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TECHNOLOGICAL STRATEGIES TO INCREASE SOLUBILITY OF ALBENDAZOLE: A REVIEW ABOUT INCLUSION COMPLEXES AND SOLID DISPERSIONS

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Abstract:

The aim of the present review is to summarize and discuss the main strategies for addressing the poor solubility of Albendazole (ABZ) with pharmaceutical carriers, as well as the most used methodologies for physicochemical characterization of such compounds. ABZ is a benzimidazole-derived drug widely used in the treatment and control of helminths, being the first choice therapy for several parasitic diseases. Since ABZ belongs to the class II in the Biopharmaceutical Classification System, it is poorly absorbed by the oral route and has low bioavailability. This work covers from the formation of inclusion complexes with cyclodextrins (highlighting β-cyclodextrin) to the use of several polymers for the formation of solid dispersions. Techniques such as infrared absorption spectroscopy, thermal analysis, X-ray diffractometry, nuclear magnetic resonance, microscopies, dissolution tests, in vivo studies, among others, are discussed here, highlighting how these drug delivery systems are capable of modulating the crystalline properties of ABZ, which culminates in increased dissolution rate and may improve oral drug bioavailability

Keywords: *Albendazole. Inclusion complexes. Solid dispersions. Characterization. In vivo studies.*

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1.INTRODUCTION:

Poorly water-soluble drugs are considered particularly challenging (1), as their dissolution in gastrointestinal fluids usually leads to insufficient bioavailability. Several commercially available drugs along with over 70% of new chemical entities are expected to present this problem (2).

Heterocyclic molecules have important therapeutic activities for several pathologies, such as the benzimidazole class, which has several derivatives with antimicrobial, anti-inflammatory/analgesic and anticancer activities (3). Carbamate benzimidazoles are specifically used as anthelmintics in the treatment of nematode infections. One of the well-known representatives of this subclass is Albendazole (ABZ), a drug widely used against Ascaris, Trichuris and hookworms, also reported to treat other neglected diseases in combination with other drugs (4,5). In addition to the antiparasitic activity, studies reported ABZ with potential cytotoxic activity against diverse tumors (6). From a biopharmaceutical perspective, ABZ is included in Class II of the Biopharmaceutical Classification System (BCS) – which classifies drug molecules according to their solubility and permeability in the human organism – which means that ABZ presents low solubility and high permeability (7,8).

Among the technological strategies for increasing drug efficacy, inclusion complexes (formed with cyclodextrins - CD) (9–14) and solid dispersions (constituted by association with various polymers) have been widely used as strategies to increase aqueous solubility of drugs, improve dissolution kinetics, and thus enhancing drugs bioavailability (15–18).

Cyclodextrins are part of the cyclic oligosaccharides family, containing a hydrophilic outer surface and a central cavity with lipophilic properties (19,20). There are 3 types of natural cyclodextrins: α, β, and γ-CDs. The difference between them is in the number of glycosidic units joined by α-1,4-type bonds (α-CDs: 6 units, β-CDs: 7 units and γ-CDs : 8 units) and the intrinsic solubility of each molecule (21). Several chemical changes in CD are described in the literature. Each hydroxyl (OH) grouping has a distinct chemical reactivity within the structure, and its substitution may produce a significant increase in solubility due to a decrease in the crystalline state of the CD molecule. In addition, such substitutions may also be useful regarding a decreasing in renal damage, such as those reported for natural cyclodextrins (19,22,23). These modifications basically occur in the primary and / or secondary OH groups (24), by the linking of different functional groups.

Hydroxypropyl-β-cyclodextrin is an example that the addition of chemical clusters combine greater flexibility to the OH group on the outside of the CD, extends the hydrophobic cavity space, increases the formation of hydrogen bonds between the complexed drug and the CD, also reflecting the increased stability of the inclusion complex formed. The solubility of cyclodextrin complexed drugs therefore depends on the type of CD used. The greater the degree of chemical group substitution in these glycosylated structures, the greater the solubility granted (22,25).

Within the pharmaceutical industry, β-cyclodextrin is the most commonly used CD in the development of formulations. This fact is probably related to its low production cost, since it is easily purified from the original reaction medium (25). In addition, factors such as its great potential for complexation and safety for human use are well-reported (4).

In order to promote increased solubility, solid dispersions have become one of the most researched proposals in pharmaceutical technology, since they also provide a significant reduction in drug particle size, and an increase in uniformity and contact surface, as well as enable rapid absorption and dissolution rates(24,26,27). The compatibility analysis between the chosen carrier and the drug is of great importance, since each other can influence in sustaining the release of the drug and modulating its therapeutic action. For instance, if the compatibility is poor, the drug will not be dispersed properly. Generally, in solid dispersions the drug is in amorphous state, directly impacting dissolution, bioavailability, among other properties. In addition to the solubility enhancing property, they can also be used to increase the chemical stability of drugs in solutions or suspensions (26) (26,28).

From a formulation scientist's point of view, solid dispersions are conducive to improving dissolution rate by preventing aggregation of drug particles as well as reducing solid-liquid surface tension (29). However, the dissolution performance of solid dispersions can be affected by several factors such as the type of polymer employed, the relationship and interactions between the active pharmaceutical ingredient and the polymer, the aqueous solubility of the components, wettability and physical stability. Some authors report that the solubility of solid dispersions depends on the method of preparation (30).

Thus, the solubility of polymers has the ability to change the release mechanism and drugs kinetics, either through controlled dissolution using soluble polymers or through controlled diffusion when the polymers are largely insoluble (31).

2. Fourier-Transform Infrared Absorption Spectroscopy (FTIR)

In Infrared Spectroscopy, molecular vibrations generated by light absorption can be classified into axial (stretches) or angular (rotational) deformations. Stretches are changes in the internuclear distance between atoms in the same molecule, increasing and decreasing this distance alternately. Rotational deformations may consist of a change in the binding angle between atoms. These vibrations are called absorption bands and are produced due to the interaction of the produced radiation by vibration at the dipolar moment of the bond with the electromagnetic waves of light, thus resulting in absorption (32,33).

The FTIR technique usually provides only qualitative information, which, for instance, helps in proving the formation of the inclusion complex between drug and carrier. When ABZ molecules are placed into CDs cavities, besides the presence of characteristic bands from the CD and drug molecules, significant changes in the intensity and vibrational wavelengths of ABZ molecules are sometimes observed. These changes in vibrational frequencies indicate the formation of inclusion complexes rather than physical mixtures. (4,34,35).

The spectrum of Albendazole alone shows typical bands at 3350 and 2950 cm^{-1} for N-H vibrations. In the 1626 and 1567 cm^{-1} regions the characteristic C=N stretch of the structure. At 1442 cm^{-1} a characteristic band from the C-C bond vibration can be observed. Regarding β-CD, at 1741 cm^{-1} an intense band due to the C=O vibration from the acetyl group of the molecule can be noticed (Figure 1).

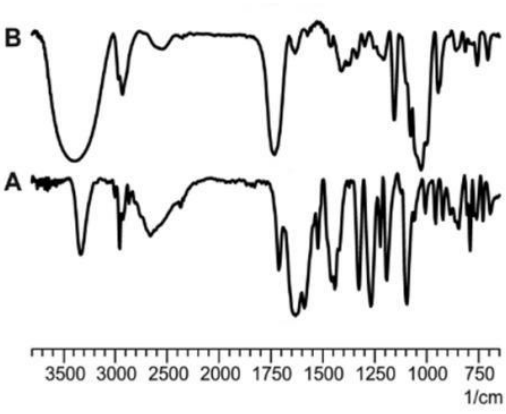

Figure 1. Infrared absorption spectra of Albendazole (a) and β-CD (b) (from GARCIA et al., 2014)

Studies by Chattah et al. (2017) investigated the increased solubility of complexes formed between β-CD and two polymorphic forms of Albendazole (I and II). Frequency shifts in the spectra of both inclusion complexes were observed; bands at 2953 and 1708 cm^{-1}, related to C-H bonding from the methyl and carbonyl group, respectively, disappeared in the spectrum of the inclusion complex containing ABZ I, while the same bands remained unchanged in the system containing ABZ II. However, in the latter spectrum mentioned, the bonding band from the amide group was not observed, which indicates the formation of an inclusion complex (37).

Studies by Cetin et al. (2011) confirmed the interaction of ABZ and β-CD in three increasing molar ratios of CD at 1:1, 1:2, 1:3. Considerable changes in the complex spectra were observed as well as in the intensity of characteristic bands from ABZ in all studied proportions, providing evidence of interactions between the components (38).

Nevertheless, in some studies cyclodextrin inclusion complexes may have limitations regarding the FTIR technique. As example, the vibrational bands of the CD may not show significant changes when complexes are formed, especially in the range between 1100 to 2000 cm^{-1}, since the encapsulation of molecules in their cavity is mainly due to Van der Waals forces and hydrophobic interactions, which do not promote significant changes in these spectra (39). Another important point comprises the drug mass and stoichiometry used in the studies, where significant changes in the spectra are more observed when the drug mass does not exceed 5 - 15% of the complex mass, otherwise the excess of ABZ will not be able to interact with the amount of CD available, and then, masking the results from the molecules that complexed with the carrier, as noted in studies made by Moriwaki et al. (2008) (25).

In the inclusion complexes obtained by suspending ABZ in β-CD solution, an overlap of the bands referring to the two compounds occurred (Figure 2) and thus, by this technique it is not possible to confirm the real complexation between the two components (19). The same phenomenon occurs when there are physical mixtures of these materials, as noted by Chattah et al., and Garcia et al., Indicating that only physical interaction is not sufficient to generate bonds between the chemical groups involved (37,40).

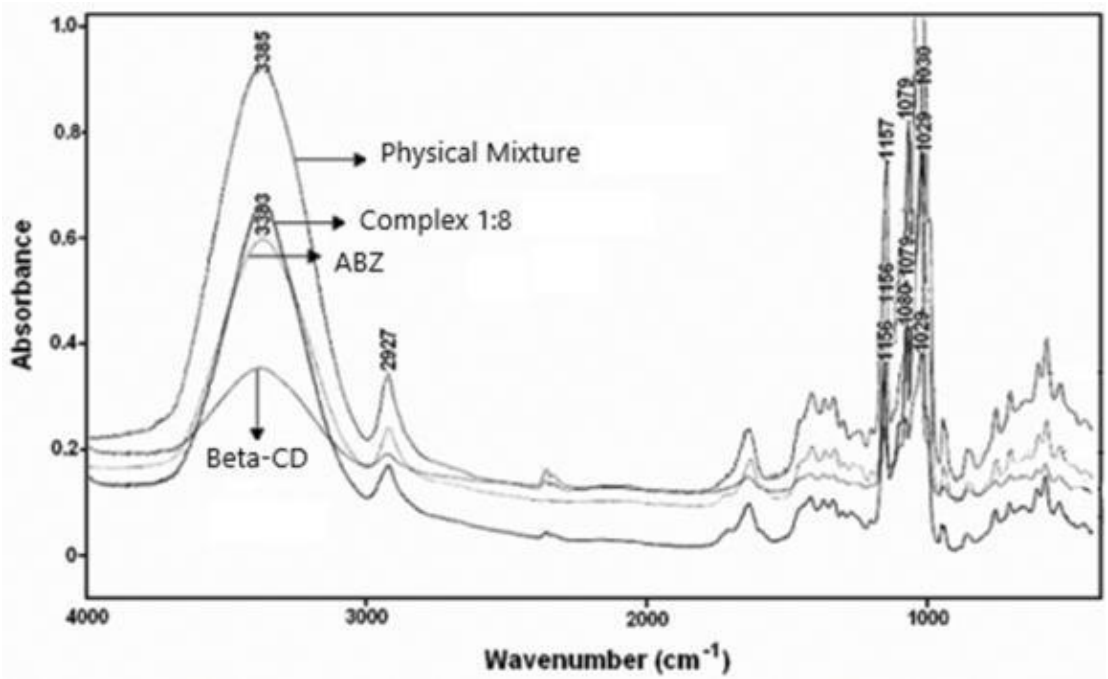

Figure 2. Infrared absorption spectra of Albendazole, β-Cyclodextrin, physical mixture and inclusion complex (from Moriwaki et al, 2008)

Whenever methanol was used to solubilize ABZ prior to contact with CD, the drug-related bands undergo decreases in intensity, enlargement and displacements in specific regions (C=O, C=N, C-O-C) which is suggestive of interaction between components, showing that previously solubilized drug tends to interact more easily with β-CD (37,38). The literature reports that regarding the structurally modified β-CD using acid, a band at 1732 cm^{-1} in the cyclodextrin spectrum can be seen, which is related to the ester group formed by the reaction between the acid carboxylic groups and CD hydroxyls. Regarding the complex obtained with Albendazole, it is noted that there is also a minimization in its characteristic bands, where the authors suggest that there may have been changes ABZ crystalline structure due to its complexation with β -CD (41).

In ABZ solid dispersion studies, as well as in some inclusion complex works, spectra with only additive events of the individual components were observed, showing that the ABZ bands remained unchanged and in the same wavelength bands, demonstrating that interaction occurred between ABZ and carriers (Table 1) (42,43). These possible physicochemical interactions that may occur between the components of solid dispersions may affect the dissolution profile of the drug. In some studies, such as those published by Tripathy; Kar; Majeed (2013), suggestive changes of hydrogen bonding between ABZ and polymer or the surfactant used in dispersions are evidenced, causing reduced recrystallization.

In the study reported by Santos et al. (2017) solid dispersions containing Albendazole and two carriers - PEG-15000 (a polymer) and Gelucire 50/13 (a nonionic surfactant) - were prepared through the fusion methodology (15).

ABZ characteristic bands were strongly suppressed when analyzed from dispersions, suggesting possible interactions between ABZ chemical groups and the polymer or surfactant used. Regarding physical mixtures, an overlapping of the compound bands was observed, which may be associated with the lack of new chemical bonds between the substances. The methodology for obtaining each of these systems is decisive when it comes to the formation of a new chemical compound (drug and polymers linked together), because the use of heat, agitation, and wetting fluids can promote bond breakage, and consequent formation of new ones. Since in physical mixture the constituent substances are not chemically combined, it provides fewer (if any) chemical changes that can be visualized by infrared spectroscopy.

Table 1. Events found in solid dispersion FTIR spectra.

Reference	Carrier / Polymer	Main observations
(43)	Kollicoat IR® / PVP K30	No change in spectra
(44)	Nicotinamide	ABZ N-H band reduction and displacement, suggesting hydrogen bonds between drug and carrier
(45)	Polyethylene glycol 6000 / Polaxamer 188	No change in spectra
(46)	Sodium Lauryl Sulfate + other excipients	No change in spectra
(47)	Pluronic 188 / Polyethylene glycol 6000	No change in spectra
(15)	Gleucire 50/13 Polyethylene glycol 1500	Intensity reduction of all bands. No registration of new bands nor absence or change of representative bands
(48)	Pluronic 188	No change in spectra
(49)	Polaxamer (188/407) + PVP K30	No change in spectra
(50)	Eudragit E-100	N-H vibration changes. Band disappearance at 2665 cm^{-1} (possible combination with C-H group vibrations at 2958 cm^{-1}). Carbonyl frequency displacement
(51)	Urea / PEG / Polaxamer	ABZ-Urea: Reduction in urea carbonyl frequency as urea ratio increased. Possible hydrogen bonding. ABZ-PEG: Transmittance intensities of the ABZ N-H elongation band have been markedly reduced and shifted. ABZ-Polaxamer: Observations similar to those found in ABZ-PEG

In addition to inclusion complexes and solid dispersions, other polymers have been associated with ABZ, such as the natural chitosan polymer, aiming at increasing solubility and improving dissolution rates. In this sense, the infrared absorption spectra were useful in verifying if proper incorporation of the drug into the chitosan matrix occurred.

The infrared absorption spectrum of chitosan presents some characteristics bands from the polymer groups, referring to the groups -NH2, -OH and C-O-C. Lee et al. (2016) observed that the characteristic bands of Albendazole are suppressed when it is incorporated into the nanoparticles containing PLGA-Poloxamer 188 (P188-20), in with PLGA band remained around 1700 cm^{-1}, suggesting that some chemical bonds were broken and other new ones were formed between the drug and polymer in the nanosystem. Wang et al. (2011) observed the same pattern of behavior when the drug was inserted into the chitosan and alginate matrix, with greater visualization of the system bands than the drug itself, suggesting once again the chemical interactions between ABZ and polymers.

3. X-ray Diffraction Spectroscopy

Several macromolecules, as inorganic and mineral compounds can form crystals. Through X-ray

diffraction (XRD), it is possible to relate the chemical composition and the crystalline ordering of the molecules, which is a technique that enables high precision in the quantitative and qualitative results of solid mixtures. This tool makes use of X-ray scattering through organized structures (crystals), providing morphological studies on materials, determining their crystal structure and their crystalline fraction. Among the advantages of this technique the simplicity of the method, time and robustness can be cited, considering that each diffractogram is characteristic and distinct of each substance, with different intensities and positions, also called interplanar distances (54).

Substances with a predominant crystal structure, such as ABZ, tend to express typical results in X-ray diffraction, showing several peaks, which indicates the diverse reflectance of radiation. To further improve the results obtained with CD, studies have shown that CD-derivatives in association with ABZ may result in better drug complexation and greater reduction in crystallinity, since CD-derivatives have amorphous structure. Regarding solid dispersions, the associated polymers usually promote results ranging from a slight decrease in peak intensity to suppression (44).

Usually, the most intense peaks are peculiar from each molecule and, for Albendazole, literature data describe them as occurring (2θ scale) at 7.23º, 11.51º, 17.85º, 22.09º and 24.54º, as can be seen in Figure 3. Studies by Chattah et al. (2017), showed that when the drug is associated with β-CD, its signals considerably decrease, suggesting that modifications in its crystalle properties occurred (22,36,55). Such observations can be confirmed by complementary techniques such as scanning electron microscopy and thermal analysis. Moreover, it is worth noting that in the simple physical mixture of the components there is no evidence about formation of a new solid state, since only peaks from the isolated components are observed.

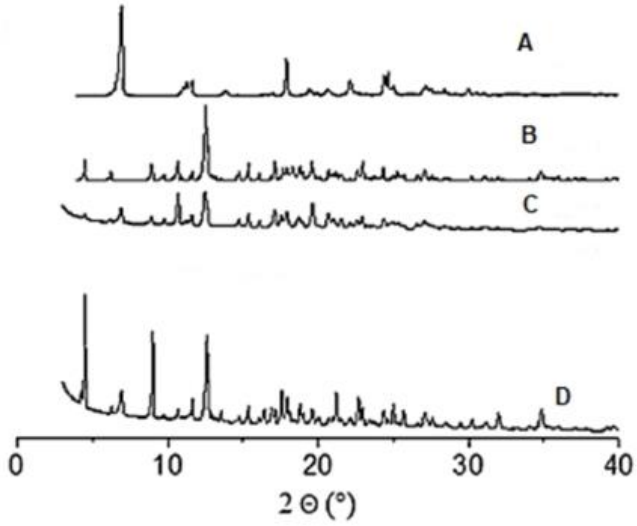

Figure 3. Diffractometry - A: Albendazole alone, B: β-CD, C: ABZ-β-CD (complexed), D: ABZ-β-CD (physical mixture) (from Chattah et al., 2017)

Most of the published studies about inclusion complexes, solid dispersions and polymeric systems, demonstrated, the decrease in ABZ peak intensity, suggesting amorphization of the associated drug (Table 2). The extent of phase crystallinity can influence in the dissolution of the dosage forms. An amorphous or metastable form, for example, can dissolve in a faster rate due to its higher internal energy and greater molecular motion, which improves thermodynamic properties when compared to crystalline materials (56).

Table 2. Main observations found in the diffractograms of inclusion systems containing Albendazole.

Reference	**Carrier**	**Obtaining Method**	**Main Observations**
(22)	RM-β-CD (CD methylated)	Spray drying	Broader intense peaks implying that ABZ is in an amorphous state
(57)	C-β-CD (Citrate Derivative)	Spray drying	The diffractograms of the systems showed fewer peaks, which were broader and less intense, showing only two peaks related to the drug, suggesting ABZ amorphous state.
(37)	β-CD	Malaxage / Coprecipitation	In the obtained systems, significant differences were observed in the reflections and crystallinity of the materials.
(58)	PVP K12	Hot Melt Extrusion	Characteristic halo from amorphous materials.
(44)	Nicotinamide	Malaxage	Crystallite size reduction as carrier ratio increased
(45)	Polyethylene glycol 6000 Polaxamer 188	Hot fusion	Diffractogram without relevant changes confirming FTIR data
(56)	Gelucire 44/14 e PEG 8000	Hot fusion	Some changes in ABZ peak positions. Reduction of peak drug intensity
(59)	Kollidon® Soluplus® Eudragit® E PO	Hot Melt Extrusion / Spray drying	Spray-dried ABZ with Kollidon® VA 64 and Soluplus® indicated ABZ amorphization. ABZ remained partially crystalline in the spray-dried ABZ-Eudragit® E PO formulation
(46)	Sodium Lauryl Sulfate + other excipients	Spray drying	Some acute ABZ peaks disappeared and the intensity of the remaining peaks decreased substantially.
(47)	Pluronic 188 Polyethylene glycol 6000	Hot fusion / Spray drying	Slight reduction in crystallinity
(15)	Gelucire 50/13 Polyethylene glycol 1500	Hot fusion	Diffractogram without relevant changes
(51)	Urea / PEG / Polaxamer	Hot fusion / Coprecipitation/ Malaxage	ABZ-urea: absence of ABZ peaks, which indicated that ABZ was converted to the amorphous form in crystalline urea. ABZ-PEG and ABZ-PX: weak diffraction peaks from ABZ.

(49)	Polaxamer (188/407) + PVP K30	Hot fusion	At the 50%: 48%: 2% ABZ: PVP: P407 ratio, a slight reduction in crystallinity of some ABZ peaks was observed.
(60)a	HPMC / PVP / PVA	Fusion + Spray drying	The intensity of the ABZ crystalline diffraction peaks in the systems was decreased as the polymer ratio increased until completely disappeared at 1:4 ratio.
(48)	Pluronic 188	Hot fusion / Spray drying	Slight reduction in ABZ peak intensity

Spray drying is a predominant technique for producing amorphous solid ABZ dispersions in a polymeric matrix in addition to the hot melt method. The technique comprises a co-current spray dryer that is suitable for thermally sensitive drugs due to the short evaporation time, resulting in less thermal degradation of products. Surasarang et al. (2016) showed that ABZ dispersions prepared by spray drying become amorphous, also having a better shelf life, while those made by hot extrusion have been degraded by heat and shear stress.

Solid dispersion, in some cases, does not influence ABZ crystallinity, even using conventional polymers and obtaining methods. Even so, substantial improvement in drug dissolution can be achieved, demonstrating that sometimes the presence of a polymer network can influence in the drug release profile (15).
Castro et al. (2013) showed that the use of Poloxamer 188 (hydrophilic polymer) was not able to alter significantly the crystalline state of ABZ (when it was in solid dispersion), since there were no major changes in the diffraction peaks of the drug, but slight decreases in intensity.

Kalaiselvan et al. (2006) evaluated solid dispersions of ABZ prepared from three different vehicles (Urea / PEG / Polaxamer) and mixing ratios and methods, attempting to improve drug solubility and dissolution rate (51). The Polaxamer system had the highest dissolution rate and efficiency over the drug alone for all mixing ratios and preparation methods, although urea was able to amorphize ABZ. The mixing ratio and preparation method influenced significantly particle size reduction, but the reduction in crystallinity was not reflected in the dissolution improvement in the 1:1 ratio. This fact may be attributed to the recrystallization of the drug in the medium during the study.

Another work, using other hydrophilic polymers (HPMC, PVP and PVA), reported that with the increasing proportion of carriers, there is a disappearance of some peaks in the diffractogram, as can be seen in Figure 4. In this sense, such an event may not be due solely to the use of the chosen carriers, but also to the obtaining techniques by fusion methodology and spray-drying, which are capable of generating powders with different aspects, due to the used atomization (61).

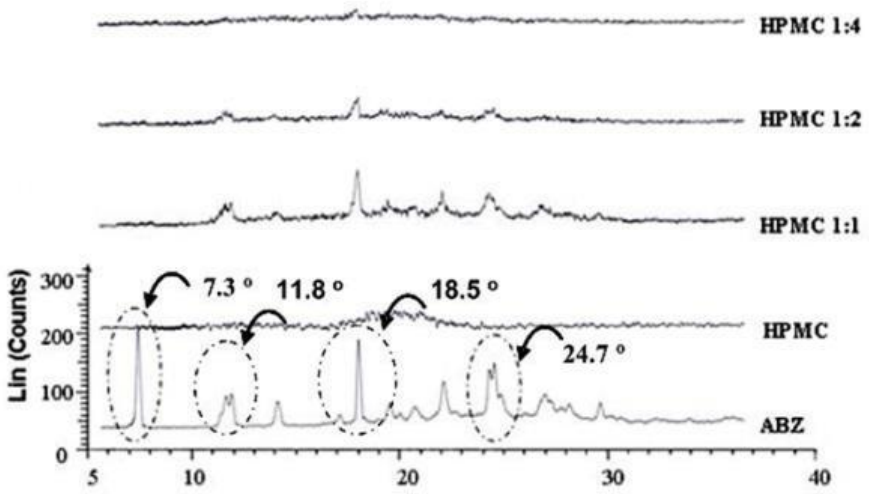

Figure 4. Diffractogram ABZ alone, carrier (HPMC), and Drug + carrier at different proportions (from Alanazi et al., 2007)

In systems using chitosan, diffractometry is employed to check the formation of polyelectrolytic complexes with the substances of choice, as well as to verify that the drug has been properly encapsulated. This can be evidenced through the decreasing or disappearance in crystallinity peaks of the drug. Chitosan is recognized as a low crystallinity material and it is expected that when a drug is properly dispersed in its structure, the same pattern will occur. This is evidenced in some works, such as those made by Piccirilli et al. (2014), where chitosan microparticles containing ABZ where prepared (summarized in Figure 5) (62) microcrystals, as its name suggests, are crystalline structures that can be visualized only by microscopy. Priotti et al. (2017) elaborated chitosan microcrystals containing ABZ and the diffractograms showed that there were no major changes in the crystal structure of the drug (Figure 6), attributing this fact to the stability of the formulation. This may be correlated with changes in the polymorphic form of the drug after treatment in microcrystals preparation and a certain degree of dispersion in the chitosan (8).

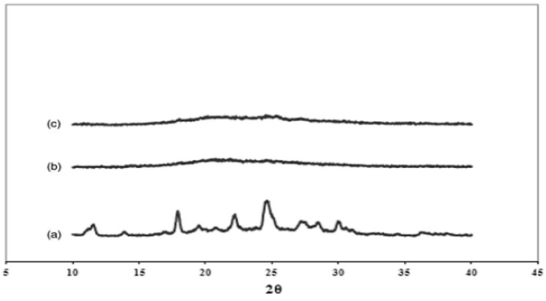

Figure 5. Microparticle diffractograms obtained by Piccirilli et al. (2014), where: (a) Albendazole, (b) dispersed chitosan, (c) ABZ systems (from Piccirilli et al., 2014)

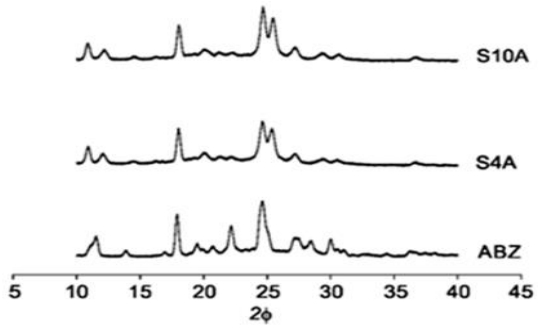

Figure 6. Diffractograms of microparticles obtained by Priotti et al., 2016. System S10A corresponds to chitosan microcrystals and S4A to hydroxyethyl cellulose microcrystals (from Priotti et al., 2016)

4. Scanning electron microscopy (SEM)

There is a close relationship between the water solubility of a substance and its crystal structure, therefore, it is of great importance to study the crystalline structure of the molecule. The amorphization of organic compound could lead to increased aqueous solubility of these molecules. Scanning electron microscopy (SEM) is a type of electron microscopy that produces images by scanning the surface with a focused beam of electrons. It provides photomicrographs that are employed in pharmaceutical sciences to obtain information about crystal shapes. Through SEM it is possible to perform a qualitative and quantitative evaluation of the crystals, observing the homogeneity and determining the size and shape of the particles. This technique allows to observe the change in particle morphology of isolated and complex constituents (63).

In the case of cyclodextrins, the physical interaction between the inclusion complex components can also be elucidated mainly when the host material has porosity or cavities available to accommodate the guest molecules. Each type of cyclodextrin natural or its derivations have distinct characteristics that are taken into account to better explain the interaction between these host molecules and drugs. The type of CD and the obtaining method have great influence in inclusion complex production, as one can be seen in the following works. GARCIA et al (2018) suggested the formation of a new solid-state structure between ABZ and itacolyl-β-CD where system obtained by spray drying generated spherical particles different from smooth surfaces of the derivative and irregular ABZ structure, different from the physical mixtures, where the characteristics of the isolated components were observed (40).

The other study used different obtaining method to elucidated complexation efficiency of β-CD with two tautomeric solid form of ABZ. Both ABZ solid types showed distinct morphological structure. ABZ I showed a crystalline structure with small irregular particles of different sizes and shapes and ABZ II particles form a smooth surface lamellar structure, as can be seen in Figure 7. On the inclusion complex obtained by kneading and co-precipitation methods it was not possible to differentiate the individual components. Thus, SEM analysis adds valuable information regarding morphological characterization, contributing to elucidation of the phenomenon of inclusion complex formation (36).

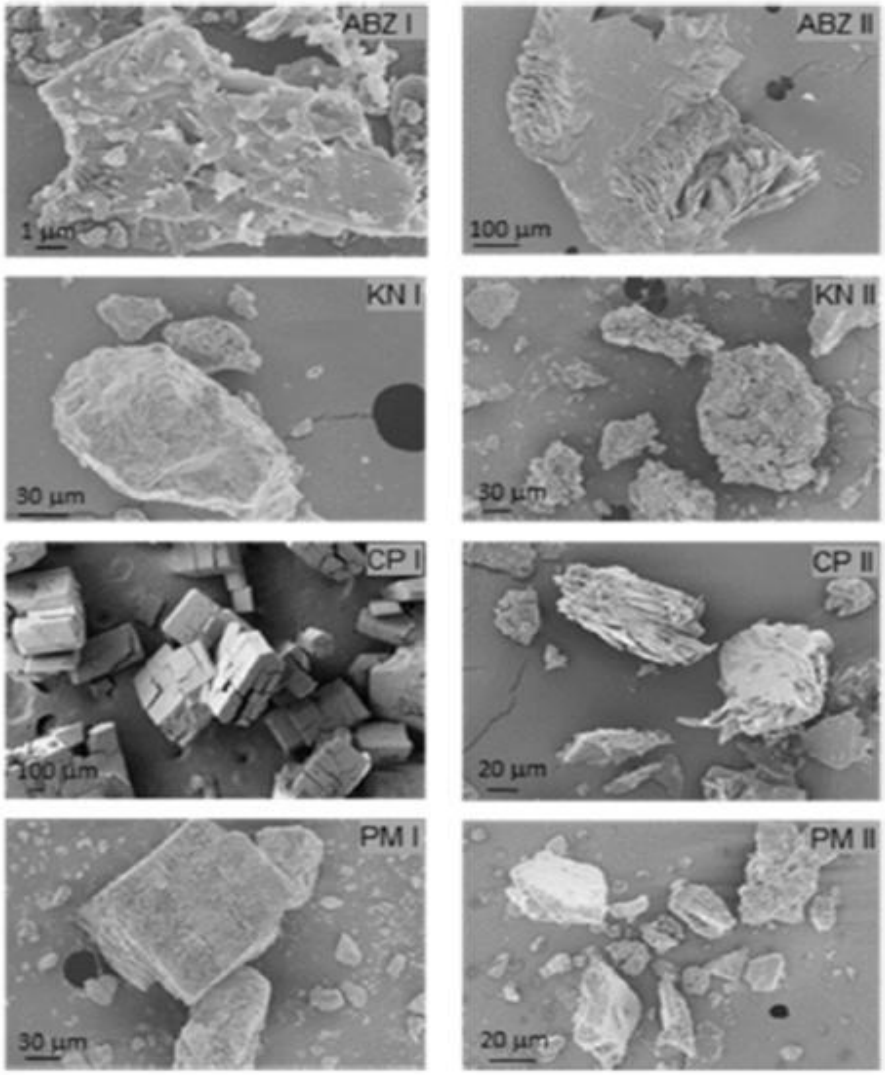

Figure 7. Microphotographs of ABZ I, ABZ II and their respective systems obtained by kneading (KN), co-precipitation (CP) and physical mixtures (PM) (from Chattah et al., 2017)

Microscopy analysis of solid dispersions allow visualization of drug distribution upon the carrier by evidencing the physical interaction between the raw materials. This and other characteristics are important to validate the obtaining method efficiency of the solid dispersion (43,56)

The methodologies for obtaining and drying the solid dispersions also influence the morphology of the obtained product, there is a clear morphology difference between a simple physical mixture and the formation of the inclusion complex. Figure 8 illustrate the SEM analysis performed in the studies by Surasarang et al. (2016) for morphological characterization of ABZ solid dispersion with Kollidon® VA 64 and Soluplus®. The drying product showed a spherical shape with high surface area, a characteristic of materials submitted to Spray Dryer, this morphology can contribute to a better dissolution of the material.

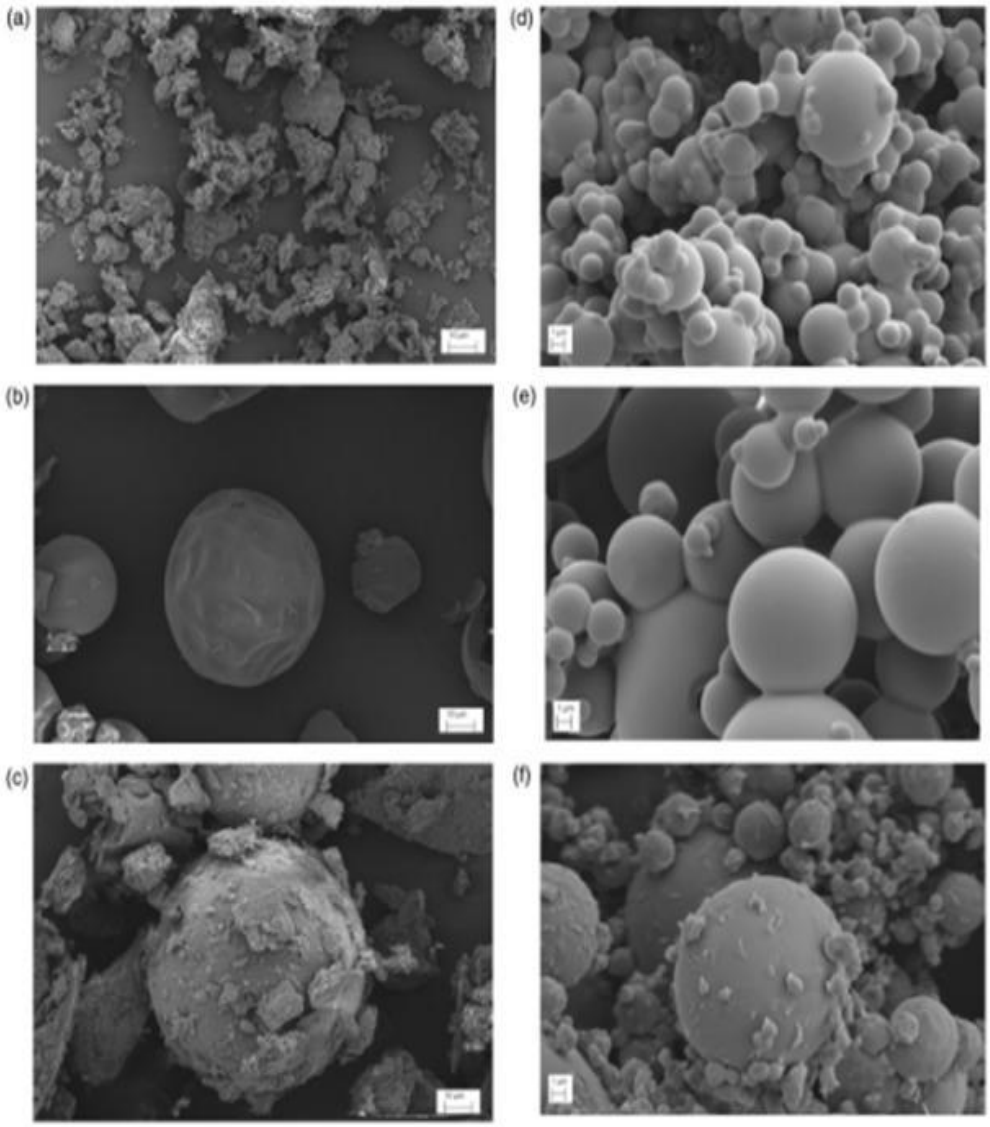

Figure 8. Imagens from SEM analysis of bulk ABZ (a), KollidonVR VA 64 (b), physical mixture of ABZ and Kollidon VA 64 (c), ABZ-polymer spray-dried formulations (20:80) with Kollidon VA 64 (d), Soluplus (e), and Eudragit E PO (f).(from Surasarang et al., 2016)

Table 3 summarizes some studies that used SEM analysis to characterize the morphology of the raw materials and their respective solid dispersions, presenting the carrier used, the processing method and the phase transformation observed in the material.

Table 3. Main observations found in photomicrographs of solid dispersions with ABZ.

Carrier	Processing method	Phase transformation	Reference
PEG 8000	Solvent evaporation	The irregular crystallized form of ABZ and the smooth particles of the polymer take the form of semi-spherical particles in the solid dispersion.	(65)
Poloxamer 188	Melting	In solid dispersion and physical mixtures, there were no alterations. Irregular morphology of ABZ crystals and Poloxamer spheres were maintained.	(48)
Gelucire 44/14 and PEG 8000	Melting	Difficulty in distinguishing drug and polymer morphological in SD, due to uniform and homogeneous distribution between components, suggesting incorporation of the drug crystals in the molten polymer mass. Easier recognition of components in physical mixture.	(56)
PEG 8000 and Poloxamer 188	Melting	SD showed similar irregularities to the isolated raw materials, presenting smaller particle agglomerates and particle larger PEG particles with a rough surface.	(48)
Nicotinamide	Kneading method	Slight morphological changes in the irregular crystal structure of ABZ produced by the carrier.	(44)
PVP K-30 and Kollicoat IR®	Spray drying	The SD at 1:1 and 1:4 ratio took the form of small spheres with the homogeneously dispersed drug in them.	(43)
Sugars, Polyols, Ionic and Nonionic surfactants	Spray drying	The drying technique provided the visualization of the characteristic spheres. The addition of Cremophor A 25 surfactant caused the spheres to acquire a certain surface roughness.	(46)
PVP K12	Hot extrusion	There was a higher homogeneity of extruded materials in comparison to physical mixtures. The material became more porous as the drug concentration increased, due to the relaxation of the extrudate.	(58)
Kollidon® VA 64, Soluplus® and Eudragit EPO	Hot extrusion and Spray drying	Spray-drying SD formulations presented low crystallinity and have a non-collapsed spherical shape, and the Eudragit EPO dispersion presented crystalline drug fractions. Physical mixtures showed reduced particle size.	(64)

5. Differential scanning calorimetry (DSC)

Differential exploratory calorimetry (DSC) provides important information about the thermodynamic changes present in thermal transitions of materials, such as melting point, crystallization and glass transitions, as these events are unique for each type of material. The melting point is the main event analyzed in the characterization of drugs that are candidate to form inclusion complexes with CDs or to be dispersed in polymeric matrices (35).Knowing the properties of the drug and the selected cyclodextrin is essential before performing the thermal analysis of inclusion complexes. For example, the decomposition temperature of β-CD is in the range of 250 to 300 ºC (19). Another relevant factor that confirms the formation of the inclusion complex is the reduction of an endothermic peak in the temperature range of 80-110 ° C. The reduction in this peak and its respective energy variation refers to cyclodextrin dehydration, which indicates that fewer water molecules are present in the CD cavity due to the presence of the guest molecule within the cavity (66).

Table 4 summarizes the most common findings of research groups studying the formation of inclusion complexes with ABZ.

Table 4. Main observations found in DSC analysis of inclusion complex with ABZ.

CD used	Motivation	Thermal transitions and observed changes for CD and ABZ	Reference
β-CD and HP-β-CD	Improve ABZ solubility and stability through ternary complexation with CDs and hydroxy acids.	Isolated ABZ presented a melting peak at 200 °C, an intense reduction at the same peak was observed in multicomponent systems obtained by kneading compared to co-evaporation. The formation of the ternary system was also confirmed by the reduction of the dehydration enthalpy for the two CD isoforms with emphasis on obtaining by co-evaporation.	(67)
α-CD, β-CD and γ-CD. Poly-α-CD, Poly-β-CD and Poly-γ-CD	To compare the effectiveness of natural cyclodextrins and their polymerized forms in increasing ABZ solubility and stability by forming inclusion complexes.	The endothermic peak referring to ABZ melting point at 196.84 °C was also observed in the physical mixtures with all CDs and their polymerized forms. However, the same melting peak was absent in the systems obtained by freeze drying, indicating the formation of the inclusion complex and/or drug amorphization.	(21)
β-CD	Increase the aqueous solubility of the drug by forming inclusion complexes with a natural CD, also using acetic acid as an enhancer.	The melting point of the drug was observed around 200 °C. The endothermic peak was reduced in the formulation with CD, especially in the 1:8 ratio (drug:CD).	(19)
C-β-CD	Increase the drug dissolution rate and water solubility by forming the inclusion complex with β-CD citrate derivative.	A sharp endothermic ABZ peak was exhibited at 196.84 ° C. This melting peak had a lower intensity in the spray drying system compared to the physical mixture.	(68)
Succinyl-β-CD (S- β-CD)	Formation of an inclusion complex between ABZ and a β-CD derivative obtained by green synthesis.	Similarly, the ABZ intense peak was also found ate 196.84 °C. The decreased melting peak of the drug, which was more pronounced in Spray-Drying systems when compared to physical mixtures, indicated the formation of the inclusion complex.	(69)
β-CD[G2]-OH	Achieve greater efficiency in increasing ABZ solubility by forming inclusion complex with a new β-CD-poly (ester) derivative.	The drug meting peak (210 °C) and CD derivative endothermic dehydration event (80-110 °C) disappeared completely in systems, while in the physical mixtures they remain clear.	(70)
Itaconyl-β-CD	To evaluate the formation of the inclusion complex between ABZ and a new CD derivative in order to obtain new oral pharmaceutical forms with anthelmintic activity.	The spray drying system with the new derivative (I-β-CD) was also able to reduce the intensity of the melting peak (196.84 °C), which indicates the formation of the inclusion complex and possibly the reduction of ABZ crystallinity.	(40)
β-CD and HP-β-CD	Increase ABZ solubility by obtaining inclusion complexes using different CDs and adding PVP polymer.	The greatest attenuation of the melting peak of the drug occurred in the multicomponent system formulated with the co-complexation of the polymer.	(11)

As in the inclusion complexes analysis, in the characterization of solid dispersions, the reduction or disappearance of the melting point of the drug is also considered the main factor on DSC analysis. When it comes to polymer analysis, another characteristic event is also seen in DSC analysis, which is the glass transition temperature that characterizes the transition from a less energetic state, called glass state, to a more energetic state, where the polymer presents a more liquid and rubbery appearance. Another important feature in DSC analysis of polymers, especially hydrophilic polymers, is the presence of a wide endothermic peak, which indicates the water molecules loss by dehydration of the polymeric carrier. In Figure 9, the visualization of the characteristic dehydration peak of Kollicoat SR ® is very evident in solid dispersions thermograms, thus

confirming its presence in solid dispersions with ABZ (43). Even with a significant reduction in this peak, the thermogram suggests the formation of the inclusion complex.

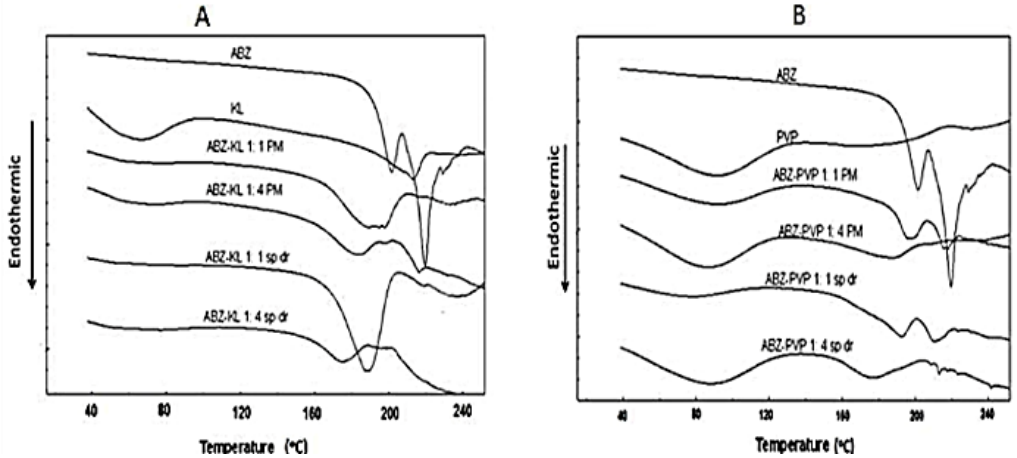

Figure 9. DSC thermograms of ABZ-KL spray dried and physical mixtures in drug: polymer ratios 1: 1 and 1: 4 compared to the individual components, and B = DSC thermograms of ABZ-PVP spray dried and physical mixtures also in drug: polymer ratios 1: 1 and 1: 4 compared to the individual components (from Ibrahim; Shazly; El-Badry, 2014).

There are several methods for obtaining solid dispersions, such as physical mixture (50), melting method (56), solvent (51), kneading (44) , spray drying (49) and hot extrusion. The method used has a great influence on the amorphization degree of the sample, and therefore, the choice of the most suitable obtaining method is essential to the development of a solid dispersion formulation with the desired pharmaceutical properties. Table 5 lists several studies that used DSC analysis as an important technique for solid dispersion characterization. Different carriers were evaluated in order to identify the most suitable to achieve ABZ solubility increment.

Table 5. DSC analysis of ABZ solid dispersions with multiple carriers.

Carrier used	**Processing Method**	**Thermal transitions and changes observed for ABZ and carrier**	**Reference**
Eudragit E-100	Physical mixture	ABZ melting endothermic peak at 200 °C. There was a reduction and a slight anticipation of this peak, suggesting a compatible interaction between the dispersion components.	(51)
PEG 6000 and Poloxamer 407	Melting, solution and kneading method	The solid dispersions of 1:5 ratio (ABZ:carrier), regardless of the method of obtaining, showed a an intense reduction of the ABZ melting point (195-200 °C), when compared to the physical mixture.	(50)
PVP K-17	Solvent Method	The high glass transition temperature (81-85 ° C) indicates a high stability of the polymeric system.	(66)
Gelucire 44/14 and PEG 8000	Melting method	The ABZ melting peak at 210 ° C disappeared in both DS and physical mixtures. An exothermic peak appeared due to recrystallization of the material.	(56)
Nicotinamide	Kneading method	The solid dispersions obtained by kneading method presented absence of the albendazole melting peak, while the physical mixtures presented the still	(44)

		prominent peak.	
PVP K-30 and Poloxamer 407	Spray drying	ABZ:PVP solid dispersion showed a slight reduction in drug melting and polymer dehydration endothermic peaks.	(49)
PVP K-30 and Kollicoat IR ®	Spray drying	The drugs melting point was shallow and broad (218°C) in physical mixtures in 1:4 ratio. The ABZ endothermic peak disappeared in the solid dispersion with Kollicoat in the two tested ratios.	(43)
Sugars, Polyols, Ionic and Nonionic surfactants	Spray drying	The drying of the drug with sugars presented ABZ endothermic peak with lower enthalpy value, when compared to the isolated drug.	(46)
PVP K-12	Hot extrusion	The melting point of ABZ disappeared in the physical mixture and in extrudates in all stoichiometric proportions, presenting stability of 6 months.	(58)
Kollidon® VA 64, Soluplus® and Eudragit EPO	Hot extrusion and spray drying	Endothermic peak reduction in solid dispersions for all polymers tested.	(64)
Gelucire 50/12 and PEG 15000	Melting method	ABZ melting point disappearance (208 ° C) in solid dispersions and physical mixtures with all polymers used in the formulations.	(15)

6. DISSOLUTION TESTS:

When it comes to dissolution studies, involving Albendazole and its possible systems and physical mixtures, the authors bring in their publications the dissolution medium that simulates gastrointestinal fluids as being ideal, since the base character of the drug makes it dissolves better under these conditions (22,37,40,44).However, depending on the carrier used to improve ABZ release, there are those who choose to use ultrapure water to assess the ability of a hydrophilic compound to provide this effect. Pacheco et al (2018) analyzed β-CD and HP-β-CD inclusion complexes to improve ABZ solubility and found that the later performed better than the former, since it presented higher aqueous solubility (11). In the same studies, the use of a multicomponent system between the best performing cyclodextrin (HP-β-CD) and PVP-K30 (hydrophilic polymer) and even better performance was observed, when compared to the sum of results provided by both types of carriers.

Given the consensus regarding the *in vitro* release of ABZ, the researchers use 0.1 N hydrochloric acid (HCl) in almost all of their tests. Following this approach, inclusion complexes as well as solid dispersions are obtained to achieve *in vitro* drug release.

The lower the complexity of designing the system involving CD, the lower the dissolution of ABZ in vitro and certainly in vivo. The behavior of ABZ alone compared to the performance of a physical mix is estimated to be similar, as reported by Garcia et al (2014b and 2016). The dissolution profile of ABZ alone is estimated to be similar to that of physical mixing, as reported by Garcia et al (2014b and 2016) (22,71).

In this approach, it is taken into account that when the intermolecular interactions between ABZ and cyclodextrin molecules are insufficient to displace the equilibrium to the formation of the inclusion complex, thus, most ABZ molecules remain free, and therefore tend to maintain their crystalline conformation. The same behavior is observed when analyzing physical mixtures with polymer, as described by Castro et al (2010), where the humectant and / or solubilizing properties of these compounds are not present, resulting in low dissolution rates of ABZ (48). Studies involving inclusion complexes usually bring natural β-CD and its derivatives. The substitution of any of the hydroxyl groups, even by hydrophobic moieties such as methoxyl groups, resulted in dramatic increase of their aqueous solubility (72).

Garcia et al. 2014a evaluated the dissolution performance of ABZ from Randomly Methylated-β-CD (RAM-β-CD) inclusion complexes, where in 10 minutes of assay 100% of the drug concentration was solubilized, representing a dissolution efficiency of approximately 93%, when compared to of ABZ alone (22). This is probably due to hydrophobic interactions between substituents group of RAM-β-CD and nonpolar moieties of Albendazole molecule, which when combined, modify the drug crystalline conformation, which becomes more soluble (73). The inclusion complex formed may be even more stable when the CD and the drug to be encapsulated have opposite charges (74). With this in mind, a number of studies have compared ABZ dissolution rate in inclusion complexes formed by β-CD and its acidified derivatives: β-CD citrate derivative (C-β-CD), β-CD succinyl derivative (S-β-CD) and itaconic acid derivative (I-β-CD).

In ascending order of results, 88% of ABZ was solubilized within 60 minutes for the inclusion complex containing I-β-CD as host, compared to 46.6% from β-CD; 95.6% in 60 minutes from S-β-CD complexes in contrast with 46% from β-CD; and 100% soluble Albendazole within 20 minutes of assay from C-β-CD in comparison to approximately 40% for β-CD inclusion complex (Figure 10).

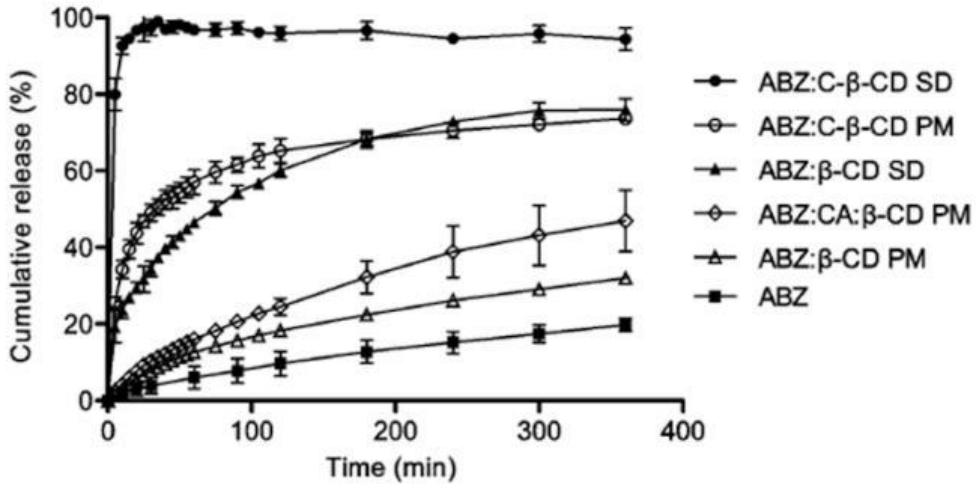

Figure 10. Dissolution profile of ABZ, inclusion complexes with β-CD, C-β-CD and their respective physical mixtures (from García et al., 2014).

Solid dispersions also capable of increasing ABZ solubility. However, depending on the size and type of the polymer network, the release performance of the drug is modified.

In general, solid dispersions (DS) provide drug particle size reduction, generate changes in crystal conformation, increase wettability, and decrease drug particle aggregation. However, unlike cyclodextrins, polymers can be applied to either increase solubility or modify drug release (44).

Polymers with gelling properties tend to slow the release of their charged molecules as their diffusion to the external medium becomes slower. The use of Polaxamer 188 (P188)

An example of this is when Polaxamer 188 (P188) is used with ABZ, where the low ratio of polymer:drug generate better dissolution rates (in 15 minutes, 85% of ABZ was soluble from 50:50 ratio), in contrast to 35% of soluble ABZ from 95:5 ratio. This behavior is related to P188 gelatinous character at physiological temperatures (37ºC), which would be an advantage if the goal of SD was to administrate the drug in a specific cavity (48).
The opposite behavior can also be observed when polymers that require higher concentrations to act as a wetting / solubilizing agent, such as polyethylene glycol of 6000 dalton (PEG 6000), are used. Leonardi et al (2009) observed that in the PEG:ABZ solid dispersion dissolution test (9: 1 ratio) 92% of Albendazole was soluble after 10 minutes.

In a single study, Ibrahim, Shazly and El-Badry (2014) present two situations that summarize what was addressed: they obtained microparticles of ABZ with PVP K30 and Kollicoat IR®, the higher the proportion of Kollicoat IR® the higher the dissolution rate of the drug. In accordance with what has already been discussed, the same phenomenon was not seen with PVP K-30 (43). Figure 11 illustrates such an observation.

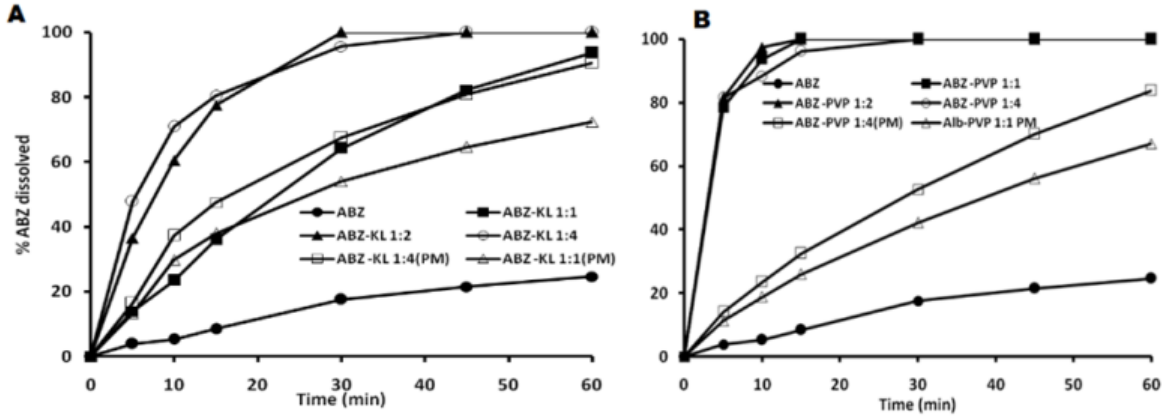

Figure 11. ABZ dissolution profile and their respective solid dispersions and physical mixtures with Kollicoat IR® (A) and PVP K-30® (B), in different proportions (from Ibrahim, Shazly and El-Badry, 2014)

Inclusion complexes and solid dispersions obtained with ABZ have shown promising results. Polymers with less gelling properties and modified CDs are suitable to achieve increased solubility of ABZ. The choice is basically related to the matrices acquisition costs and the time of the obtaining process. It is noteworthy that the technologies for obtaining inclusion complexes seem to be less complex and cheaper, on the other hand, the cost of the raw material ends up being higher than the polymeric matrices.

7. In vivo studies

Regarding the biological activities of inclusion complexes or solid dispersions of Albendazole, the literature brings several studies trying to increase the solubilization properties of the drug. Like other benzimidazoles, ABZ has pharmacological activities against several parasites affecting animals and humans, as well as a potent cytotoxic activity against cancer/tumor lines. We discuss here the impact that orally administered inclusion complexes or solid dispersions of ABZ have on certain pathological conditions in preclinical models.

Garcia et al. showed that the dissolution rate of ABZ directly impacts the efficacy/speed of its anthelmintic activity (22,57). When comparing the use of ABZ alone and the inclusion complex of ABZ:RM-β-CD plus chitosan-based microparticles in rats infected with *Trichinella spiralis*, the groups treated with the inclusion complex showed better results. The use of cyclodextrin seemed to offer an even more homogeneous response, as immediate drug release *versus* prolonged release from the chitosan polymer matrix makes ABZ bioavailability more constant and uniform.

Leonardi et al. (2009) and Barrera et al. (2010) tested, respectively, ABZ solid dispersions containing PEG 6000 and chitosan in rats infected with *Toxocara canis*. The experimental protocol was the same in both studies. Chitosan, despite being a solubilizing agent for hydrophobic molecules, also exerted a differential modulation in drug release. Both SD achieved better results face to ABZ alone, however, the polymeric structure of PEG 6000 demonstrates a more efficient solubilization and release, which directly impacts in pharmacological results (65,75).

The choice of the polymeric matrix that will constitute a SD really can impact on the biological response to be evaluated. Other study to use chitosan in SD can be seen in Abdellatif et al. (2018). In their experimental model, the researchers infected goats with *Haemonchus contortus* and divided them into groups that received ABZ alone, ABZ:Eudragit RS 100 micro-sponges, and no treatment. Fecal egg reduction was 100% in both ABZ:Eudragit MS and free ABZ treated groups 3 days post treatment, but that the solid dispersion presented a sustained release oral dosage form and achieved higher plasma levels and absorption extent without compromising both liver and kidney functions.

In the study conducted by PENSEL et al. (2015), 80 rats infected with *Echinococcus granulosus* were divided into two large groups in order to assess prophylactic activity and the clinical efficacy (administration of the substances after 4 months without complementary treatment) of ABZ and a DS ABZ:Polaxamer 188. In the prophylaxis group, a suspension of pure ABZ and DS ABZ:P188 had a similar chemotherapeutic effect, which was predictable since the effects of parasitic infection were not yet placed and even the insoluble drug would kill the worms, as is currently seen in the clinic, when using ABZ as a mass treatment to prevent several parasitologies (76).

In order to test the solubilizing properties of both cyclodextrins and polymers, PALOMARES-ALONSO et al., (2010) tested ABZ with β-CD:Pectin and β-CD:PVP multicomponent systems. The experimental model consisted of mice infected with *Taenia crassiceps*, which received (in distinct groups) these ABZ-systems or ABZ alone. Since they have different characteristics, PEC and PVP lead to different wettability and dispersibility of the drug, which changes its bioavailability. This situation was revealed in the measurement of parasite cysts at the end of treatment, where the multicomponent that contained the synergism of the β-CD and PVP properties was 20 times better than the other system, which had its result compared to the drug suspension (77).

Regarding the cytotoxic activity of ABZ, PRIOTTI et al. (2018) compared the efficacy of drug alone and the complexed drug with C-β-CD. The chemical modification in the structure of β-CD is considered very promising when compared to its natural form, since it has a superior solubility (78). At the end of the study, tumor growth speed in mice receiving ABZ:C-β-CD was lower than that observed in those receiving the drug in crystalline form, with impaired in aqueous dissolution. In 2012, EHTEDA and colleagues compared the effectiveness of an anticancer treatment based on an inclusion complex and solid dispersion (ABZ:HP-β-CD and ABZ:HPMC, respectively) (79). Knowing the properties of HPMC as a polymeric matrix, the researchers used a three-fold higher ABZ concentration in DS, and yet the best performance was attributed to ABZ complexed with modified cyclodextrin (HP-β-CD). The plasma concentration of ABZ from each system can be seen in Figure 12, where the longest survival (2x) was attributed to the one that achieved the highest bioavailability.

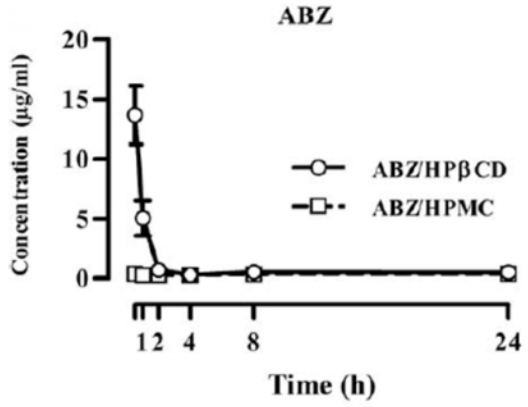

Figure 12. Mean plasma ABZ concentration from the ABZ/HP-β-CD inclusion complex and the ABZ/HPMC solid dispersion (from Ehteda et al., 2012)

Finally, the application of cyclodextrin systems and/or solid dispersions depends on the therapeutic applicability of Albendazole. In cases of acute infections or more emerging situations, cyclodextrins appear to offer the best pharmacological results for ABZ.

8. CONCLUSION:

Different pharmaceutical technology researchers have been continually studied techniques for improving drug solubility and thereby increasing the effectiveness of these drugs, without the expensive of developing new chemical entities. Albendazole, a well-established drug used for the treatment of a variety of parasitic infestations, may be expanded through new pharmaceutical forms for other therapeutic purposes if it has an improvement in its pharmaceutical properties. In the literature there are several alternatives to increase the solubility of ABZ, highlighting the use of release modulating excipients, such as cyclodextrins and polymeric matrices, each with its attributes. In addition to the physicochemical characterization, several *in vivo* studies show that the optimization of ABZ solubilization properties positively impact its oral bioavailability. Cyclodextrin-containing systems appear to provide faster and more homogeneous responses due to immediate release of the active ingredient. Most of the solid dispersions related in literature have a slower ABZ release profile, which makes their therapeutic performance inferior to the inclusion complexes. Pharmaceutical technology challenges include not only increasing the solubility of the drug itself, but also choosing the best excipients and the least costly production process, as Albendazole is a drug classically employed in the treatment of neglected diseases that reach underdeveloped countries. In addition, the product must improve drug efficiency and also ensure the patients safety.

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