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Preformulation Study on Enhancing the Solubility of Albendazole

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For low aqueous solubility drugs, the challenge of making solid dispersions is in choosing the amount of carrier that would increase the aqueous solubility while keeping the overall oral dosage size small. Solubility parameters have been used to predict the solubility of drug in a carrier which in turn determines the extent of solubility in an aqueous medium. Solubility parameters alone are not enough and other parameters such as crystallinity index can also be used to improve the drug solubility during formulation. This study used solubility parameters and crystallinity index to select carriers which increased the aqueous solubility of albendazole (ABZ). Four polymers, Polyethylene Glycol 8000 (PEG), hydroxypropyl methyl cellulose (HPMC), polyvinyl pyrrollidine (PVP K90) and carboxymethyl cellulose (CMC), were used individually as carriers in various ratios with ABZ and formulated as solid dispersions using the solvent evaporation method. The results obtained showed that both solubility parameters and crystallinity index when used together indicated that the polymers and ABZ were miscible in each other. The solid dispersions formulated further showed increased ABZ solubility which was evident from reduced peak obtained from FT-IR spectra while dissolution tests confirmed increased dissolution of ABZ solid dispersions as compared to ABZ alone. PVP K90: ABZ solid dispersions showed the highest increase in dissolution rate as compared to solid dispersions of ABZ with HPMC and CMC.

Key words: Solid dispersion, solubility parameter, Crystallinity Index.

INTRODUCTION

According to World Health Organization, worm infestations affect more than two billion people especially those who live in squalid conditions with low income and poor sanitation [1]. In African nations including Kenya, worm infestations are endemic. These populations require inexpensive drugs to decrease the disease burden. These drugs should also be easily administered by non-medical personnel such as teachers and social workers to ensure constant reach to a wide proportion of the population. This is easily possible when these drugs are formulated as oral dosage forms such as tablets or capsules. Such oral dosage forms must disintegrate and undergo dissolution in order to be absorbed through the gastrointestinal tract. The challenge facing many formulators is that many newly discovered drugs belong to BCS class II or BCS Class IV that have poor aqueous solubility in common [2].

Albendazole (ABZ) is one of the drugs used to treat worm infestations and belongs to the benzimidazole group of antihelminthics. ABZ is classified as BCS class II active pharmaceutical ingredient due to its poor water solubility but unlimited intestinal permeability [2].

ABZ tablets have erratic bioavailability attributed to slow dissolution in biological fluids. It is therefore very crucial to improve ABZ solubility and enhance dissolution in order to increase absorption and have a predictable bioavailability [3]. For BCS class II drugs, release is a critical phase for drug bioavailability. Enhancing the drug release profile improves bioavailability and reduces side effects.

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A number of techniques have been used to enhance solubility of practically water insoluble active pharmaceutical ingredients (API). One of these approaches is to make solid dispersions. Solid dispersions refer to molecular mixtures (in amorphous or crystalline particles) of hydrophobic drugs in hydrophilic carriers which themselves can be crystalline or amorphous. The drug release profiles is driven by the polymer properties [4].Tablets made by solid dispersion approaches have higher drug dissolution profiles compared to regular tablets [5,6]. The approach of solid dispersions greatly increases drug dissolution, absorption and consequent bioavailability of BCS Class II drugs. Solid dispersions are generally prepared using two methods namely, the melting (fusion) process and the solvent evaporation process [4].

Solubility parameters (SP) have been used to predict interactions between materials especially between API and polymeric carriers in solid dispersions. Solubility parameter (δ) can be defined as the square root of cohesive energy density (cohesive energy per unit volume) [7]. SPs have also been used to describe many physico-chemical properties of materials including solubility, melting point, and incompatibility. Drugs and carriers (polymers) that have similar solubility parameters, where differences between the parameters are less than 7 $MPa^{0.5}$, are predicted to have good miscibility whereas differences that are greater than $10MPa^{0.5}$ are anticipated to have immiscibility issues [8]. The solubility parameters are calculated for drugs and polymers from the chemical structure using the group contribution as described by Hoftyzer and Van Krevelen [9].

Crystallinity index (CI) is defined as the volume fraction of crystallinity of one phase in a given sample and represents a measure of average crystal size, perfection and ordering in a sample [10,11]. Being a quantitative measure, crystallinity can aid the determination of solubility of an active pharmaceutical ingredient in a solid dispersion.

An amorphous drug has higher apparent solubility than its crystalline form [12]. In making solid dispersions, the aim of the formulator is to decrease crystallinity (amorphization) of the active pharmaceutical ingredient (API) in order to increase its apparent solubility in water during dissolution process in the gastrointestinal fluids with the goal of increasing the bioavailability especially BCS Class II drugs. The extent of the decrease in crystallinity of an API during the formulation and subsequent solubility and miscibility can be determined by measurement of crystallinity Index in the solid dispersions. From literature search, measurement of CI has been done on human tooth enamel and synthetic hydroxyapatites [10], cellulose [13] and rock quartzite crystals [14]. CI measurements however, have not been applied on pharmaceutical formulations especially during formulation development. Methods for calculating CI include X-Ray Powder Diffraction (XRPD), Fourier Transform Infrared Spectroscopy (FTIR) and Raman Spectroscopy [11]. The CI is measured from analysis of their spectra.

Solid dispersions made using solvent evaporation technique were used to do a pre-formulation study that is anticipated to lead to formulation of albendazole tablets that will have superior drug release profiles and hence increased bioavailability. This study was aimed at doing a pre-formulation study in order to enhance the solubility of ABZ in various carriers for the purpose of developing a formulation that would result in an ABZ tablet that has superior drug release profile at minimal cost and also would greatly benefit the world's poor. Solubility parameters were used as a tool to choose possible suitable carriers. Crystallinity Index (CI) was calculated from analysis of FTIR spectra to evaluate the degree to which crystallinity was decreased (and conversely solubility) in the formulations.

MATERIALS AND METHODS

Materials

Albendazole powder, sodium carboxyl methyl cellulose hydroxyl propyl methyl cellulose, all provided by ELYS Industries, (NBI, Kenya), Polyvinyl pyrrollidine (PVP K90), donated by

BASF, (Ludwigshafen, Germany), while Polyethylene glycol 8000 (PEG 8000) was donated Universal Corporation, (NBI, Kenya). All excipients were pharmaceutical grade while reagents and solvents were analytical grade.

Equipments

Fourier Transform Infrared Spectrophotometer (Shimadzu IR prestige 2.1, Tokyo, Japan), Oven drier (Memmert, Germany), Weighing balance (Sartorius, England), Electronic light microscope, UV spectrophotometer (Shimadzu UV-1800, operating on IR Solution software Ver. 1.3, Tokyo, Japan), Hot plate.

Calculation of drug carrier solubility parameters

The solubility parameters of ABZ shown in table 1 were calculated from its chemical structure (figure 1) using the group contribution method as described by Hoftyzer and Van Krevelen [9].

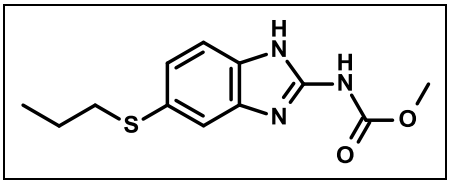

Figure 1. Chemical structure of Albendazole.

Table1: Calculation of Solubility Parameters of ABZ

Functional Groups	**No.**	**F_{di}**	**F^2_{pi}**	**E_{hi}**	**$\sum^z V/cm^3mol^{-1}$**
$-CH_3$	2	840	0	0	67
$-CH_2-$	2	540	-	-	32.2
–S-	1	440	--	-	12.0
Phenylene		1270	110	-	52.4
–NH-	2	320	420	6200	9
–N=	1	-	-	-	5
–COO	1	390	490	7000	18
C=	1	70	0	0	5.5
ring	1	190			16
∑		4060	1020	13200	217.1
		4060/217.1	√1020/217.1	√(13200/217.1)	
		18.70	0.15	√60.8	
∑		20.3			

Preparation of Solid Dispersions of CMC, HPMC, PVP K90 and PEG 8000.

The method used to prepare solid dispersions is as described previously [15]. Briefly, drug to carrier ratios of 1:2.5, 1:5 and 1:10 (40%, 20% and 10% of Polymer by weight) for each of the carriers were chosen (CMC, HPMC, PVP K90, and PEG 8000). The amount of the drug and carrier was weighed so as to result in 6 grams of each of the batches. The solid dispersions was prepared by the solvent evaporation method. Briefly the weighed polymer was dissolved in a minimum amount of solvent in a 200ml beaker by heating to 80oC to give it an appropriate consistency and viscosity. The drug was first wetted in a small amount of ethanol before being mixed with the dissolved polymer while stirring. The solvent was then evaporated using the hot plate method till a small amount of solvent remained before being dried in an oven for 24 hours at 80°C to control the evaporation rate. The resultant solid mixture was pulverized to diminish the particle size and screened using mesh number 60. The ground solid dispersions were then transferred into a labeled container. Samples of the different solid dispersions were analyzed by UV spectroscopy to determine the percentage of dissolved ABZ before being subjected to Infrared spectroscopy.

Ultraviolet (UV) analysis.

Preparation of a calibration curve.

The calibration curve for analyzing albendazole was prepared as had been done previously by Tella et al. [16]. Briefly, 10 mg of ABZ was transferred to a 100 ml volumetric flask and dissolved with 2 ml of acidified methanol. This was made up to the volume using 0.1N NaOH as the diluent. The resulting stock solution was diluted to yield a final concentration of 3µg/ml, 5µg/ml, 10µg/ml and 15µg/ml. A calibration curve of the absorbance difference between 308nm and 350nm (y-axis) vs concentrations (x-axis) was plotted.

Determination of dissolved ABZ in the solid dispersions

An equivalent of 25mg of each batch of solid dispersion was dissolved in 100ml of 0.1N HCl by stirring at 38^{o}C for 20 minutes followed by filtration using a filter paper. Subsequently, 4 ml of the filtrate was diluted to 100ml in a volumetric flask with 0.1 N NaOH as the diluent. The absorbances at 350nm and 308nm were recorded and the differences calculated. The concentrations were then read from the calibration curve.

Fourier Transform Infrared Spectroscopy

FTIR spectroscopy was done as previously described by Saikia *et al.* [16]. Briefly, an Infra-red spectrum of the drug, Carboxymethyl cellulose, Hydroxypropyl methylcellulose, Polyvinyl pyrrolidone K90 and Polyethylene glycol 8000 carriers, the physical mixtures of the carriers and ABZ (1:1 ratios) and the solid dispersions was obtained and recorded on FTIR spectrophotometer in the range of 4000- 400cm^{-1} as potassium bromide discs.

Calculation of Crystallinity Index (CI)

Crystallinity Index is calculated by the following formula:

CI = a/b (the ratio of peak intensity at around 1630cm^{-1} (a) to peak intensity at around 1450cm^{-1} (b) which were determined by baseline method) as shown in figure 2 [14,17].

The CI is inversely proportional to crystallinity. It therefore follows that when CI is minimum the sample shows high levels of crystallinity and if CI is maximum, the sample is considered to show low levels of crystallinity (i.e. high level of amorphization) [17].

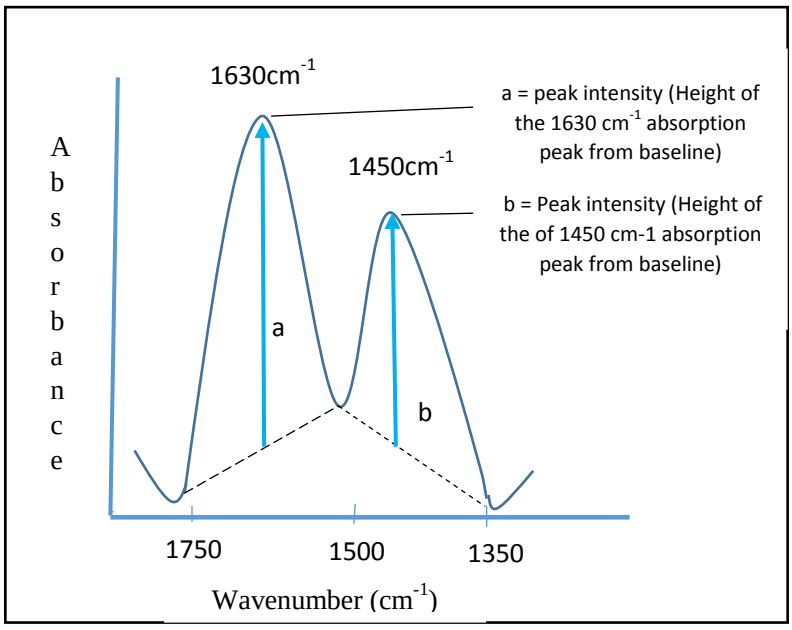

Figure 2: Calculation of Crystallinity Index in relation to changes in absorption peaks 1630/1450 cm^{-1} infrared spectrum.

RESULTS

Solubility Parameters

The solubility parameters of the ABZ and polymer carriers are shown in table 2. The solubility parameters range from 19.8 for PEG to 28.7 for HPMC. The solubility parameter for ABZ was calculated to be 20.3. The differences between the solubility parameter of ABZ and carriers range from 0.5 (PEG) to 8.4 (HPMC).

Table 2: Solubility parameters of ABZ and the polymers.

API/Carrier polymer	Solubility parameter ($MPa^{1/2}$)
ABZ	20.3 (calculated)
PEG	19.8 [18]
CMC	24.35 [19]
PVP K90	24.3 [20]
HPMC	28.7 [21]

ABZ: Albendazole, PEG: Polyethylene glycol 8000 CMC: Sodium carboxy methyl cellulose PVP: Polyvinyl pyrrolidine K90, HPMC: Hydroxy propyl methyl cellulose

FTIR Crystallinity Index (CI) Results.

Table 3: Calculated Crystallinity Index of the solid dispersions

	Crystallinity Index			
ABZ to carrier ratio	PEG	HPMC	PVP	CMC
1:2.5	2.94	4.8	4.4	4.4
1:5	2.73	3.17	7.33	3.17
1: 10	2.24	4.17	2.54	4.44

Table 4: Percentage of dissolved ABZ over 20 minutes

ABZ: carrier	PEG	HPMC	PVP	CMC
1:2.5	48.1 ±1.2	70.4 ±1.05	63.2 ± 1.55	32.5 ± 1.35
1:5	71.9 ± 0.7	65.2 ± 0.85	80.7 ± 0.5	26.8 ± 1.55
1:10	66.4 ±1.45	69.5 ± 0.8	81.0 ± 0.75	32.1 ± 2.35

n=3, ± standard deviation (SD)

DISCUSSION

The crystallinity index of PEG was lower than all the other polymers as shown in table 3 and figure 2. The lower CI shows there is higher crystallinity in the PEG solid dispersions which partly accounts for the lower dissolved drug in the other solid dispersions. From the calculated solubility parameters in table 2, PEG, having a solubility parameter of 19.8 would be expected to dissolve the ABZ (SP of 20.3) more readily because of the close values of their calculated SPs (i.e. difference is 0.5). However as shown in table 3 and 4 the dissolved ABZ is lower in CMC solid dispersions than that of PVP and HPMC. The SP parameter of HPMC is 28.7 (table 2) giving a difference of 8.4 when compared to SP of ABZ. This would have predicted lower dissolved values of ABZ since good predicted solubility envisages a difference of less than 7 $MPa^{0.5}$ [9]. Nonetheless the solubility of ABZ in HPMC (Table 4) was quite high, only lower than solubility of ABZ in PVP. The CI of HPMC solid dispersions were also higher than that of PEG solid dispersions which was confirmed by the higher solubility of the API in HPMC (tables 3 and 4).

The SP of PVP K90 was 24.3 which is practically the same as that of CMC. The difference between the polymer and drug SP was 4. PVP solid dispersion as shown in table 3 had one of the highest CI at 7.33. The PVP solid dispersions also had the highest percentage of dissolved drug at 81% in PVP polymer, an indication of the extent of its amorphousness.

The CMC polymer had the same SP as PVP giving the same difference of 4 (table 2). However, despite the fact that the CI of CMC solid dispersions were high (table 3), the percentage solubility of ABZ in CMC was the lowest among the four polymers at about 30%.

CONCLUSION

From the above observations, HPMC, PVP and PEG solid dispersions with ABZ in various ratios should be investigated further since they evidently increased the solubility of ABZ. It is suggested therefore that techniques such as

Raman Spectroscopy, X-Ray Powder Diffractometry and Differential Scanning Calorimetry should be used to confirm crystallinity indices and comparisons be made. The use of CI calculated by Tangent basement method in pre-formulation studies can be adopted as another tool to test the suitability, miscibility and compatibility between polymers and API for formulating solid dispersions. Most drugs that are being discovered fall under the BCS class II and solid dispersions not only improve their aqueous solubility, but also enhance dissolution thus leading to increased bioavailability.

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