Development of Albendazole Nanodispersion for the Effective Treatment of Helminthiasis

Subadharshini
Department of Biomedical Sciences
Alagappa University, Karaikudi, Tamil Nadu, India

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Abstract
Albendazole is a drug used to treat parasitic worm infections. ALB results in the tegument and intestinal cells of the worm undergoing degenerative changes, which ultimately lead the parasite to become immobile and die. The purpose of the study was to improve the solubility and effectiveness of an ALB-loaded solid nano dispersion for the effective treatment of helminthiasis.ALBFs were generated by a solvent evaporation procedure involving PVPK30 and carbopol, which may improve the stability of controlled drug release rates. The newly found ALBFs are more soluble than pure albendazole and have a better bioavailability. ALBFs allow for the optimization of therapeutic efficacy while lowering potential side effects and modulating enzymatic resistance, degradation, and drug release rate. Thus, the created ALBFs demonstrated successful helminthiasis treatment with lower dose frequency.

Keywords: Albendazole, PVPK30, Carbopol, Nanodispersion, Helminthiasis

Introduction

vway of administering the drug is oral drug delivery system [2, 3] due to the increased stability, reduced bulk, precise dosing, and simplicity of production. A medication that dissolves more slowly in the gastrointestinal fluid than it absorbs is said to be weakly water soluble [4]. Oral bioavailability issues arise from drugs with limited water solubility because they dissolve slowly [5, 6].

A drug called albendazole is used to treat a number of infestations caused by parasitic worms. By reducing the worm's ability to produce energy, albendazole produces degenerative changes in it that ultimately result in the parasite's immobilization and death. The medication formulation of albendazole is chosen as a paradigm for nanodispersion. This medication has a high permeability and low solubility. Thus, improving the solubility is difficult.

Nanodispersion is a dispersed system that disperses medication in a continuous media using nanoparticles, which are typically smaller than 1000 nm in size. Drugs' bioavailability can be effectively increased by using nano dispersions to speed up the rate of dissolution [2].

Povidone, also known as poly vinyl pyrrolidone (PVP), is an amorphous, hygroscopic synthetic polymer made up of linear 1-vinyl-2-pyrrolidinone groups. PVP is used as a binder in concentration ranges of 0.5% to 5% w/w. It is commonly identified by its viscosity

in aqueous solution in comparison to water and is represented by a K value between 10 and 120. Spray-dried povidones with K-values < 30 are produced in the form of spheres. PVPK30, a white, crystalline PVP homopolymer that is cross-linked, functions as a water a white crystalline cross linked homopolymer of PVP acts as a water solubilizing carrier enhancing the bioavailability.

Simple-to-use liquid thickeners called carbopol polymers are used to stabilize, suspend, and regulate the release of pharmaceutical medicines in a
ddition to thickening and improving flow characteristics. Their characteristics in aqueous solutions are influenced by pH and temperature. The gel is more liquid at low pH values. The goal of the research is to make albendazole more soluble and to create a nanodispersion that is a more effective medication against parasites [7, 8].

Materials and Methods

The source of albendazole was Madras Pharmaceutical Pvt. Ltd. in Chennai. From the lab, we removed Poly Vinyl Pyrrolidone K30, carbopol ethanol, methanol, Glacial Acetic Acid, and milliQ water. The generated ALB loaded solid nanodispersion's morphology, size, charge, behavior during in vitro release, anthelmintic activity, and stability investigations were all further examined.

Fourier Transform Infrared Spectroscopy (FTIR)

Using an FT-IR spectrometer, the compatibility of ALB with PVPK30, carbopol, and ALBF formulations was examined. The samples were combined individually with IR-grade potassium bromide (KBr) and compressed into pellets using a hydraulic press that applied 5.5 metric tons of pressure. The produced pellets were scanned in an FT-IR spectrometer across a wave number range of 4000 – 400 cm-1 [11].

Preparation of Albendazole Nanodispersion

While ALB was separately solubilized in a 1:1 ratio of methanol and acetic acid and added dropwise to the polymer solution that was held in a magnetic stirrer for six hours, the weighed amounts of PVPK30 and carbopol polymer were dissolved in ethanol. The resulting dispersion was dried at 60°C for the entire night in a vacuum oven. Several experiments were conducted with differing concentrations of carbopol (50-100 mg) and PVPK30 (50-100 mg) to gather and characterize the outcomes.

Particle Size and Zeta Potential Analysis

The zeta sizer (Malvern S4700 PCS system, Malvern, UK) was used to measure the particle size. After weighing 20 mg of ALB formulations and dissolving them in 200 µl of milliQ water, 200 µl of ALBFs were distributed in 2 ml of milliQ water.

Quantification of ALBFs using UV Spectrometer

After sonicating the ALBFs for 15 minutes in a 1:1 methanol to acetic acid ratio, 200µl of the sonicated solution was added to 2ml of buffer solution (phosphate buffer 7.4). At 291 nm, further absorption was recorded.

Transmission Electron Microscope

JEM-2100 (JEOL- Japan) transmission electron microscopy (TEM) was used to examine the unique morphology of ALBFs. A drop of the diluted ALBFs was applied to a copper grid that had been coated with carbon to create the TEM sample, which was then observed. [10]

In-Vitro Release Study

A dialysis bag containing 20 mg of ALBFs (equal to 20 mg of ALB) was used. After that, it is knotted and put in 100 milliliters of phosphate buffer (pH 7.4). Release samples (1 ml) were taken out and replaced after 30 minutes to up to 7 hours. The amount of ALBFs released into the buffer solution was measured at 291 nm using a UV Spectrophotometer.

Stability Study

We examined the ALBFs' stability under various storage scenarios. For thirty days, the optimized formulations were kept at both room temperature and refrigerator conditions. In addition, measurements of the zeta potential and particle size were made for ALBFs.

Anthelmintic Activity

40mg of ALBFs, blank formulation, Albendazole pure drug are dissolved in distilled water kept in a petri dish. 1 ml of Take the albendazole suspension and dilute it with 5 milliliters of purified water. A control of 5 milliliters of pure water was used.

Result and Discussion

The results of FTIR Spectrometric analysis indicated the compatibility nature of ALB, PVPK30; Carbopol. The created mixture exhibited the shape of solid wax, with particle sizes varying from 558.5 ± 212.2 nm to 934 ± 81.2 nm. Additionally, the surface charge varied between 0.061 ± 0.024 mV and 3.23 ± 0.665 Mv.

FTIR Spectroscopic Analysis

Albendazole's distinctive absorption bands were seen at 3329.70 cm-1, 1524.89 cm-1, and 1445 cm-1, respectively. These bands indicated the stretching of the N-H aliphatic main anime, the N-O nitro compound, and the bending of the C-H alkane. The bands of albendazole formulation that were observed were 3424.93 cm-1, 1711.14 cm-1, and 1634.82 cm-1, respectively. These bands indicated the stretching of the N-H primary anime, the C=O carboxylic acid, and the alkene. In a similar vein, carbopol showed peaks at 1712.18 cm-1 and 1245.28 cm-1, which indicated that the COOH carboxylic group was stretching. Following this, bands of polyvinylpyrrolidone measuring 1651.43 cm-1 and 1225.41 cm-1 of the carbonyl group's C-N were observed.

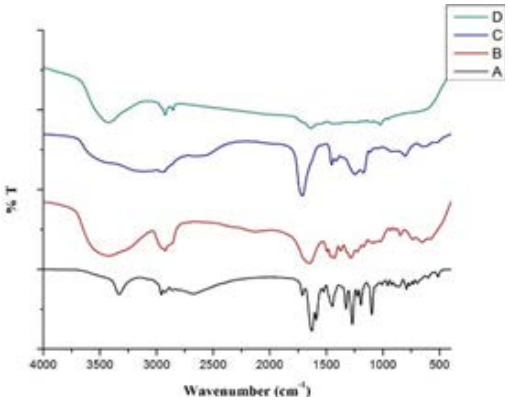


Figure 1 The FTIR Spectra of Created ALBFs, PVPK30, Carbopol, and ALB Demonstrate that there is No Significant Interaction between ALB and the Excipients used, Indicating the Compatibility of These Compounds

Development of ALBFs

Albendazole nanodispersion was prepared by solvent evaporation technique. Carbopol and PVP is used in the preparation of albendazole nanodispersion. PVP may act as a steric barrier and this may elicit smaller particles with uniform size distribution and enhance the solubility. Besides, carbopol is to stabilize, suspend and control the release of pharmaceutical products [9].

By varying, the PVP K30 concentration (50mg to 100mg) three different trials were performed solid dispersion is formed by dispersing a certain fraction of the drug in the matrix. Herein albendazole nanodispersion may get released as solid wax particle when the nanodispersion was exposed to an aqueous medium. The dissolution rate and bioavailability of poorly water–soluble drugs may get improved due to enhanced surface area. To improve the bioavailability of albendazole by increasing solubility through nanodispersion method.

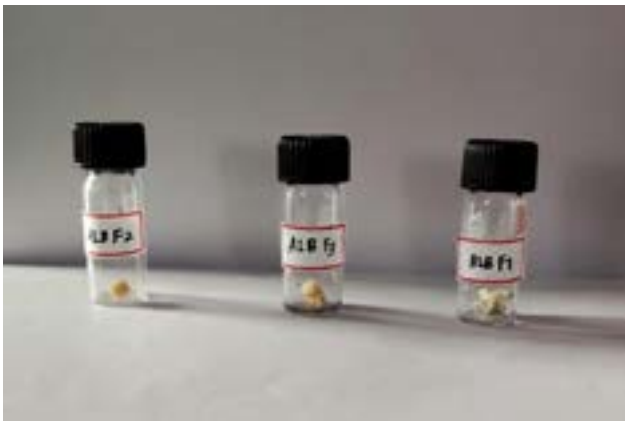
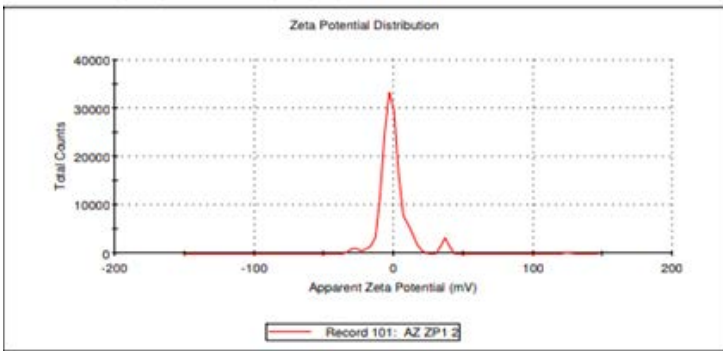


Figure 2 Albendazole Nanodispersion Formulations ALBF1, ALBF2, ALBF3

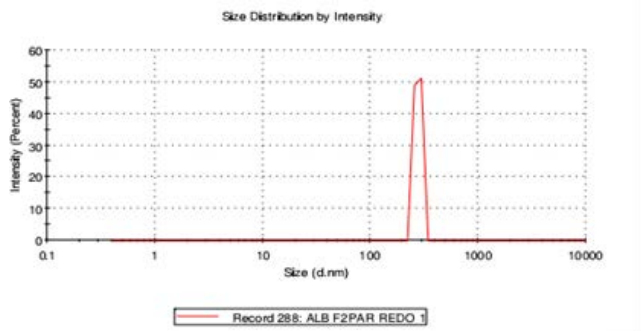
Table 1 Formulation Layout and Invitro Characterization Data (Particle Size, Zeta Potential, Quantification) of ALBFs

Formulation	Particle Size (nm)	PDI	Zeta Potential (Mv)	Quantification (mg)
F1	750± 32.0	0.549±0.105	0.061±0.024	15.56±0.126
F2	934± 81.2	0.578±0.069	36.5±92.26	10.41±0.076
F3	558.5± 212.2	0.635±0.078	3.23±0.665	34.98± 7.650

A) Zeta Potential Report



B) Particle Size Report



For each loaded nanodispersion (ALBFs1, ALBFs2, and ALBFs3), the particle size and zeta potential ranged from (0.549±0.105 nm, 0.158±0.467 nm, 0.666±0.192 nm), while the zetapotential ranged from (0.061±0.024 mV, 0.446±0.187 mV, 3.23±0.665 mV). These results suggest that the particle size of ALBFs increases and decreases. Similar results demonstrate that there is variation in the mean particle size of nanodispersion in the narrow span the 168–283 nm range. The mean size of all formulations was found to be less than 500 nm, making them appropriate for the delivery of pharmaceutical drugs.

Quantification of ALBFs

ALBFs underwent a 1:1 treatment with methanol and acetic acid, followed by a further dilution with phosphate buffer. The drug concentration in each formulation was measured using a UV spectrophotometer, and the results were as follows: ALBFs1 -10.41 ± 0.076, ALBFs2- 15.56 ± 0.126, and ALBFs3 -34.9±7.65.

TEM Analysis

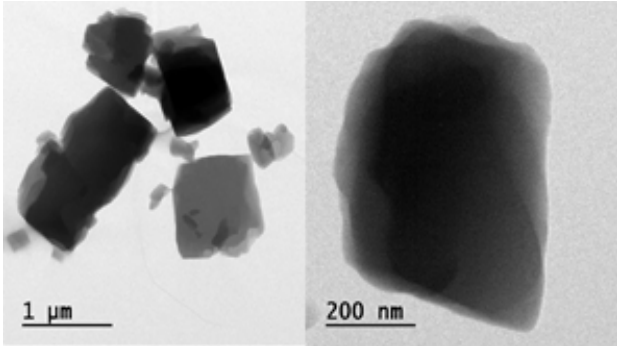


Figure 3 Transmission Electron Microscopy Image of ALBF3

The transmission electron micrograph of ALBFs revealed that the particles are spherically shaped with a solid core structure.

Invitro Release Study

The release rate of ALBFs in vitro increases dramatically. Compared to the end release rate, the beginning of the release exhibits a lower amount of drug release. The whole 7-hour release of ALBFs demonstrates PVPK30's capacity for regulated drug release. The formulation's stability

is preserved by carbopol. In contrast to a different formulation, ALBFs1 obtains effective control release when comparing the three formulations. 40% of the medication is thus released in 7 hours.

The rate of drug release from PEG liposomes was lower than that of conventional liposomes, whereas the rate of release from free drug was highest. It appears that the drug release rate from the liposomes may drop in its values when PEG is added. Drugs that are poorly soluble in water are supplemented with non-aqueous solvents. Liposomes encapsulated in albendazole, using a release medium consisting of 25% (V/V) methanol and 7% (V\V) PEG [12].

The ability of albendazole guar gum matrix tablets to withstand the enzymatic activity of a colonic centrifuge operated at 2500 rpm for 15 minutes was tested. The filtrate was then subjected to HPLC analysis after the supernatant liquid was filtered through a 0.4 µm membrane filter. The protocol for the initial in vitro drug release tests was followed exactly. buffered saline containing 4% w/v of caccal contents of rats given metronidazole/tininidazole and guar gum dispersion treatments. At the end of the 24-hour trial, the formulation broke down into two to three pieces in the presence of the caecal contents of rats given guar gum treatment, releasing roughly 44% of the albendazole. [15]. Using the dialysis method, the invitro release behaviors of both drug-loaded solid lipid nanoparticles (SLNs) and free pharmaceuticals were investigated. Within the first 30 minutes, 90% of the medication was released [16].

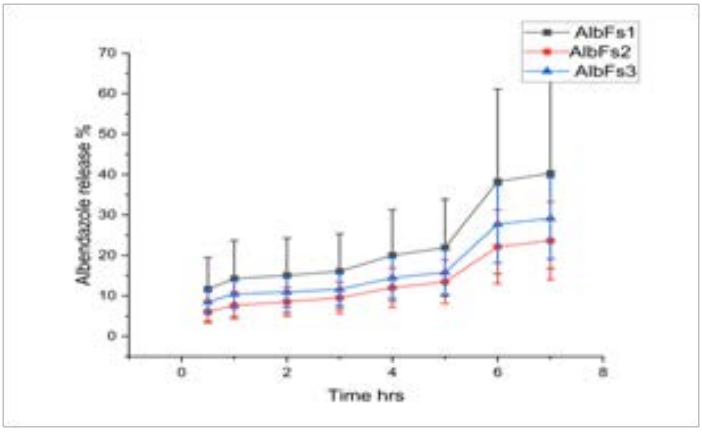


Figure 4 Invitro Release Profile of ALBFs Loaded PVPK30 Showing Controlled Drug Release Rate of 40% at 7hrs

Stability Study

The invitro stability studies reveal that the developed nanodispersion showed a decrease in particle size for 30 day (425.4± 92.08) compared to the 0th day (943±127.3) and there is no variation observed in zeta potential during the study period (0- 30 days). This indicates the stability of ALBFs upon the storage period. The mean size of nanoparticles changed slightly and was kept at two different storage conditions for 30 days. though the zeta potential increased from 0.48 ±0.16 to 14.8± 0.87 within period, the data remained nearly same in subsequent measurements. Therefore, storing under refrigerator condition could effectively prevent reduction in particle size compared to storing under room temperature condition.

Table 2 Stability Study for Albendazole Nanodispersion Formulation

Datas	Initial Day	Room Temperature (30th day)	Refrigerator Temperature (30th day)
Particle Size	943±127.3	425± 92.08	713.9±25.75
Zeta Potential	0.48± 0.16	14.8±0.87	14.5±1.41

Anthelmintic Activity

The adult Indian earthworm Perionyx excavatus and the smaller African earthworm Eudrilus eugeniae were used to perform the anthelmintic activities. They were chosen due to their easy accessibility and physiological and anatomical similarities to the human intestinal roundworm parasite. The five control groups for the collected earthworms are: distilled water, blank formulation, alb suspension (commercial drug), ALBFs3, and pure albendazole medicine, in that order. Each of the five petri dishes was filled with 40 milligrams of the sample and 5 milliliters of distilled water. Each petri dish contains earthworms. The worm's time to paralysis and death was used to make observations. It's paralysis time. were noted when the worms didn't move at all, save from when they shook violently. When worms were submerged in hot water, they stopped moving and lost their body colors, indicating that they had died [13].

Tests were conducted on the anthelmintic activity of various groups against the conventional medication, albendazole. Fifteen worms in all were placed in the appropriate solutions. Subsequently, the worms' paralysis and death times were noted. This trial was conducted for up to 120 minutes and was contrasted with the conventional drug albendazole. Worms killed by M.charantia extract took 35.12 ± 0.5 minutes to die, while AgNPs killed them in 59± 0.3 minutes [14].

Comparing the anthelmintic activity of Ficus benghalensis root extract to that of the usual medication, it was discovered that the plant exhibited strong anthelmintic properties. Ficus benghalensis aqueous extracts at a concentration of 20 mg/ml exhibit paralysis at 3.44 minutes and death at 4.34 minutes, while methanolic extracts exhibit the same paralysis at 3.02 minutes and death at 4.36 minutes. There is good anthelmintic activity in these two extracts.

Petroleum ether (20 mg/ml) results in paralysis at 4.03 min and death at 6.18 min, while chloroform (20 mg/ml) produces paralysis at 3.71 min and death at 4.91 min. Albendazole, the typical medication, causes paralysis in 2.68 minutes and death at 5.29. Each value is given as mean ±SEM (n = 6) [17]. Adult earthworms were used to test the anthelmintic activity of Calotropis procera's crude latex. Dried latex extracts, both fresh and aqueous, demonstrated responses to pin-prick stimulation and a dose-dependent suppression of spontaneous movement (paralysis). At greater concentrations (100 mg/ml of dry latex aqueous extract and 100 % fresh latex), the results were similar to those of 3 % piperazine. Nevertheless, in the instance of worms treated with latex, there was no ultimate recovery.possesses wormicidal activity and thus may be useful as an anthelmintic [18].

Table 3 Antihelmintic Activity Carried Out in the Worm Perionyx Excavatus

Group	Sample	Concentration (mg\ml)	Time taken for Paralysis (in mins)	Time taken for Death (in mins)
1	Control	5ml	0	0
2	Blank	40mg \ 5ml	0	0
3	ALBFS	40mg\5ml	25	64

4	Albendazole marketed suspension	40mg\ml	74	125
5	Albendazole puredrug	40mg \5ml	122	185

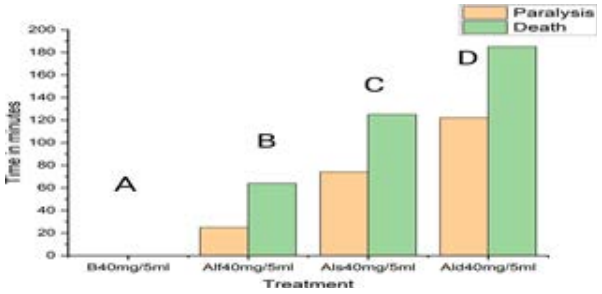


Figure 5 Anthelmintic Activity of Perionyx Excavatus Represents Paralysis and Death of the Earthworm

A – Blank Formulation	B – Albendazole formulation
C – Albendazole marketed suspension	D – Albendazole pure drug

Figure 6 Anthelmintic Activity Carried out in Perionyx Excavatus Earthworm Species

Table 4 Anthelmintic Activity Carried Out in the Worm Eudrilus Euginiae

Group	Sample	Concentration (mg\ml)	Time taken for paralysis (in mins)	Time taken for death (in mins)
1	Control	5ml	0	0
2	Blank	40mg\ml	0	0
3	ALBFs	40mg\ml	20	46
4	Alb marketed suspension	40mg\ml	35	70
5	Alb pure drug	40mg\ml	86	140

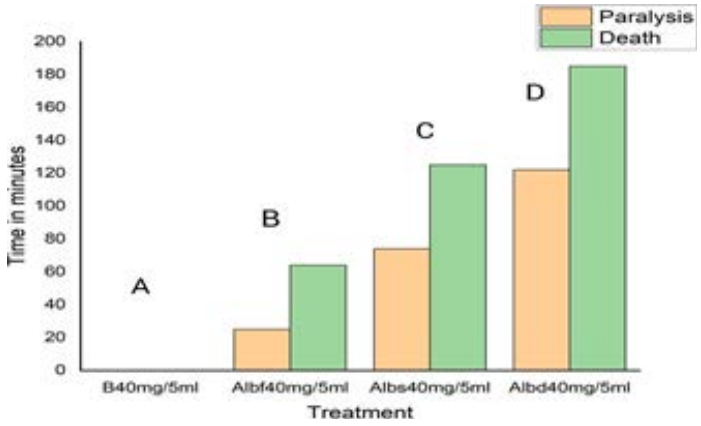


Figure 7 Anthelmintic Activity of Eudrilus Euginae Represents Paralysis and Death of the Earthworm

A – Blank Formulation
B – Albendazole Formulation
C – Albendazole marketed suspension
D – Albendazole pure drug

Figure 8 Anthelmintic Activity Carried out in Eudrilus Euginae Earthworm Species

Summary and Conclusion

Summary

As anticipated, the synthesized ALBFs have higher solubility and improved bioavailability when compared to pure albendazole medication. We can conclude that the ALBFs modulate enzymatic resistance, degradation, and drug release rate while optimizing therapeutic efficacy and limiting potential side effects. As a result, the created ALBFs demonstrated efficient helminthiasis treatment with lower dosage frequency.

Conclusion

Albendazole's solubility was increased, and its effectiveness was increased by turning it into a nanodispersion. There were a few minor issues with the particle size reduction. Earthworms are used to test the efficacy of albendazole nanodispersion anthelmintic activity, and the results are successful as predicted. In comparison to other commercially available drugs, the results demonstrate that albendazole nano dispersion effectively kills earthworms. Therefore, in the near future, it is anticipated that this strategy will serve as a foundation for the commercialization of numerous subpar water-soluble and water-insoluble medications in their nanodispersion formulation.

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