDs into their backbones during polymerization or attachment to their side chains via post-polymerization reactions. The presence of covalently bonded CDs in polymers serves to increase their acceptance and retention of additives, such as dyes, fragrances, anti-bacterials, etc. They may also be further reacted or treated through their covalently bonded CDs to cross-link and form networks or to form blends with other polymers having a propensity to thread through their attached CD cavities [79].

Drug controlled release and applications in the design of some novel delivery systems

CDs, due to their ability either to complex drugs or to act as functional carrier materials in pharmaceutical formulations, can serve as potential candidates for efficient and precise delivery of required amounts of drugs to targeted site for a necessary period of time. In drug delivery, the concept of entrapping CD-drug complexes into liposomes combines the advantages of both CDs (such as increasing the solubility of

drugs) and liposomes (such as targeting of drugs) into a single system and thus circumvents the problems associated with each system.

It was suggested that crosslinked β-CD microcapsules, because of their ability to retard the release of water-soluble drugs through semipermeable membranes, can act as release modulators to provide efficiently controlled release of drugs. In the presence of a high percentage of highly soluble hydrophilic excipients, complexation may not improve the drug dissolution rate from microspheres. Two applications of CDs have been found very promising in the design of nanoparticles: one is increasing the loading capacity of nanoparticles and the other is spontaneous formation of either nanocapsules or nanospheres by nanoprecipitation of amphiphilic CDs diesters. Both the new techniques were reported to be useful due to great interest of nanoparticles in oral and parenteral drug administration [80].

CONCLUSIONS

Poor solubility continues to impact the development of a large number of potential drug candidates. Most of the promising NCEs are poorly water soluble drugs, which may present a lack of therapeutic effect, because of their low bioavailability. Solid dispersions are one of the most attractive processes to improve drugs' poor water solubility. Can improve their stability and performance by increasing drug-polymer solubility, amorphous fraction, particle wettability and particle porosity. CDs represent a true added value in this context. These starch derivatives are useful solubilizers, enabling both liquid oral and parenteral dosage forms. In addition they can increase the oral bioavailability of solids through an increase in dissolution rate secondary to increasing the apparent solubility of a compound. While inclusion complex formation is certainly the major mechanism associated with the solubilization potential of CDs, effects related to non-inclusion complexation and supersaturation may be important contributors to solubilization in certain circumstance. These substances acting isolated and forming complexes and systems are efficient solutions in solubilization of drugs.

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