Development and Characterization of Mucoadhesive Nanoparticles of Albendazole

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

School of Pharmacy
BRAC University
September 2022

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "Development and Characterization of Mucoadhesive Nanoparticles of Albendazole" submitted by Ifti Ara Islam (18346015) of Summer, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on September 2022.

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Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

Albendazole is broad spectrum anthelmintic agent with poor aqueous solubility. It is usually available in the form of chewable tablets and often require administration in large doses to overcome the reduced therapeutic efficacy issue due to low solubility. High drug loading often leads to patient incompliance and side effects. The aim of this study was to develop a mucoadhesive nanoparticle formulation of Albendazole to improve its aqueous solubility as well as to prolong its duration of therapeutic activity at the target site. To prepare the mucoadhesive nanoparticles, hydrophilic polymers such as chitosan, sodium alginate and HPMC K4M were used. Dissolution study of the formulation was performed followed by its characterization. The dissolution profile showed 5.5 fold (81%) increase in the amount of drug released compared to crystalline Albendazole, indicating an increase in solubility. Furthermore, the physicochemical characterization demonstrated nano-size distribution of particles, enhanced surface area, advent of amorphous state and negligible interaction between Albendazole and polymers.

Keywords: Albendazole; Dissolution; Mucoadhesive; Nanoparticles; Polymers

Dedication

To my parents

Acknowledgement

I would like to convey my gratitude to my supervisor, Tanisha Tabassum Sayka Khan (Lecturer, School of Pharmacy, BRAC University), for allowing me to conduct research and work under her supervision. Without her support, I would probably fall short of finishing the project. She has provided me with valuable advice that has aided me in this research. Additionally, I would like to express my gratefulness to Professor Dr. Eva Rahman Kabir (Professor and Dean, School of Pharmacy, BRAC University). Throughout the course of the project, she was there to support and inspire me. Her insightful suggestions made the research much easier to conduct and resulted in solid findings. Moreover, I want to express my sincere gratitude to Dr. Shimul Halder (Associate Professor, Department of Pharmaceutical Technology, University of Dhaka) for his guidance and support. His commitment to this line of work is certainly remarkable, and having him instruct us with all the information was a wonderful experience. Also, I would like to express my special thanks of gratitude to Namara Mariam Chowdhury (Lecturer, School of Pharmacy BRAC University) and Professor Dr. Hasina Yasmin (Assistant Dean and Program Director, School of Pharmacy, BRAC University) for constantly supporting me in completing my project. I am also thankful to all the lab officers of the School of Pharmacy, BRAC University who have given their immense support and time whenever I needed help with any technical instruments. At last, I would like thank all my faculty members for their valuable guidance and support throughout this journey.

Table of Contents

List of Tables

List of Figures

List of Acronyms

ABZ	Albendazole
MANP	Mucoadhesive Nanoparticle
GIT	Gastrointestinal Tract
DLS	Dynamic Light Scattering
DSC	Dynamic Scanning Calorimetry
SEM	Scanning Electron Microscopy
FTIR	Fourier Transform Infrared Spectroscopy
XRD	X-ray Powder Diffraction

Chapter 1 Introduction

1.1 Background

The population of Bangladesh is highly prone to helminthic infestations which affects the physical growth and cognitive development. Albendazole (ABZ), a BCS Class II anthelmintic drug, has demonstrated wide pharmacological activities against different worm related infestations. In addition, the Bangladesh government has enlisted ABZ in the essential medicine category. However, despite the attractive health benefits of ABZ, its clinical applications are limited by its low aqueous solubility (Halder et al., 2021). ABZ is a locally acting drug which kills the parasites in the intestine. The drug needs to dissolve properly for it to reach the target site in the correct amount. However, because of its low aqueous solubility it needs to administered at a high dose. High dose leads to the formulation of large tablets, which is inconvenient for the patients to administer. An increase in the aqueous solubility of ABZ will reduce the dose of the drug and hence, reduce the size of the tablets which will improve patient compliance. Since dose is lowered, the safety profile of ABZ will also enhance. Therefore, this study aimed to reduce the particle size of ABZ to a nanometer range as reduction in particle size will increase the surface area and hence, solubility. A mucoadhesive formulation of ABZ was also developed to prolong the duration of therapeutic action in the intestine where the parasites resides, thereby further increasing therapeutic efficacy of the drug.

1.2 Albendazole

Albendazole is a broad spectrum benzimidazole antiparasitic agent which has vermicidal, ovicidal and larvicidal activity. ABZ is used in the treatment of echinococcosis, hydatid cysts, neurocysticercosis which is caused by nematodes and cestodes. It is classified as a BCS Class II drug, with high permeability but low aqueous solubility. It has an aqueous solubility of 0.2 µg/mL at 25 °C, molecular weight of 265.33 g/mol and melting point of 208-210℃. ABZ works by blocking the uptake of glucose by the parasites leading to deprivation of energy required to survive. Moreover, it inhibits the polymerization of beta tubulin into microtubules (Schulz et al., 2019). The chemical structure of Albendazole has been depicted in Figure 1.

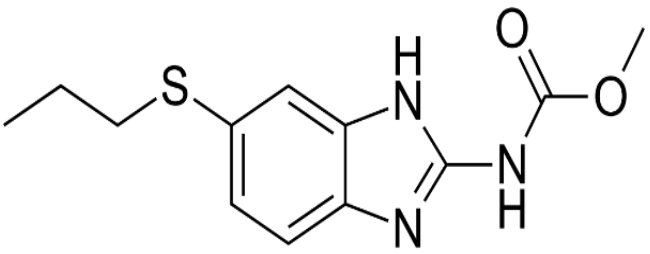

Figure 1: Chemical structure of ABZ.

1.3 Biopharmaceutical Classification System

The Biopharmaceutics Classification System (BCS) is a predictive approach designed to relate certain physicochemical characteristics of drug substances to the *in vivo* bioavailability. The basis for this classification scheme is the fundamental parameters which define the absorption of oral drugs. The classes are as follows:

BCS Class I: High solubility and high permeability drugs

BCS Class II: Low solubility and high permeability drugs

BCS Class III: High solubility and low permeability drugs

BCS Class IV: Low solubility and low permeability drugs

Based on this classification scheme, standards are set for the methods developed to correlate *in vitro* drug dissolution testing with the *in vivo* process. This classification scheme further provides the basis for establishing *in vitro-in vivo* correlations (Shah & Amidon, 2014).

1.4 Solubility Enhancement Techniques

1.4.1 Physical Modifications

a. Particle size reduction:

The solubility of a drug is intrinsically connected to particle size. The smaller the particle size, the larger the surface area which helps to increase solubility by interacting with solvent. Hence, reduction in particle size increases the solubility and provides an enlarged surface area. Also, a thinner diffusion layer dramatically increases the dissolution rate and improves the bioavailability (Sandri et al., 2014). The particle size can be reduced by the following methods-

• **Micronization:** This is a common technique where the particle size is reduced by ball mills, jet mills and high-pressure. As the particle size is reduced, surface area is increased which help to improve the dissolution rate

• **Homogenization:** This technique is used to make nanosuspension which helps to increase the surface area and improves the rate of dissolution. This method involves passing a suspension of drug and surfactant through homogenizer while it is under high pressure which help to reduce the particle size (Savjani et al., 2012).

b. Solid dispersion:

Solid dispersion plays an important role by increasing the dissolution rate and solubility of the drugs. Solid dispersion is performed by various techniques-

• **Hot-melt method:** This method is suitable for the drug which are thermostable. This method is prepared by the physical mixture of a drug and water soluble carrier which are heated directly till the two melts. After that, mixture is quickly placed on an ice bath. Then the solid mass is crushed and compressed into a solid dosage form (Zhang et al., 2018).

• **Solvent evaporation method:** In this method, the drug and hydrophilic carrier are dissolved in an organic solvent to produce a solution of the highly lipophilic compounds. The greatest advantage of this method is thermal decomposition of drugs or carriers at high temperature (Chen et al., 2020).

• **Hot-melt extrusion:** The process uses intense pressure and heat to mix all the ingredients and allow simultaneous melting and homogenization (Patil et al., 2016).

• **Co-crystallization:** This method is important in increasing the solubility of poorly soluble drugs and also improving other physicochemical features of the drug. It is a multi-component crystal in which all the components are usually solidified at room temperature into a crystal lattice along with API (Thayyil et al., 2020).

1.4.2 Chemical Modifications

• **Microemulsion:** This technique can be used to enhance the solubility of poorly soluble drugs as it solubilizes the drugs in oil phase thus increasing their dissolution rate.

• **Salt formation:** It is the most common and effective method to increase the dissolution rate of acidic and basic drugs by forming salt (Sareen et al., 2012).

1.4.3 Miscellaneous Methods

• **Cosolvency:** The solubility of poorly water soluble drugs can be improved by the addition of water miscible solvent known as cosolvent in which the drug has good solubility. This technique is simple to produce and it works by reducing interfacial tension between aqueous solvent and hydrophobic solute. Most commonly used cosolvents are known as methanol, ethanol and water (Jouyban, 2008)

• **Supercritical fluid:** Another cutting-edge method for improving the solubility of the drug is the formation of Supercritical fluids (SCF). SCF are fluids with temperatures and pressures above their critical points, which enable them to exhibit both liquid and gaseous properties. It reduces the particle size greatly as the SCF technique's flexibility and precision enable the micronization of the particles (Sarfraz et al., 2017).

1.5 Mucoadhesive Drug Delivery System

Mucoadhesive dosage forms have been designed to enhance the drug residency time by facilitating the attachment of the drug with the mucosal surface and prolonging the duration of action at the target site. Mucoadhesive formulation is prepared by using mucoadhesive polymers of various concentration and these polymers adhere to the mucosal surface until the release of the drug. When mucoadhesive polymers comes in contact with the mucosal surface, the polymers undergoes wetting and swelling increasing the interactions of the polymers and the mucus layer (Alawdi & Solanki, 2021).

1.6 Physicochemical Characterization

1.6.1 Dynamic Light Scattering Method

Dynamic light scattering (DLS) method is used for characterizing the particle size and distribution. In this technique, the sample is exposed to a monochromatic wave of light and the detector detects the signal (Stetefeld et al., 2016).

1.6.2 Scanning Electron Microscopy

The morphology of the nanoparticles or microparticles can be visualized by an electron microscope with high resolution power. Scanning electron microscopy (SEM) remains

distinct in its ability to examine the dimensional topography and distribution of exposed features. The ultimate resolution achieved is controlled by optimizing specimen preparation and instrumental parameters (Giuvărăşteanu, 2007).

1.6.3 Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) determine the molar heat capacity of materials related to temperature. DSC profiles offer details about the thermal stability of a compound to a certain extent. A differential scanning calorimeter is used to detect the melting temperature and the energy needed to dismantle the connections that support the structure. DSC has variety
of benefits such as it is a very quick and simple method to assess the thermal stability (Durowoju et al., 2017).

1.6.4 X-ray Powder Diffraction

X-ray power diffraction (XRPD) is used to monitor the changes in the structure. XRPD is highly sensitive to the small changes occurring in the structure which helps to identify the structural similarities and changes, especially the particle size. XRPD patterns can be used to report polymorphism, changes in the peak intensity and peak splitting that help to identify the crystal structures of the drug (Fayter et al., 2020).

1.6.5 Fourier Transform Infrared Spectroscopy

Fourier Transform Infrared (FTIR) spectroscopy is a well-known analytical method with a wide range of uses. Chemists have typically used it to describe a material's molecular composition. When a molecule is exposed to infrared light, it absorbs some of the incident radiation at a particular energy or frequency and goes through a process known as vibrational excitation, which causes it to move from the ground state to a state with increased vibrational energy. A certain chemical or functional group's specific pattern of infrared absorption results in distinctive bands in their FTIR spectra. Early changes in the biochemical composition and conformational shape can be detected by FTIR also it provides additional structural insights (Wang & Wang, 2021).

1.7 Rationale of the Study

Solubility plays a major role in the bioavailability of drugs as it is a measure of how effectively and efficiently the drug reaches its site of action. However, poor solubility has become a massive problem as the main challenge with the nature of oral dosage form lies in their low bioavailability (Sareen et al., 2012). ABZ is a poorly water soluble compound which limits its clinical application. It is necessary for ABZ to have high water solubility as without dissolution in water drug cannot be taken to the site of action in correct amount. As ABZ is a locally acting drug and it needs to go to the intestine to kill the parasites, if ABZ dissolves in the mouth aqueous fluid, it can go to the target site in its dissolved form. However, if ABZ remain undissolved, patients cannot receive the correct amount of drug required to kill the parasites. Moreover, ABZ is usually given in high dose because of its low aqueous solubility. High dose leads to formulation of larger tablets, which is inconvenient for the patients to administer as they need to keep the tablet in their mouth for a long time. So, increasing aqueous solubility of ABZ will reduce the dose of the drug and hence, reduce the size of the drug which will increase patient compliance. Since dose is lowered, safety with this drug increases as high dose may have side effects. Reducing the particle size of ABZ to a nanometer range can increase surface area and hence, solubility of the drug. Moreover, a mucoadhesive formulation can increase the drug residency time drug in the intestine resulting in optimum therapeutic efficacy. Furthermore, due to the retention of drug in intestinal mucosal surface for a long time, the drug can avoid first pass metabolism.

1.8 Objectives of the study

The experiment was conducted with a set of specific objectives. These objectives are as follows:

1. To improve the aqueous solubility of ABZ
2. To increase the residence time of ABZ in its target site of action

Chapter 2 Methodology

2.1 Materials

The materials used for the study included Albendazole, chitosan, HPMC K4M, and sodium alginate. Pure Albendazole was provided by the Beximco Pharmaceuticals Ltd. The polymers chitosan and sodium alginate, and HPMC K4M were collected from Nanoshel, India and Evonik Bangladesh Limited, respectively. The methanol solvent used was of analytical grade.

2.2 Preparation of Standard Curve of Albendazole

10 mg of standard ABZ was taken in a test tube. 100 ml of methanol solvent was used to prepare a stock solution of 100 µg/ml (0.1 mg/ml). The stock solution was diluted to a concentration of 1 µg/ml, 2.5 µg/ml, 5 µg/ml, 10 µg/ml and 20 µg/ml. The absorbance of the diluted samples was measured at 281 nm using a UV spectrophotometer. Water was used as the blank. A graph of absorbance versus concentration was plotted.

2.3 Preparation of Mucoadhesive Nanoparticles

The polymers used to prepare the mucoadhesive nanoparticles of ABZ (MANP-ABZ) were chitosan, HPMC K4M and sodium-alginate (Figure 2). 10 mg equivalent weight of ABZ was mixed with the polymers in the ratio indicated in the Table 1. The mixture was further mixed with small amount of ethanol followed by drying in an oven at 40 ˚C. The dried powder mixture was later grinded on a mortar.

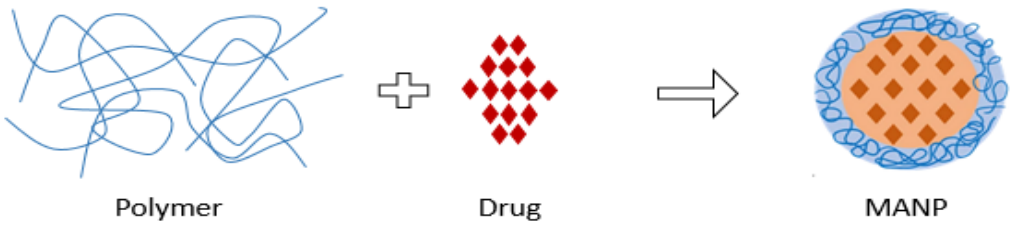

Figure 2: Preparation of MANP-ABZ

Table 1: Composition of mucoadhesive nanoparticles

Ingredients	Amount (w/w %)
Albendazole	30
Chitosan	30
HPMC K4M	25
Sodium-alginate	15

2.4 Dissolution Study

900 ml of water was used as the medium for the dissolution test. The USP type II dissolution apparatus was used. The mucoadhesive ABZ sample of 10 mg equivalent weight was added to dissolution vessels containing water as the medium. The samples were allowed to undergo dissolution for a period of 2 hours at 37℃ and 50 rpm. Samples were withdrawn from the vessels at 15 minutes, 30 minutes, 45 minutes, 60 minutes and 120 minutes. Dilution of the samples were performed. The absorbance of the samples were recorded at a wavelength of 281 nm by using UV spectrophotometer (Lee et al., 2013). Subsequently the percentage of drug released were calculated by using the following formula:

$$\text{Amount of drug released} = x\ \mu g/ml \times \text{Dilution factor} \times 900\ ml / 1000$$

$$\%\ \text{drug released} = (\text{Amount of drug released}/\text{Dose of drug}) \times 100$$

2.5 Physicochemical Characterization

2.5.1 Particle Size Analysis using DLS Method

To determine the mean hydrodynamic particle size, the dynamic light scattering technique was performed, using a Zetasizer Ultra (MALVERN, Worcestershire, UK). The concentration of ABZ was kept 10 µg/ml and the sample was suspended in Milli-Q. The measurement was performed at 25℃ and at a measurement angle of 90°. The analysis was performed in triplicates.

2.5.2 Particle Surface Morphology Analysis using SEM

The surface morphology of crystalline ABZ and MANP-ABZ were observed by SEM technique using Miniscope TM3030 (Hitachi, Tokyo, Japan). The crystalline ABZ and MANP-ABZ samples were placed on an aluminium sample holder and fixed using double sided carbon tape. A magnetron sputtering device, MSP-1S (Vaccum Device, Ibaraki, Japan) was used to coat over the samples with platinum.

2.5.3 Particle Crystallinity Study using DSC

Thermal analysis of crystalline ABZ and MANP-ABZ were done using a DSC Q1000 (TA Instruments, New Castle, DE, USA) at a heating rate of 5℃/min under purging nitrogen gas (50 ml/min). The ABZ samples were placed and sealed in aluminium sample pans. Accurately weighed (ca. 3 mg) samples were subjected to the DSC thermal analysis. Indium was used to calibrate the system as a reference standard (8-10 mg, 99.999% pure), onset at 156.6℃.

2.5.5 Particle Crystallinity Study using XRPD

The x-ray powder diffraction was performed using a Mini Flex II (Rigaku, Tokyo, Japan) with Cu Kα radiation generated at 40 mA and 35 kV. The instrument was operated at a scanning speed of 4°/min and the ABZ samples were scanned over a range of 2θ angles from 10° to 35° with a step size of 0.2°.

2.5.4 Drug-Polymer Interaction Study using FTIR Spectroscopy

To evaluate the compatibility and any potential interactions between ABZ and polymers, FT-IR analysis was conducted. By using one-channel $LiTaO_3$ pyroelectric detector IR spectra were recorded and individually samples were placed on the sample platform of the instrument (Perkin Elmer, L160000A, USA), and Spectrum 10 software was used to capture the sample's IR spectra in the 4000-700 cm-1 region. The samples were stored on a pre-assembled sealed rectangular liquid cell with windows made of potassium bromide and has a 0.5 mm path length. During the analysis, the baseline was adjusted and standardized for each sample. The acquired spectra were also smoothed using a 9-point smoothing algorithm.

Chapter 3 Results and Discussion

3.1 Preparation of Standard Curve of Albendazole

A linear calibration curve was obtained from the plot of absorbance against concentration graph with a correlation coefficient (R^2) of 0.9957 (Figure 3).

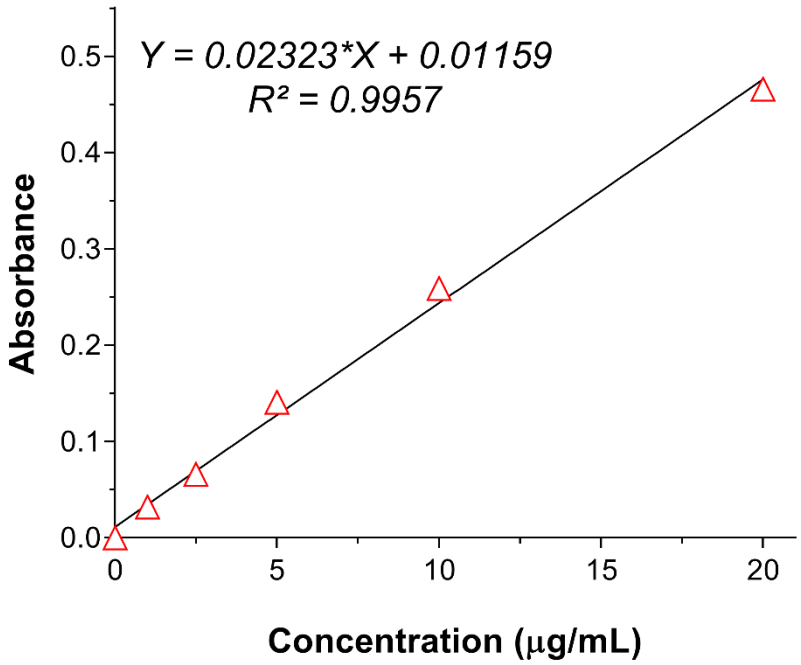

Figure 3: Standard curve for Albendazole

3.2 Dissolution Study

The dissolution rate of the formulation was compared with that of crystalline ABZ. The mucoadhesive ABZ showed quick onset of drug release compared to crystalline ABZ (Figure 4). The amount of drug released was found to be enhanced by 5.5 times (81%), indicating an increase in solubility of the drug.

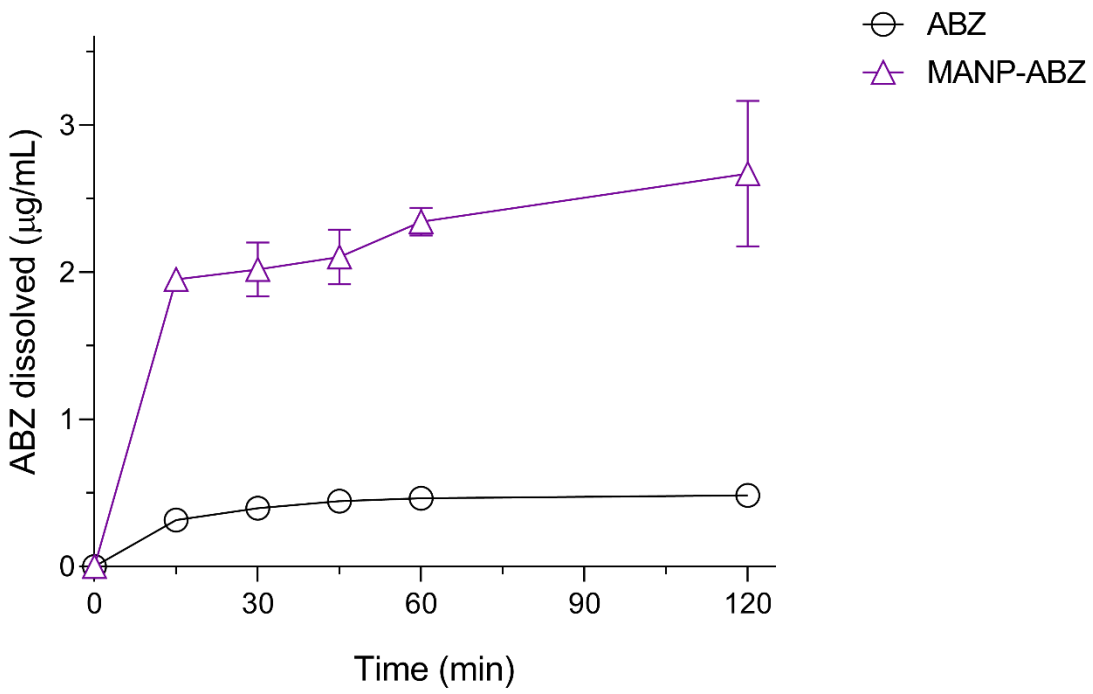

Figure 4: *In vitro* dissolution properties of ABZ samples.

3.3 Physicochemical Characterization

3.3.1 Particle Size Analysis using DLS Method

Particle size was analysed by DLS method where mucoadhesive nanoparticles of ABZ showed formation of the fine droplets with nano-size distribution when introduced in aqueous media. Maximum number of particles are in the size range between 100-1000 nm with a mean diameter of 267.6 nm. Poly-dispersity (PDI) is 0.346 which indicates the monodisperse nature of the polymers uniform particle size distribution (Figure 5).

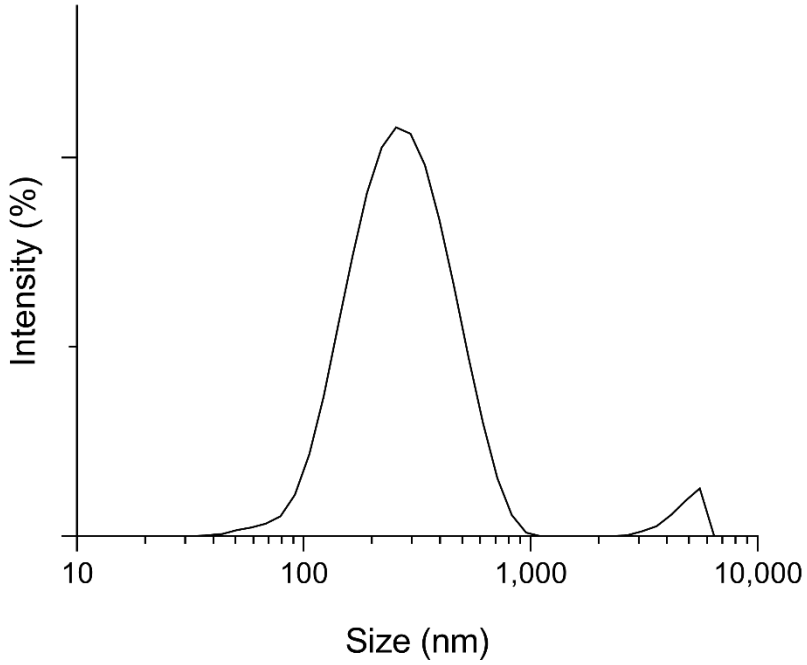

Figure 5: Particle size distribution of MNAP-ABZ sample in water

3.3.2 Particle Surface Morphology Analysis using SEM

The SEM images in Figure 6 provided information about the crystallinity state and surface area of the crystalline ABZ and MANP-ABZ from the analysis of the surface morphology. Surface morphology showed reduction in crystallinity of mucoadhesive nanoparticles and enhanced surface area.

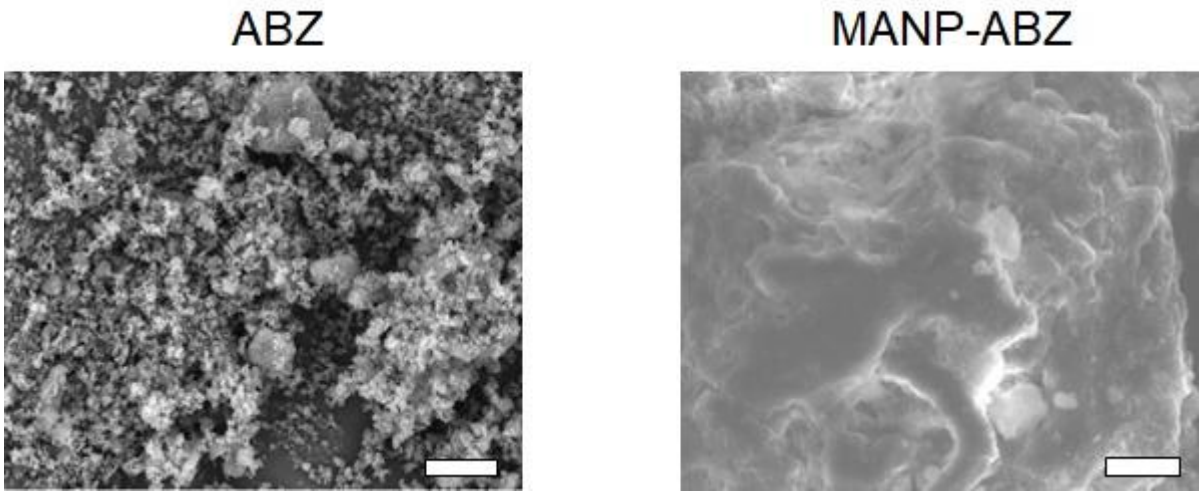

Figure 6: Scanning electron microscopy images of ABZ samples in water

3.3.3 Particle Crystallinity Study using DSC

In the DSC thermal analysis of crystalline ABZ, two sharp endothermic peaks around 220°C and 230°C corresponds to the melting point of ABZ. From the thermogram of MANP-ABZ, the characteristic melting endothermic peak for ABZ is absent (Figure 7). The absence of the peak is indicative that ABZ was dissolved in the polymers. DSC study also indicated that mucoadhesive nanoparticles of ABZ exhibited an amorphous state during preparation.

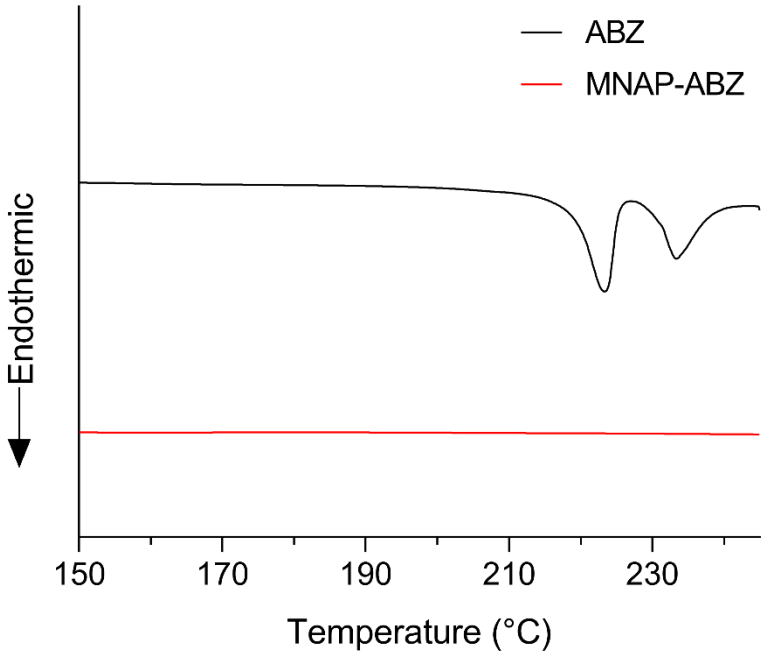

Figure 7: Differential scanning calorimetry of ABZ and MANP-ABZ

3.3.4 Particle Crystallinity Study using XRPD

XRPD analysis was performed to observe the change in the crystalline state of the formulation. In the XRPD analysis, crystalline ABZ showed a series of sharp peaks with high intensity. It is due to the long periodicity and regular distribution of molecules across dimension, which caused the characteristic high intensity narrow peaks at 2θ angles from 10° to 35°. According to XRPD patterns of MANP-ABZ, there was a reduction in the crystallinity of the particles indicating the existence of amorphous form of the particles. An amorphous form of the particles leads to enhanced solubility (Figure 8).

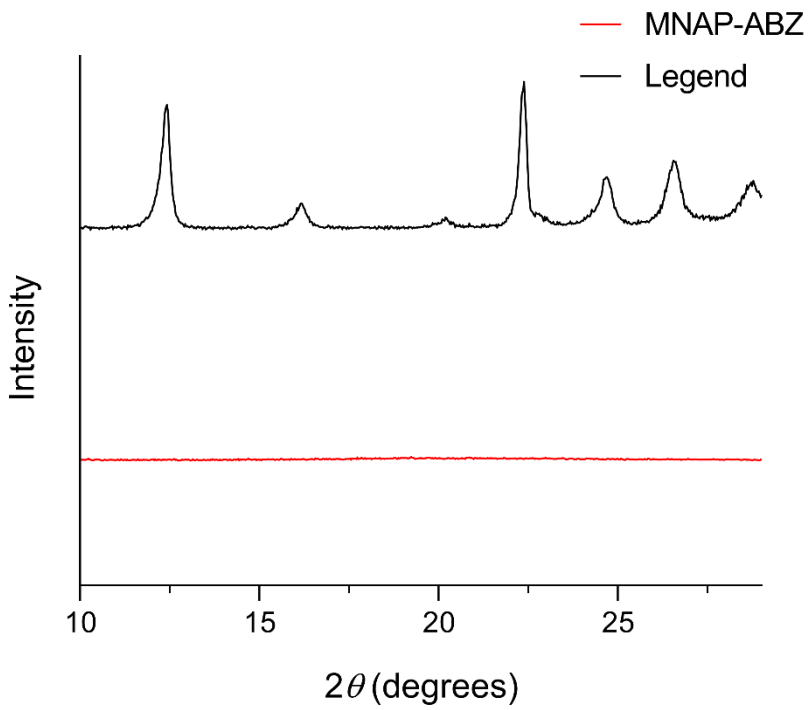

Figure 8: Crystallinity analysis of ABZ and MANP-ABZ

3.3.5 Drug-Polymer Interaction Study using FTIR Spectroscopy

FTIR was used to determine the interaction of ABZ with polymers and it showed that there were negligible interaction of Albendazole with the polymers as there was no change in the characteristic vibrational frequency of the functional groups present in the drug and polymers (Figure 9).

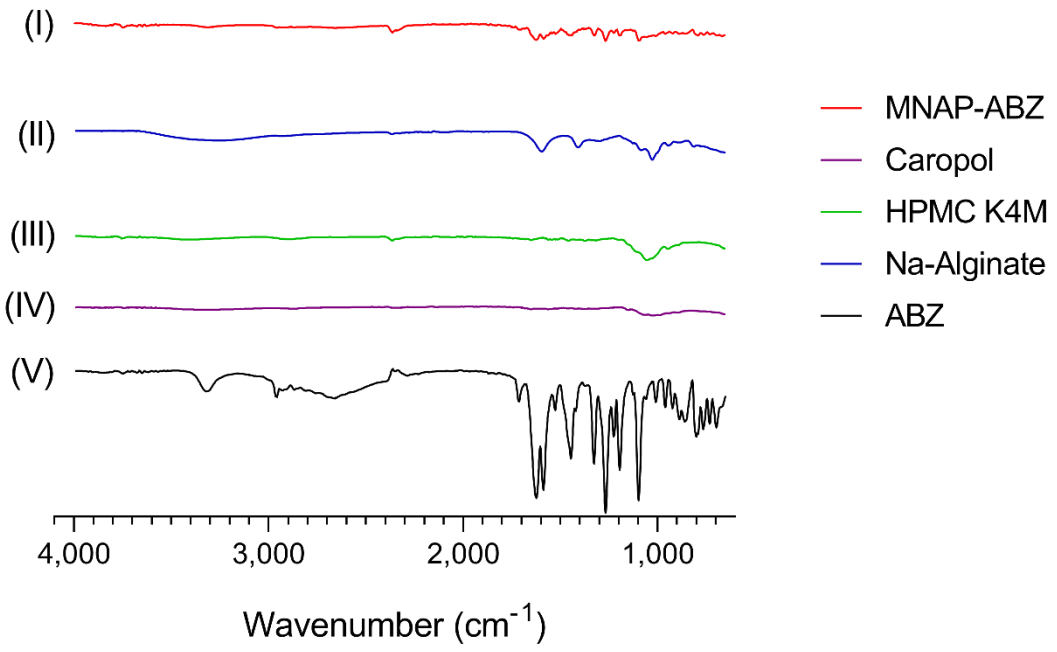

Figure 9: FTIR analysis to determine ABZ-polymer compatibility

Chapter 4

4.1 Conclusion

One of the major obstacles to attaining optimum therapeutic efficacy of ABZ is its low aqueous solubility. As a result, patients administer large single dose of the drug which leads to poor patient compliance. To overcome this issue, a mucoadhesive formulation of ABZ was developed. The formulation showed a significant increase in dissolution rate of the drug and the result of the dissolution study was supported by the information obtained from the physicochemical characterization of the formulation on particles size, surface morphology and crystallinity. By using this formulation, crystallinity was lowered significantly and an amorphous state of the drug was achieved. The DSC and XRPD studies showed that changes in drug crystallinity played the most important role in dissolution enhancement of ABZ. Moreover, the DLS study showed a reduction in particle size and hence, increased surface area. To conclude, development of mucoadhesive nanoparticle formulation could be a promising strategy to improve the biopharmaceutical behavior of ABZ.

4.1 Future direction

- In future, in vivo test will be conducted
- Mucoadhesive nanoparticles can be formulated using different ratios of polymers used in this study.
- Mucoadhesive nanoparticles can be formulated using combinations of new polymers at various ratios.

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