Study of the Interaction of Albendazole with Benzoic Acid. I

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The aim of this study was to obtain a novel binary adduct of albendazole with benzoic acid, in order to improve some unfavorable physicochemical and powder characteristics of pharmaceutical active ingredient. The recrystallization of albendazole was performed using conventional evaporation technique. The characterization of the new form solid product was done using spectroscopic and thermal analyses.

Keywords: albendazole, benzoic acid, binary adduct, FTIR study, DSC study

Bioavailability of drugs depends on the specific physicochemical properties of molecules (water solubility,crystalline form) and also on their powder characteristics [1].

Water solubility is a very important property which dictates the amount of drug available for the therapeutic response. Low aqueous water solubility is responsible for poor dissolution of drug, absorption and distribution in the body fluids, therefore improvement in solubility and dissolution are the most challenging tasks for pharmaceutical industry [2].

Pharmaceutical substances may exist in many crystalline forms. Different crystalline forms have a great impact on the bioavailability due to their powder characteristics: particle shape, size, flow properties, packability and compressibility, plastic behavior and dilution potential. Non-favorable powder characteristics of poorly soluble drugs may be overcome by increasing the surface area, by decreasing the particle size and by optimizing the wetting characteristics of the surface [3].

Many strategies to improve the unfavorable physicochemical properties of active pharmaceutical ingredients (API) have been explored by scientists working in the pharmaceutical field. In recent years, the focus on the methods which may improve both the physico-chemical and mechanical properties of API has highlighted the importance of recrystallization [1].

Recrystallization in the presence of excipients favors the formation of a new physical form with improved physicochemical properties. Aqueous solubility, a very important characteristic of an API, influences the dissolution rate and consequently, the absorption by the gastrointestinal tract. Enhanced aqueous solubility translates in improved bioavailability and therapeutic response [4,5]. A low aqueous solubility is a serious drawback in drug therapy, reducing considerably the pharmaceutical alternatives for drug formulation and administration [3].

Albendazole (ABZ) is a benzimidazole derivative used orally for the treatment of systemic infections with *Giardia lamblia* and helminth infections (fig. 1). Infection with
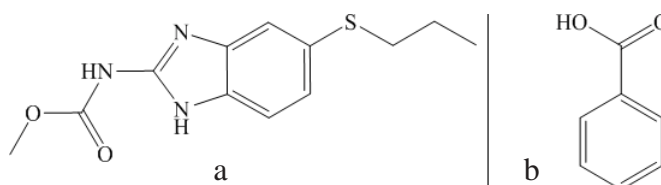

Fig.1. Structural formulas of ABZ (a) and BA (b)

Giardia lamblia is one of the most widespread waterborne illnesses, worldwide; also parasitic infections of the gallbladder may be due to *Giardia lamblia* and *Ascaris lumbricoides* infections [3,6]. Albendazole belongs to the class II of Biopharmaceutical Classification System, withlow aqueous solubilityand high permeability through the biological membranes[3,7].Due to its low aqueous solubility, ABZ is characterized by a poor bioavailability and erratic therapeutic response [3].These issues offer new challenges for developing new ABZ solid forms, with improved properties.Unfavorable properties of API may be improved by employing metastable states, salt forms or cocrystals [2]. It is worth mentioning that the physical state of API consists of single component (drug molecule only), solvates (more often hydrates), salts, cocrystals and molecular complexes, each of these states being characterized by the phenomenon of polymorphism [2].

The object of this study was to obtain a novel crystalline form in order to improve the physicochemical characteristics of ABZ by using benzoic acid. The reason of using benzoic acid was its capability to form hydrogen bonds with ABZ. For this purpose we prepared a new solid form and characterized it by means of spectroscopic and thermal methods.

Cocrystals are formed between a *host* (main) *molecule* and a *coformer, via* hydrogen bonds. In this case ABZ plays the role of N-heterocyclic hydrogen-bond acceptor and BA is the hydrogen-bond donor [2].

Spectroscopic and thermal methods are usefulanalysis to investigate crystal forms, taking into consideration that cocrystals may appear in metastable crystal form or in amorphous form. Spectroscopic methods, including infrared and UV-Vis spectroscopy, offer valuable
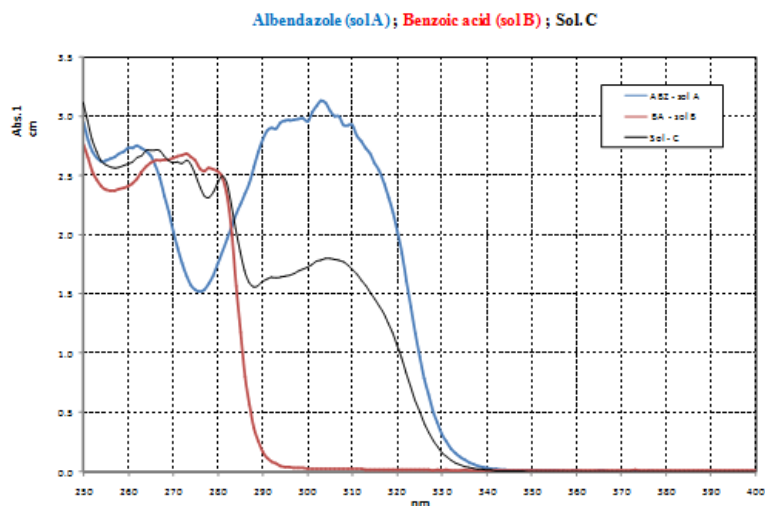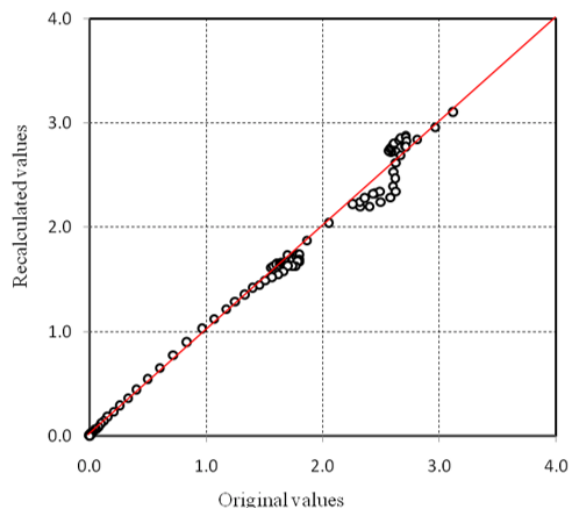
Fig.2. UV absorption spectra of solutions A, B and C

Fig. 3.Correlation between the true and recalculated absorption spectra of solution C

information to differentiate crystal forms. Thermal analysis is an important method for characterizing pharmaceuticals and other compounds, offering the possibility of identifying multiple crystalline forms and providing thermodynamic information even in early stages of research [2, 8-22].

Experimental part

Materials

Albendazole (M_w = 265 g mol^{-1}) was a gift from Biesterfeld Siemgluess and had pharmaceutical grade, benzoic acid (M_w = 122 g mol^{-1}) was obtained from Sigma-Aldrich and had purity >99%. Solvents were products of Reactivul Bucureºti. All chemicals were used without further purification.

Recrystallization of ABZ by solvent evaporation

Albendazole was recrystallized from acidified methanol (methanol:hydrochloric acid 99:2) in the presence of BA. The exactly calculated amounts of ABZ and BA, corresponding to the ABZ: BA molar ratios of 1:1 were dissolved separately in acidified methanol. The recrystallization was performed by heating the obtained solution, under continuously stirring. The stirring was continued during the evaporation process. True crystals were separated by filtration before complete evaporation of the solution, in order to remove any impurities and dried at room temperature for removal of the surface moister. The end point of the recrystallization process was considered when the least amount of solvent remained in the Erlenmeyer flask. Solvent residue was removed by vacuum oven (Pol-Eko) at 30 °C for 48 h.

UV-Vis analysis

The UV-Vis analysis was performed using a UNICAM UV/Vis, vision software V 3.40 (Unicam Limited, Cambridge, Anglia) spectrometer.

Preparation of samples

Solution A. 0.0122 g ABZ was diluted with methanol: hydrochloric acid – (99: 2), up to a final volume of 25 mL.
Solution B. 0.0640 g BA was diluted with methanol: hydrochloric acid – (99: 2) up to a final volume of 25 mL.
Solution C. 15 mL Solution A was mixed with 15 mL Solution B and 2 mL were taken and diluted at 10 mL with methanol: hydrochloric acid – (99: 2).
The Solution A, Solution B and Solution C were characterized by UV-Vis spectroscopy using a UV/Vis spectrometer.

FT-IR Analysis

ABZ, BA and ABZ-BA binary aduct were analyzed with a FTIR spectrophotometer model Vertex-70, product of Bruker. The spectrum measurements were performed using the KBr disk method in a spectral range of 4000-400 cm^{-1}. Each sample was dispersed separately with KBr andt he pellets were analyzed in order to obtain their FT-IR spectra.

Differential scanning calorimetry analysis

Samples of ABZ, BA and ABZ-BA crystals were characterized using a Mettler-Toledo DSC-1 instrument (Mettler-Toledo, Switzerland). Small amounts of samples (between 3.5 and 4.1 mg) were placed in aluminum crucibles separately and sealed with a pinhole –pierced cover. The analysis was performed in following condition: samples were heated between 25-300°C in an inert argon atmosphere under a 100 mL/min flow, with a heating rate β=5°C/min. A reference material (empty aluminum crucible with pierced cap) simultaneously underwent the same programmed time/temperature routine.

Results and discussions

Albendazole was recrystallized in the presence of BA by a conventional evaporation technique. A new solid form was obtained, with a slight red coloration, after drying.

UV-Vis analysis

The UV spectra for the three solutions (Solution A, solution B and Solution C) were recorded. The spectra are presented in figure 2.
In order to find out if there is any specific interaction between the individual components included in solution C, it was performed a regression analysis of spectroscopic data. If the spectrum of solution C may be conceived as a pondered sum of the spectra of solutions A and B, then may be concluded that there is not significant interaction of components A and B. A relevant deviation of the calculated spectrum of solution C from the measured spectrum, indicates some possible interaction between the components A and B. Figure 3. presents, in a graphic manner,the correlation of the aforementioned data. The value of correlation coefficient between the true and calculated spectra (R^2 = 0.9946) differs significantly from the theoretical value, especially in the spectral domain where the samples show elevated absorption, taking into account the precision of measurements of optical absorption values.
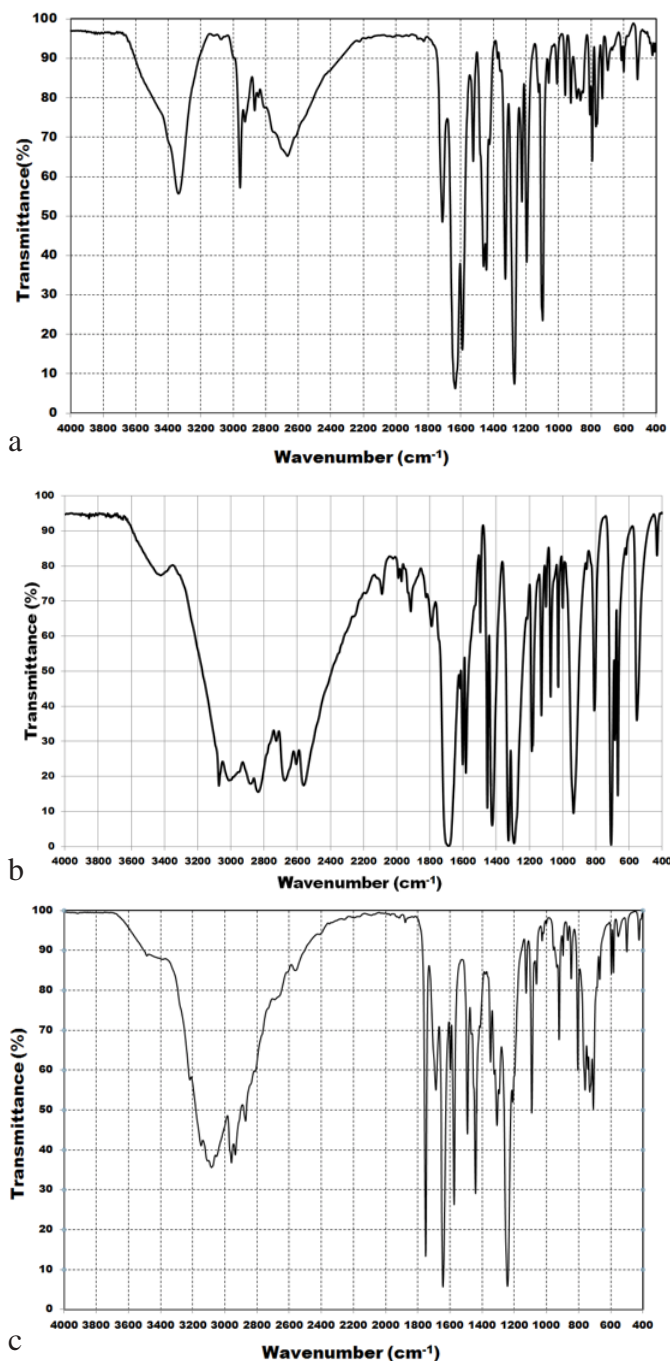
a

b

c

Fig.4. The FT-IR spectra of ABZ (a), BA (b) and ABZ-BA binary adduct(c) in the 4000-400 cm⁻¹spectral range

FT-IR Analysis

The FT-IR analysis may confirm the interaction between the components and the formation of a new solid form. The analysis affords the comparison of the IR spectra of the host molecule and the coformer, with the spectra of the new product. The modifications of the characteristic absorption bands of the host molecule and the coformer, may be indicative of the formation of a new solid form.

The FTIR spectrum of ABZ shows some characteristic bands due to the presence of different functional moieties in its structure. A broad band in the spectral range 3415-3190cm⁻¹, with peak at 3319 cm⁻¹, due to N-H stretching from amine groups,overimposed on the vibrations of N-H bond from carbamate moiety. The sharp weak bands due to stretching of alkane-type C-H bonds from the propyl moiety appear around 2956 and 2865 cm⁻¹. The C=O bond bending appear as sharp band at 1711 cm⁻¹.The benzoimidazolyl show two intense closed bands in the 1640-1590 cm⁻¹ spectral range, with peaks at 1630 and 1595 cm⁻¹. A characteristic band for the aromatic system is the band at 1523 cm⁻¹, but as well the dublet bands at 1441 and 1422 cm⁻¹. Other bands appear in the fingerprint region, below 950cm⁻¹, but are difficult to be asset to certain moieties, being represented by other vibrational bands, skeleton deformation or combination bands as mentioned in our previous paper [23].

FTIR spectrum of Benzoic acid reveals the presence of several characteristic bonds from the molecule. The intense broad band in the spectral region 3500-2500 cm⁻¹ reveals the stretching of the O-H group from the carboxyl moiety. By the aspect, the H-bonding between the molecules is noticed. The sharp bands superimposed over the O-H band are due to the stretching of C-H bonds in the aromatic ring, appearing around 3080-3030 cm⁻¹. The weak band at 3400 cm⁻¹ is an overtone of the stretching vibration of C=O band.

The C=O band is also clearly revealed as the most intense band in the spectrum, appearing at 1689 cm⁻¹. Aromatic C-C in plane vibrations appear in the 1600-1400 cm⁻¹ spectral range, and multiple peaks were noticed at 1602, 1583, 1496, 1454 and 1427 cm⁻¹.C-H in-plane deformations and monosubstitution of the benzene ring is confirmed by the bands in the 1130-1000 cm⁻¹ spectral range, with peaks at 1128, 1101, 1072 and 1027 cm⁻¹. The out of plane deformation of OH bond is observed as broad intense band at 937 cm⁻¹, while the C-H out-of-plane deformations and the benzene ring substitution is noticed

Table 1
THE SPECIFIC ABZ, BA AND BINARY ADDUCT BANDS

| Sample	Analysis of FTIR spectral regions (cm⁻¹)			
	4000-2500	1800-1400	1400-1000	1000-400
ABZ	3319; 2956; 2923; 2865; 2657	1711; 1630; 1618; 1595; 1523; 1441; 1422;	1325; 1272; 1224; 1194; 1096; 1058; 1007	957; 922; 869; 861; 791; 767; 729; 694; 597; 512; 419
BA	3458; 3074; 3024; 2894; 2848; 2732; 2648; 2611; 2569	1791; 1689; 1602; 1583; 1496; 1454; 1427;	1326; 1296; 1186; 1128; 1101; 1072; 1027; 1000	937; 810; 709; 684; 667 ; 553; 432
ABZ-BA binary adduct	3222; 3166; 3155; 3091; 3064; 2956; 2939; 2875;	1751; 1680; 1645; 1598; 1573; 1490; 1440;	1328; 1307; 1244; 1126; 1091; 1064; 1027; 1012	919; 912; 869; 846; 804; 759; 727; 707; 680; 595; 582; 555; 501; 424
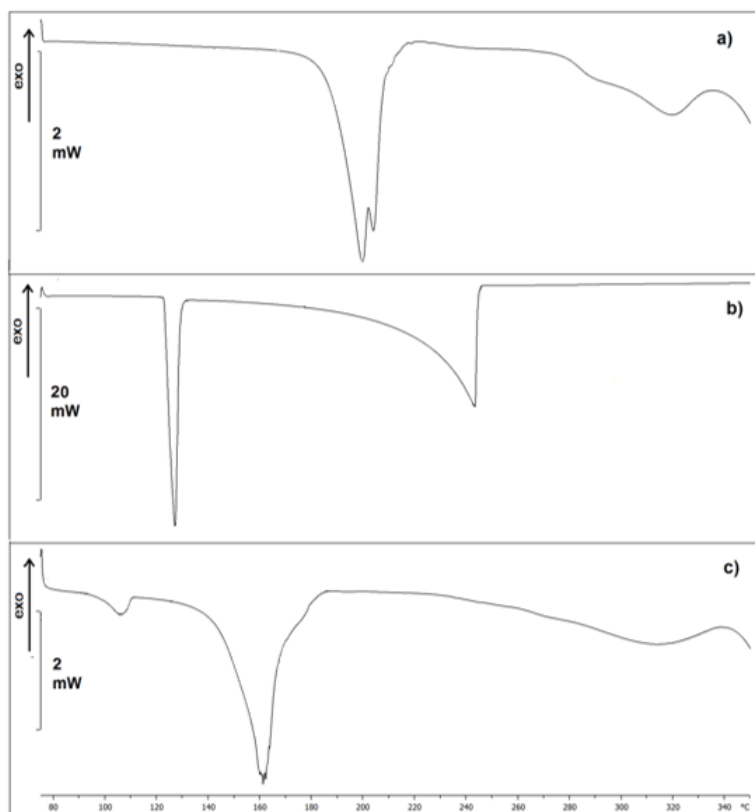
Fig.5.The DSC curves of ABZ, BA and ABZ-BA binary adduct

Sample	Thermal events revealed by the DSC curve			Thermal effect (J/g)
	T_{onset} (°C)	T_{peak} (°C)	T_{offset}(°C)	
ABZ	170	198; 203	215	127.4
BA	122	126	133	269.98
	173	249	251	866.82
ABZ-BA binary adduct	90	110	115	8.90
	127	162	190	182.88

in the 770-690 cm⁻¹ spectral range, with peaks at 709, 684 and 667 cm⁻¹ as strong bands.

The FTIR spectrum of the binary adduct shows some considerable differences from the ones drawn up for starting materials (fig.4 and table 1). These bands confirm the solid-state modification of ABZ and BA, suggesting the formation of a binary adduct. The proton transfer from BA to ABZ is confirmed by the most noticeable modification of the carbonyl band from BA, by downshifting from 1689 cm⁻¹ in BA to 1680 cm⁻¹ in ABZ-BA binary adduct. Other observed modification occur in the 3600-2200 cm⁻¹ spectral range, the broadening of the band suggest a modification of H-bonding in binary adduct vs. BA. All the characteristic bands are presented in table 1, in comparison for the binary adduct with precursors.

Differential scanning calorimetry analysis

Differential scanning calorimetry is a very useful tool to analyze the interaction in solid state between an API (ABZ) and coformer (BA). The API and coformer DSC curves are compared, in terms of shape, melting point and thermal flux with the curve recorded for the new solid form (binary

adduct). The DSC curves of ABZ, BA and ABZ-BA binary adduct are presented in figure 5.

The DSC curve for ABZ is characterized by the presence of two sharp endothermic peaks at 198 °C and at 203 °C, as previously reported in our paper [23]. The overlapping of these two endothermal events is not associated with degradation of ABZ or with the presence of impurities, but with a clear proof of existence of enantiomeric compounds or polymorphic forms [24]. The thermal effect associated with these two overlapped processes is endothermal in nature (127.4 J/g). Since of overlapping of thermal events, a correct estimation for the enthalpy of fusion can't be achieved. In table 2, the DSC data obtained for binary mixtures is presented. Other endothermal overlapping processes are observed at higher temperatures (260-350 °C).

The DSC curve of BA showed two endothermal events. First event starts at 122 °C and reaches the peak at 126 °C and represents the melting of benzoic acid. After melting, benzoic acid is stable in liquid form up to 173 °C when another endothermal event occurs, reaching a maximum at 249 °C. This last endothermal event is represented by the liquid-gas transition (boiling). The considerable higher

thermal effect associated with melting and evaporation of BA is due to the H-bondings which are strong intermolecular forces that require high energy input for their breakdown. The thermal effect for evaporation is even greater than the one required for melting, since in liquid state, H-bonding is still present, while in gaseous phase, molecules no longer interact.

The DSC curve of binary adduct showed two endothermic events, revealed by the appearance of a first broad endothermic peak at 110 °C (probably due to the formation of a eutectic mixture) and by the appearance of the second more sharp endothermic peak at 162 °C. The distinct and unique curve obtained for the binary adduct is an indicative of existence of a new solid form. Table 2 presents the data obtained for the three DSC curves.

Conclusions

Present work focuses on obtaining a binary adduct of Albendazole, which is the active pharmaceutical ingredient, with benzoic acid. The aim of this paper was to report the preparation and preliminary characterization of this new solid form (binary adduct). The new obtained solid form was characterized by spectral and DSC analyses. On the basis of the obtained results, we may assume the formation of a new solid form, very probably a cocrystal. This work is a starting point in order to study new methods of obtaining new crystalline forms of ABZ with improved physicochemical and mechanical properties.

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