Evaluation of the Formulation of Combined Dosage Form of Albendazole and Mebendazole through *In vitro* Physicochemical and Anthelmintic Study

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ABSTRACT: In the current study, the combination of albendazole and mebendazole was analyzed as a potential anthelmintic agent against *Lumbricus terrestris* (commonly known as earthworms). The *in vitro* analysis showed the combination of 400 mg albendazole and 300 mg mebendazole had more significant therapeutic activities (mean paralysis time 58 minutes and mean death time 97.33 minutes) than the others. Then the combinations were formulated as tablet using different ratios of excipients where formulation-D performed excellent flow properties (Carr's index: 14.04±0.27, Hausner's ratio: 1.19 ± 0.03, Angle of repose: 40.22 ± 0.73). The dosage form prepared from formulation-D had better hardness of 9.40 ± 0.34 kg-N and loss of weight of 0.003 mg compared to other formulations. In terms of disintegration and dissolution studies, formulation-D exhibited excellent properties. The tablet was disintegrated fully within 8.94 ± 0.37 minutes in phosphate buffer (pH 8.3) and dissolution analysis showed R^2 of 0.995 for albendazole and 0.991 for mebendazole which were statistically significant. The post-formulation anthelmintic study showed that the prepared tablet dosage form was therapeutically effective because it paralyzed and killed all the earthworms within 56 and 85 minutes, respectively. Finally, the tablet was subjected to the scanning electron microscopy (SEM) analysis which confirmed better surface morphology and drug-drug compatibility within the dosage form. The next stage of the work will focus on *in vivo* analysis for market preparation.

Key words: Anthelmintics, albendazole, mebendazole, *in vitro*, SEM, RP-HPLC.

INTRODUCTION

Now-a-days, helminthiasis is a common and chronic infection caused by the infestation of soil-transmitted helminths (STHs) such as *Ancylostoma duodenale*, *Necator americanus*, *Ascaris lumbricoides*, *Trichuris trichiura*, etc. According to World Health Organization (WHO), over 2 billion people from more than 100 countries are infected by STHs which badly affects the nutritional status and impair cognitive processes.[1,2] WHO recommends four drugs namely albendazole, mebendazole, ivermectin and pyrantel pamoate for the treatment of STHs diseases till date.[3,4] A recent study showed single-dose treatment of albendazole or mebendazole are being resistant to STHs infection and other drugs performed narrow anthelmintic effects.[5,6] In addition, concurrent administration of albendazole and mebendazole exhibited a higher cure rate (CR: 54.2%) and egg reduction rate (ERR: 94.3%) than a single-dose regimen of albendazole (CR: 15.4% and ERR: 54.9%) and mebendazole (CR: 20.4% and ERR: 66.7%).[4,7,8] Other combination therapy of albendazole-ivermectin, mebendazole-ivermectin and albendazole-pyrantel pamoate performed a low cure rate of 27.5, 47.0 and 14·5%, respectively.[5,9]

It has been reported immaculately that concurrent administration of albendazole and

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mebendazole had more significant anthelmintic properties than single drug administration.[9,10] However, concurrent administration of two or more tablets shows less patient compliance than the single-dose administration. Therefore, the main objective of this study is to formulate a combination dosage form of albendazole and mebendazole drugs (Figure 1). The ultimate goal is to improve the therapeutic efficacy of the combined dosage form as well as the patient's palatability.

MATERIALS AND METHODS

Chemicals and reagents. The active drugs (API) albendazole and mebendazole were gifted by Square Pharmaceutical Limited, Bangladesh. Additional excipients namely sodium starch glycolate (India), lactose monohydrate (China), starch (China), mannitol (Germany), sodium saccharine (China), magnesium stearate (China), talc (China) and aerosil (UK) were purchased from authorized suppliers. All the chemicals and reagents were of analytical grade.

***In vitro* anthelmintic analysis before the formulation.** The anthelmintic analysis was done on *Lumbricus terrestris* (commonly known as an earthworm). *L. terrestris* was collected from Tangail, Bangladesh with the help of a professional biology instructor. After collection, it was washed with clean, non-saline water and then dried at ambient temperature. *L. terrestris* survived for only 2 to 3 days at ambient temperature, so fresh and lively samples were collected during each analysis.

Different ratios of albendazole and mebendazole were subjected to an anthelmintic study where each drug combination contained a total weight of 700 mg. During the analysis, combination (Table 1) of albendazole and mebendazole were 400 mg + 300 mg (Combination-A); 350 mg + 350 mg (Combination-B); 500 mg + 200 mg (Combination-C); 300 mg + 400 mg (Combination-D); 200 mg + 500 mg (Combination-E) and 250 mg + 450 mg (Combination-F). All the combinations were mixed well with clean water where dimethyl formamide (DMF) was used as a solubility enhancer[12] and made a final concentration of 20 mg/mL (regarded as the standard concen-tration). The solutions were kept for 2 hr to check whether it was precipitated or not. If a clear solution was obtained after desired period, then the pH of the solutions were checked. Before anthelmintic analysis, the solutions must be neutral (pH 7.0 to 7.3). Finally, 50 mL of each combination solution was placed in a petri dish and 10 live *L. terrestris* were added to each petri dish and waited for when the earthworms were to be dead. The active drug combination of albendazole (400 mg) and mebendazole (300 mg) was subjected to formulation analyses because it killed all earthworms earlier than the others.

Table 1. Different combinations of albendazole and mebendazole.

Combination Code	Albendazole (mg)	Mebendazole (mg)
Combination-A	400	300
Combination-B	350	350
Combination-C	500	200
Combination-D	300	400
Combination-E	200	500
Combination-F	250	450

Formulation analyses of potentially active drug combination

Formulation procedure. The potential active drug combination was formulated in tablet dosage form with the help of different excipients. Six formulations were prepared and analyzed, where different ratios of excipients were used but the active drug combination was the same (Table 2). In each of the six formulations, the components were weighed firstly, then mixed and shifted using mesh No. 40. Both active substances (albendazole and mebendazole) and excipients (lactose monohydrate, starch and sodium starch glycolate) were mixed properly for ten minutes. For binder dispersion, purified water was kept in a beaker and stirred with a glass rod to disperse starch until no lumps were detected. Then, granulation of the above dry mixture was performed with binder solution and dried in the tray dryer at 40-50ºC until the moisture reduced to 2%. The dried granules and mannitol were passed

through mesh No. 30 and finally mixed with sodium saccharine, orange flavor and color carefully. At last, the above blend was lubricated with magnesium stearate, talc and aerosol-200 for two minutes. The mixture was compressed in a multi-punch rotary tablet machine (ROMACO Pharmatechnik GmbH, Germany) to formulate the combination tablet.

Table 2. Formulation pattern of combined active drug with different ratios of excipients.

Ingredients	Formulations					
	Formulation-A	Formulation-B	Formulation-C	Formulation-D	Formulation-E	Formulation-F
	Amount of ingredients (mg)					
Albendazole	400	400	400	400	400	400
Mebendazole	300	300	300	300	300	300
Albendazole	400	400	400	400	400	400
Lactose	200	200	200	200	200	200
Starch	37	35	33	31	29	27
Sodium starch	66	68	70	72	74	76
Starch for binder	34	34	34	34	34	34
Mannitol	134	134	134	134	134	134
Sodium saccharin	13	13	13	13	13	13
Magnesium stearate	8	8	8	8	8	8
Talc	8	8	8	8	8	8
Aerosil	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Orange color	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Orange flavour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Formulation analysis of prepared tablet dosage form

Determination of hardness of formulated tablet. The hardness of formulated tablet was determined by a manual hardness testing machine (Erweka GmbH, Germany). Varying in hardness indicated different dissolution and disintegration profiles (for oral solid dosage form, hardness with 8 to 10 Kg-N showed a better dissolution profile).[12]

Determination of dissolution profile. Dissolution of formulated tablets was determined by USP Type II apparatus (Electrolab, India), where the temperature of dissolution medium was 38°C. As anthelmintic drugs function in the intestine, so the media of the dissolution apparatus was phosphate buffer (pH 8.3). During the experiment, the sample was taken at an interval of 0, 5, 10, 15, 25 and 40 minutes and subjected to UV/Vis spectrophotometer (Shimadzu, Japan) at a λmax of 235 nm for albendazole and 310 nm for mebendazole.

Determination of disintegration profile. Type-A disintegration apparatus (Electrolab, India) with six baskets was used during the analysis where phosphate buffer (pH 8.3) was used as a disintegration medium. During the operation, the baskets were observed when total disintegration of the tablet took place.

Friability test. During the test, 10 tablets were subjected to a friability tester for 10 minutes at 30 rpm. After finishing desired time period, the weight of the tablets was measured and determined the loss of weight.

***In vitro* anthelmintic analysis of formulated tablet.** *In vitro* anthelmintic analysis was repeated same as previously done. *L. terrestris* was collected, cleaned, dried and studied at ambient temperature.

Tablets were first crushed and dissolved in water with help of DMSO to obtain a clear solution and made a final concentration of 20 mg/mL (regarded as the standard concentration). The solutions were kept for 2 hr to check whether it was precipitated or not. If

a clear solution was obtained after desired time period, then the pH of the solutions was checked. Before anthelmintic analysis, the solutions must be neutral (pH 7.00 to 7.3). Finally, 50 mL of each combination solution was placed in a petri dish and 10 live *L. terrestris* were added to each petri dish and waited for when the earthworms were to be dead.

Determination of physicochemical properties of formulated dosage form

Fourier transform infrared spectroscopy (FTIR). The possible drug-carrier interaction was checked by using FTIR spectroscopy (Perkin Elmer, USA). The samples (pure albendazole and mebendazole) were scanned over the frequency range of 4000 cm^{-1}-400 cm^{-1}.

Scanning electron microscopy (SEM). The shape and surface morphology of formulated tablets were studied by SEM (JEOL JSM-6490LA). The samples were mounted on double-sided adhesive tape that has previously been secured on aluminium stubs and analyzed at a magnification of 500x, 1000x, 2000x, and 9000x with acceleration voltage of 20 KV.

RESULTS AND DISCUSSION

***In vitro* anthelmintic analysis before the formulation.** In the current study, *in vitro* anthelmintic properties of albendazole and mebendazole were observed with different ratios of each drugs. Among six combinations, Combination-A which contained 400 mg albendazole and 300 mg mebendazole showed potential therapeutic activity. The mean paralysis time and mean death time of Combination-A were obtained as 58 and 97.33 min., respectively whereas the mean paralysis time and mean death time of other combinations were to be found as 72 and 110 min., respectively; 86.67 and 112 min., respectively; 89.67 and 162.33 min., respectively; and 106.67 and 165.67 min., respectively (Table 3). The study showed that Combination-A had desired therapeutic efficacy.

Table 3. *In vitro* anthelmintic activity of albendazole and mebendazole combination.

Drug combination	Paralysis time (min)	Mean paralysis time (min)	Death time (min)	Mean death time (min)
	52		98	
Combination-A	64	58	101	97.33
	58		93	
	69		112	
Combination-B	72	72	98	110
	75		120	
	88		110	
Combination-C	82	86.67	114	112
	90		112	
	120		164	
Combination-D	124	122	156	158
	122		154	
	88		149	
Combination-E	95	89.67	166	162.33
	86		172	
	108		162	
Combination-F	102	106.67	157	165.67
	110		178	

Qualitative analyses of different formulations of powder. After preliminary *in vitro* anthelmintic screening of drug combination, Combination-A was subjected to a formulation study where six different

formulations were prepared with different ratios of excipients. In all the formulation types (A to F drugs were in same ratio. Then formulations A to F were subjected to flow property analysis. All the types showed Carr's index (20.81±0.71, 16.69±0.50, 18.34±0.57, 14.04±0.27, 21.02±0.46, 18.01±0.27); Hausner's ratio (1.41±0.03, 1.65±0.07, 1.69±0.05, 1.19±0.03, 1.31±0.03, 1.31±0.02) and angle of repose (50.77±0.50, 41.96±0.24, 40.91±0.66, 40.22±0.73, 39.55±0.52, 38.13±0.47), respectively (Table 4). Among six formulations, formulation-D showed significant flow properties with Carr's index of 14.04±0.27, Hausner's ratio of 1.19±0.03 and angle of repose of 40.22±0.73. According to Abdullah *et al*. (1999)[13], Carr's index below 15 indicates good flow properties of formulation granule whereas Faqih *et al*. (2006)[14] showed granule with better flowability had Hausner's ratio below 1.25. The above study revealed that formulation-D had more excellent flowability than the other formulations.

Table 4. Analyses of granulation properties for different formulations of albendazole and mebendazole combination.

Sl. No.	Carr's index	Mean Carr's index ± SD	Hausner ratio	Mean Hausner ratio ± SD	Angle of repose	Mean angle of repose ± SD
Formulation-A	21.77		1.44		51.34	
	20.12	20.81 ± 0.71	1.37	1.41 ± 0.03	50.19	50.77 ± 0.50
	20.53		1.41		50.77	
Formulation-B	16.20		1.55		41.67	
	16.49	16.69 ± 0.50	1.72	1.65 ± 0.07	42.26	41.96 ± 0.24
	17.37		1.69		41.94	
Formulation-C	18.75		1.62		41.19	
	17.54	18.34 ± 0.57	1.75	1.69 ± 0.05	40.00	40.91 ± 0.66
	18.73		1.69		41.55	
Formulation-D	14.32		1.15		40.72	
	13.69	14.04 ± 0.27	1.23	1.19 ± 0.03	39.19	40.22 ± 0.73
	14.11		1.18		40.74	
Formulation-E	20.59		1.32		39.22	
	20.81	21.02 ± 0.46	1.27	1.31 ± 0.03	39.14	39.55 ± 0.52
	21.66		1.34		40.28	
Formulation-F	17.77		1.30		38.69	
	18.39	18.01 ± 0.27	1.34	1.31 ± 0.02	38.17	38.13 ± 0.47
	17.87		1.29		37.53	

Formulation analysis of prepared tablet dosage form. After flow properties analysis, all the six formulations were subjected to multi punch rotary tablet machine and tablets from each formulation were tested to determine hardness, friability, disintegration and dissolution profiles. All the six formulations A to F showed better punch strength of 7.80 ± 0.20, 8.04 ± 0.06, 7.04 ± 0.19, 9.40 ± 0.34, 7.59 ± 0.49, and 7.98 ± 0.38 Kg-N (Table 5), respectively. On the other hand, the friability test showed that the formulated tablets did not lose significant weight after 10 minutes at 30 rpm of the machine. The six formulations revealed mean loss of weight of 0.005 g, 0.008 g, 0.006 g, 0.003 g, 0.003 g, and 0.003 g, respectively (Table 5). In both cases, formulation-D had better hardness and friability than other tablets.

Again, all the tablets were subjected to type-A disintegration apparatus with phosphate buffer as a disintegration medium. The test showed satisfactory results for all the tablets where formulations A to F had mean disintegration times of 10.11 ± 0.49, 8.44 ± 0.07, 11.74 ± 0.47, 8.94 ± 0.37, 10.66 ± 0.47, and 12.32 ± 0.08 minutes, respectively (Table 6). The analysis performed that formulated dosage forms disintegrated properly in phosphate buffer medium.

Table 5. Hardness and friability test of formulated tablets of albendazole and mebendazole combination.

Sl. No.	Hardness (Kg-N)	Mean hardness ± SD (Kg-N)	Initial weight/tablet (g)	Final weight/tablet (g)	Mean loss of weight (g)
Formulation-A	7.96		1.121	1.118	
	7.52	7.80 ± 0.20	1.153	1.149	0.005
	7.91		1.123	1.115	
Formulation-B	8.02		1.164	1.160	
	8.12	8.04 ± 0.06	1.137	1.131	0.008
	7.98		1.151	1.138	
Formulation-C	7.24		1.187	1.182	
	7.09	7.04 ± 0.19	1.153	1.138	0.006
	6.79		1.151	1.149	
Formulation-D	8.99		1.131	1.124	
	9.81	9.40 ± 0.34	1.164	1.151	0.003
	9.38		1.183	1.175	
Formulation-E	7.33		1.108	1.102	
	7.17	7.59 ± 0.49	1.144	1.132	0.003
	8.26		1.167	1.158	
Formulation-F	7.63		1.194	1.183	
	8.51	7.98 ± 0.38	1.168	1.162	0.003
	7.80		1.183	1.176	

Table 6. Disintegration test of formulated tablets of albendazole and mebendazole combination.

Sl. No.	Disintegration time (min)	Mean ± SD (min)
Formulation-A	10.30	
	10.59	10.11 ± 0.49
	9.43	
Formulation-B	8.44	
	8.53	8.44 ± 0.07
	8.36	
Formulation-C	11.28	
	11.55	11.74 ± 0.47
	12.39	
Formulation-D	8.47	
	9.00	8.94 ± 0.37
	9.36	
Formulation-E	10.39	
	11.32	10.66 ± 0.47
	10.27	
Formulation-F	12.33	
	12.41	12.32 ± 0.08
	12.22	

Finally, all the formulated tablets were subjected to a dissolution study using USP-II dissolution apparatus where phosphate buffer was used as a dissolution medium. The apparatus contained six baskets where six tablets from different formulations were placed. The sample from each basket was picked with the help of a syringe at different time periods of 0, 5, 10, 15, 25 and 40 minutes and the absorbance of each sample was calculated at λmax 235 nm for albendazole and 310 nm for mebendazole.[15,16] The study showed tablets from formulations A to F had better *in vitro* release profiles at different time period which was signified by R^2 values. In case of albendazole R^2 values of the formulations A to F were found to be 0.997, 0.988, 0.994, 0.995, 0.986 and 0.994, respectively where for mebendazole were 0.993, 0.992, 0.990, 0.991, 0.963, and 0.975, respectively (Table 7). The above study revealed that tablets from formulation-D had desired hardness, friability, disintegration and dissolution profiles than tablets from other formulations.

Table 7. The dissolution profile of formulated tablets of albendazole and mebendazole combination.

Sl. No.	Time (min)	Absorbance of albendazole	R^2 value	Absorbance of mebendazole	R^2 value
Formulation-A	0	0.056		0.063	
	5	0.234		0.232	
	10	0.342	0.997	0.438	0.993
	15	0.451		0.606	
	25	0.778		0.833	
	40	1.22		1.311	
Formulation-B	0	0.088		0.0.88	
	5	0.329		0.227	
	10	0.571	0.988	0.328	0.992
	15	0.681		0.572	
	25	0.996		0.859	
	40	1.441		1.278	
Formulation-C	0	0.073		0.078	
	5	0.315		0.301	
	10	0.45	0.994	0.498	0.990
	15	0.604		0.647	
	25	0.888		0.886	
	40	1.318		1.342	
Formulation-D	0	0.065		0.083	
	5	0.248		0.232	
	10	0.386	0.995	0.437	0.991
	15	0.474		0.597	
	25	0.711		0.807	
	40	1.112		1.228	
Formulation-E	0	0.073		0.096	
	5	0.315	0.986	0.254	0.963
	10	0.45		0.521	
	15	0.68		0.774	
	25	0.888		0.998	
	40	1.323		1.338	
Formulation-F	0	0.083		0.142	
	5	0.266		0.327	
	10	0.476	0.994	0.528	
	15	0.592		0.755	0.975
	25	0.866		0.887	
	40	1.311		1.322	

***In vitro* anthelmintic analysis of formulated tablet.** After formulation analyses of the prepared dosage form, *in vitro* anthelmintic tests were conducted to confirm the efficacy of the tablets. The anthelmintic test was conducted thrice and each time 10 helminths were subjected to the study. Tablets from each of the six formulations were dissolved in water with the help of DMSO and 50 ml of the solution was transferred to Petri dish. All the six formulations (A to F) showed potential therapeutic

efficacy against earthworms with mean paralysis times of 64.33 ± 1.89, 59.33 ± 1.25, 58.00 ± 1.41, 56.00 ± 1.41, 72.67 ± 3.68, and 66.67 ± 3.68 minutes, respectively. Besides this, mean death times were 90.67 ± 1.89, 91.00 ± 1.63, 94.67 ± 1.70, 84.67 ± 1.70, 88.33 ± 3.30, and 92.33 ± 4.19 minutes, respectively for all six formulated dosage forms (Table 8). All the studies revealed that tablets from formulation-D paralyzed all the 10 earthworms within 56 ± 1.41 minutes and completely killed them within 84.67 ± 1.70 minutes.

Table 8. *In vitro* anthelmintic analysis of tablets from combined albendazole and mebendazole formulations.

Sl. No.	Paralysis time (min)	Mean paralysis time ± SD (min)	Death time (min)	Mean death time ± SD (min)
Formulation-A	63		88	
	67	64.33 ± 1.89	92	90.67 ± 1.89
	63		92	
Formulation-B	59		91	
	61	59.33 ± 1.25	93	91.00 ± 1.63
	58		89	
Formulation-C	60		93	
	57	58.00 ± 1.41	97	94.67 ± 1.70
	57		94	
Formulation-D	55		83	
	58	56.00 ± 1.41	87	84.67 ± 1.70
	55		84	
Formulation-E	77		92	
	68	72.67 ± 3.68	89	88.33 ± 3.30
	73		84	
Formulation-F	67		98	
	71	66.67 ± 3.68	88	92.33 ± 4.19
	62		91	

Determination of physicochemical properties of formulated dosage form. Physicochemical properties of the tablets from formulation-D were ascertained by FTIR, SEM and RP-HPLC analyses. It was reported that albendazole contained stretching at N-H, aromatic C-H, CH3-C-H, C-H, aliphatic C-H, amide-I bond and aromatic ring (Figure 1), where mebendazole had N-H stretching, aromatic C-H stretching, CH3 stretching, C-H stretching, amide-I band, and benzoyl C=O stretching (Figure 2). FTIR study showed albendazole spectrum had stretching vibration at frequency 3327 cm^{-1} (N-H stretching), 2956 cm^{-1} (aromatic C-H stretching), 2860-2754 cm^{-1}

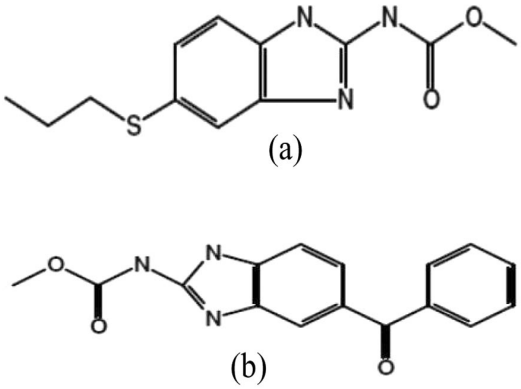

Figure 1. Chemical structures of albendazole (a) and mebendazole (b).

(CH3-C-H stretching), 2667 cm^{-1} (aliphatic C-H stretching), 1712 cm^{-1} (amide I bond) and 1631 cm^{-1} (aromatic ring stretching). On the other hand, figure 3 revealed stretching vibrations at frequency of 3400 cm^{-1} (N-H stretching), 3020 cm^{-1} (aromatic C-H stretching), 2951-2805 cm^{-1} (CH3-C-H stretching), 2750-2667 cm^{-1} (C-H stretching), 1716 cm^{-1} (amide-I band), and 1651 cm^{-1} (benzoyl C=O stretching). The two spectra confirmed the supplied drug components were albendazole and mebendazole.

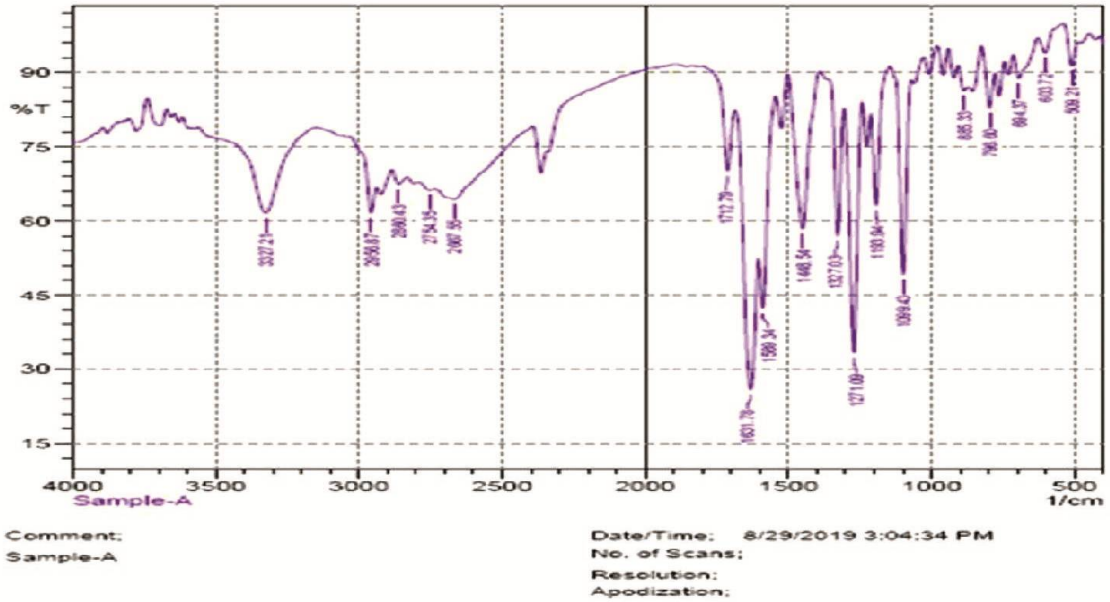

Figure 2. FTIR spectrum of albendazole.

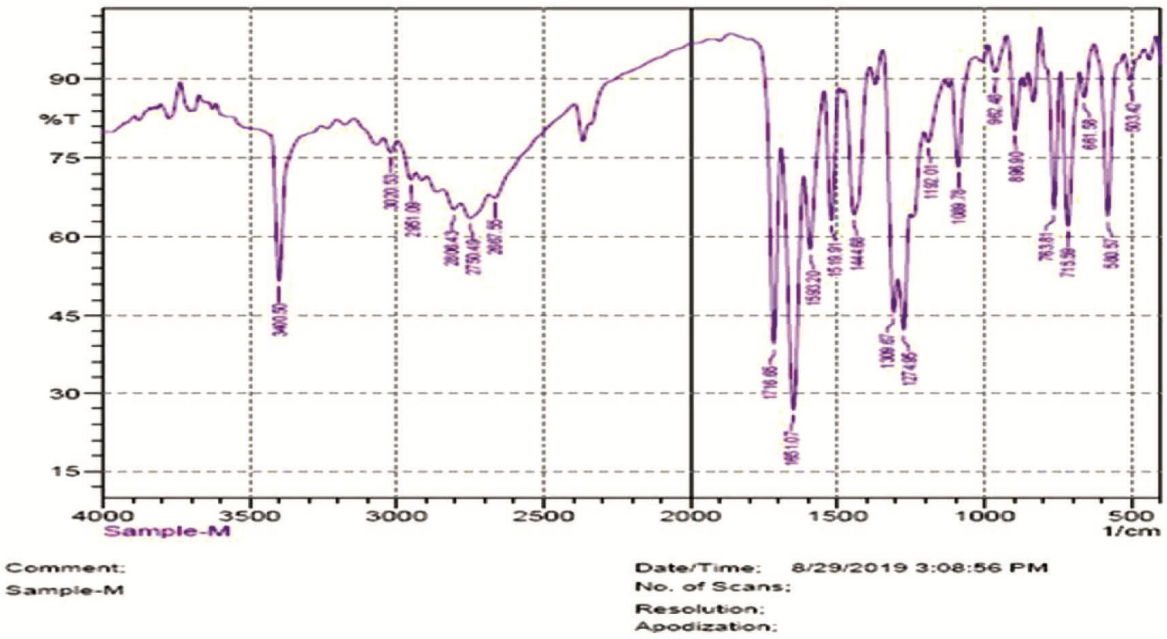

Figure 3. FTIR spectrum of mebendazole.

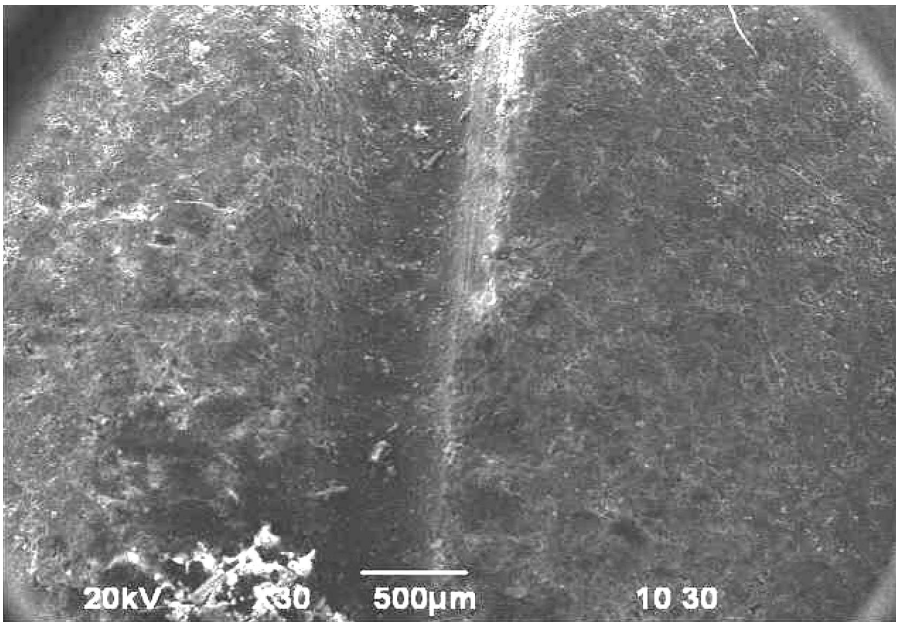

Figure 4. SEM analysis of the tablet of formulation-D.

After identification of albendazole and mebendazole using FTIR analysis, the selected tablet from formulation-D was analyzed by SEM to determine the surface morphology. The SEM monograph showed tablets had a uniform and smooth scaly surface. This indicated that tablets of formulation-D were properly formulated, mixed and compressed and no interactions took place after tableting (Figure 4).

CONCLUSION

The research finding showed that combinations of albendazole and mebendazole had significant anthelmintic effects on earthworms (*L. terrestris*). Among six different combinations, albendazole and mebendazole of 400 mg and 300 mg performed maximum therapeutic effects. Moreover, this combination was then formulated using different polymers and the physicochemical properties of the formulations (A to F) were tested. However, the flow property, hardness, friability, disintegration and dissolution test firmly affirmed that formulation-D has better physical stability and a satisfactory release rate compared to other formulations. In addition, SEM and FTIR analyses revealed that the drugs were in crystalline forms and there were no interactions between drugs and polymers in formulation-D. The results of the study suggested that dosage forms containing albendazole and mebendazole combination have promising anthelmintic effects. In the future, the project will focus on the *in vivo* experiment aiming to commercial use of the combination with better therapeutic efficacy and patient compliance.

REFERENCES

1. WHO. 2015. Assessing the epidemiology of soil-transmitted helminths during a transmission assessment survey (TAS) in the global programme for the elimination of lymphatic filariasis. Geneva: World Health Organization. pp. 1-40.
2. Mahesh, B.M., Shashikant, C.D. and Prasad, G.J. 2015. Helminthiasis and medicinal plants: a review. *Asian Pac. J. Trop. Dis*. **5**, 175-180.
3. Keiser, J., Lucienne, T., Roberto, A. and Mireille, V. 2012. Effect of combinations of marketed human anthelmintic drugs against *Trichuris muris in vitro* and *in vivo*. *Paras. Vec.* **5**, 292-303.
4. Cowan, N., Mireille, V. and Jennifer, K. 2016. *In vitro* and *in vivo* drug interaction study of two lead combinations, oxantel pamoate plus albendazole and albendazole plus mebendazole, for the treatment of soil-transmitted helminthiasis. *Antimicrob. Agents Chemother*. **60**, 6127-6133.

5. Knopp, S., Khalfan, A.M., Benjamin, S., Hattendorf, J., Simba, I.K., Alipo, N.K., Russell, J.S., David, R., Hanspeter, M. and Jurg, U. 2010. Albendazole and mebendazole administered alone or in combination with ivermectin against *Trichuris trichiura*: a randomized controlled trial. *Clin. Infect. Dis.* **51**, 1420-1428.
6. Peter, S., Utzinger, J., Zun-Wei, D., Jin-Yong, J., Jia-Xu, C., Jan, H., Hui and Xiao-Nong, Z. 2011. Efficacy of single-dose and triple-dose albendazole and mebendazole against soil-transmitted helminths and *Taenia spp*.: a randomized controlled trial. *PLoS One* **6**, 1-8.
7. Beach, M.J., Streit, T.G., Addiss, D.G., Prospere, R., Roberts, J.M. and Lammie, P.J. 1999. Assessment of combined ivermectin and albendazole for treatment of intestinal helminth and *Wuchereria bancrofti* infections in Haitian school children. *Am. J. Trop. Med. Hyg.* **60**, 479-486.
8. Namwanje, H., Kabatereine, N.B. and Olsen, A. 2011. Efficacy of single and double doses of albendazole and mebendazole alone and in combination in the treatment of *Trichuris trichiura* in school-age children in Uganda. *Trans. R. Soc. Trop. Med. Hyg.* **105**, 586-590.
9. Speich, B., Said, M.A., Shaali, M.A., Isaac, I.B., Rainer, A., Jorg, H., Marco, A., Jan, H., Jürg, U. and Keiser, J. 2015. Efficacy and safety of albendazole plus ivermectin, albendazole plus mebendazole, albendazole plus oxantel pamoate and mebendazole alone against *Trichuris trichiura* and concomitant soil-transmitted helminth infections: a four-arm, randomized controlled trial. *Infect. Dis*. **15**, 277-284.
10. Dennis, K., Kuei-Ju, C. and Lawrence, F. 2002. RP-HPLC assay for albendazole and metabolites in human plasma for clinical pharmacokinetic studies. *J. Pharm. Biomed. Anal*. **30**, 801-813.
11. Josefina, P., Codina, A.V., Leonardi, D., Vasconi, M.D. Hinrichsen, L.I. and Lamas, M.C. 2017. Albendazole microcrystal formulations based on chitosan and cellulose derivatives: physicochemical characterization and *in vitro* parasiticidal activity in *Trichinella spiralis* adult worms. *AAPS Pharm. Sci. Tech.* **18**, 947-956.
12. Abdelaziz, B., Salim, B. and Rachid, C. 2013. Investigation into Brinell hardness test applied to rocks. *World J. Eng*. **10**, 369-382.
13. Abdullah, E.C. and Geldart, D. 1999. The use of bulk density measurements as flowability indicators. *Powder Technol.* **102**, 151-165.
14. Faqih, A., Chaudhuri, B., Alexander, A.W., Davies, C., Muzzio, F.J. and Silvina, T.M. 2006. An experimental/ computational approach for examining unconfined cohesive powder flow. *Int. J. Pharm*. **324**, 116-127.
15. Semahat, K., Beniz, G. and Esma, K. 2008. Development of a spectrofluorimetric method for determination of albendazole in tablets. *Anal. Lett.* **41**, 104-118.
16. Gunasekaran, S. and Uthra, D. 2008. Vibrational spectra and qualitative analysis of albendazole and mebendazole. *Asian J. Chem*. **20**, 6310-6324.