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Formulation Development and Evaluation Of Chewable Tablet Of Mebendazole Nanoparticle

Pengembangan dan Evaluasi Formulasi dari Tablet Kunyah Nanopartikel Mebendazol

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ABSTRACT

Mebendazole is a benzimidazole derivative with broad spectrum anthelminthic activity and excellent tolerability. Orally it is rapidly absorbed and metabolized to sulfoxide and sulfone, which may be responsible for its anthelminthic action. This research aimed to formulate mebendazole nanoparticle chewable tablet to increase its dissolution velocity and impact saturation solubility.

Mebendazole nanoparticle chewable tablets (300 mg) were prepared by direct compression. The tablets prepared by this method were evaluated by different parameters such as average weight, hardness, friability, disintegration, drug content and *in vitro* dissolution *etc.* All the parameters were found within the specifications.

The study on the dissolution profile revealed that F_1 had better dissolution rate while compared to F_2, F_3 and mebendazole microparticle, respectively. Assay values were within the limits of 90% to 110%.

Keywords: *Mebendazole, Nanoparticle, Direct compression, Chewable tablets*.

ABSTRAK

Mebendazol merupakan turunan benzimidazol karbamat, sebagai antelmintik berspektrum luas. Efektif untuk pengobatan penyakit hydatid dan cysticercosis.Absorbsi peroral sangat cepat dan dimetabolisme menjadi sulfoksid dan sulfon. Penelitian ini bertujuan untuk mendapatkan tablet kunyah mebendazol nanopartikel untuk meningkatkan kecepatan disolusi dan kelarutannya.

Tablet mebendazol nanopartikel dosis 300 mg dibuat dengan kempa langsung. Evaluasi tablet meliputi bobot tablet, kekerasan, kerapuhan, waktu hancur, kandungan obat dan uji disolusi *in vitro*.

Semua tablet baik F_1 , F_2 dan F_3 memenuhi persyaratan. Uji disolusi in vitro F_1 lebih baik dibandingkan dengan F_2, F_3 dan tablet mebendazol mikropartikel. Kandungan obat berada pada batas yang dipersyaratkan yaitu 90-110 %.

Kata kunci : *Mebendazol, Nanopartikel, Kempa langsung, Tablet kunyah*

INTRODUCTION

Human helminthic infestations are common and have significant worldwide health implications. They can be responsible for delayed child growth and development, probably via a mechanism of iron-deficient anaemia. The preferred treatment is anthelmintic therapy such as pyrantel, albendazole or mebendazole, all of which are efficacious and cost effective. Some encapsulated helminthic infestations may however require surgical intervention followed by chemotherapy. Mebendazole (methyl-5-benzoyl benzimidazole-2-carbamate), a broad-spectrum anthelmintic drug of the benzimidazole class, effective against a number of nematodal and cestodal species (Liebenberg et al., 1998), is recommended for the treatment of non-surgical cases and as a supplementary treatment prior to and post-surgery. The World Health Organization (WHO) has identified mebendazole as an essential drug, based upon its clinical efficacy and low cost. However, it has been observed that in vivo results are far from being as effective as those demonstrated in vitro due to its low absorption at the gastrointestinal level

Mebendazole (MBZ), IUPAC name (5-benzoyl-1Hbenzimidazole- 2-yl)-carbamic acid methyl ester ($C_{16}H_{13}N_3O_3$, MW: 295.293 g/mol, chemical structure shown in Fig. 1). Mebendazole is practically insoluble in water and only 5–10% of the ingested drug is absorbed from the human gastrointestinal tract. Drug absorption is increased when taken with food, particularly fatty food (Himmelreich et al., 1977., Ferreira et al., 2010).

An approach that is commonly used to increase dissolution velocity and impact saturation solubility of sparingly soluble compounds such as mebendaole is to formulate it as nanometer-sized particles, particles usually less than 1 μm in diameter.

For example, when the particle size of the drug is reduced from 8 μm to 200 nm, there is 40-fold increase in the surface area to volume ratio. This increase in surface area can provide substantial increase in the dissolution rate if the formulation disperses into discrete particles (Liversidge & Cundy, 1995).

Administration of drugs through oral route is the most common and the easiest way to administer a drug.

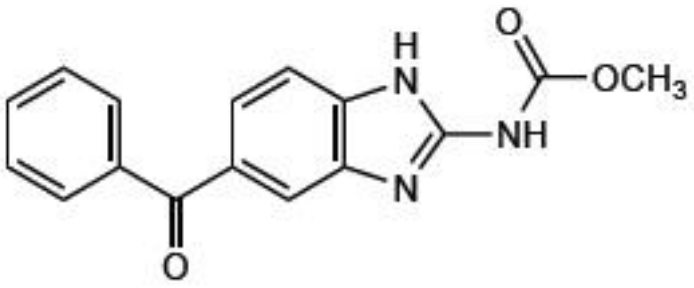

Figure 1. Chemical structure of mebendazole

Hence it was decided to formulate mebendazole chewable tablet to improve the compliance in children. Chewable tablets are the tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing (Herbert *et al,* 1989). The advantages of chewable tablets include palatability, stability, precise dosing, portability and ease of delivery. The available literature suggests that chewable tablets provides a safe, well-tolerated alternative to traditional pediatric drug formulations and offer significant advantages in children with two years of age and above (Durga et al, 2010). In the present paper mebendazole chewable tablets were prepared by direct compression methods and all the three formulas were evaluated. The main objective of the present study was to formula and evaluate mebendazole chewable tablet by direct compression and to evaluate these using different parameters.

MATERIALS AND METHODS

Materials

Pure drug sample of mebendazole was purcased from Indo Farma Ltd**.** All other ingredients *viz.* Lactose monohydrate*,* Mannitol, Aerosil, Magnesium stearate, Aspartame etc used were of pharmaceutical grade.

Method

Direct Compression

All the ingredients were separately weighed and sifted using mesh no. 40. Mebendazole, Mannitol (pearlitol200), Lactose monohydrate was passed through mesh no 30. Aspartame, Yellow color and lemon flavor were passed through 100 mesh and required quantities were blended for ten minutes in poly bag. Finally the above blend was lubricated with Magnesium stearate and Aerosil for two minutes. The powder blend was evaluated for the flow properties and was found to be good. The evaluated blend was compressed into tablets of 1000 mg weight each. A minimum of fifty tablets were prepared for each formulas. The manufacturing formulas for the tablets used in the above were given in **table I**.

Evaluation of Tablets

General appearance

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance involves measurement of attributes such as a tablet's size, shape, color, presence or absence of odour, taste, surface textures, physical flaws and consistency. Hence the tablets were checked for the presence of cracks, depressions, pinholes, uniformity of color, and the polish of the tablet (Lachman et al, 1991).

Dimensions

The shape and dimensions of compressed tablets were determined by the type of tooling during the compression process. At a constant compressive load, tablet thickness varies with changes in die fill, particle size distribution and packing of the powder mix being compressed and with tablet weight. While with a constant die fill, thickness varies with variation in compressive load.

Table 1: Manufacturing formulas for preparation of Tablet

No	Ingredients	F_1 (mg)	F_2 (mg)	F_3 (mg)
1.	Mebendazole	300	300	300
2.	Mannitol	300	300	300
3.	Lactose monohydrate	368,50	363,50	358,50
4.	Aerosil	10	10	10
5.	Aspartame	10	10	10
6.	Magnesium stearate	5	10	15
7.	Yellow colorant	5	5	5
8.	Lemon flavour	1,5	1,5	1,5
	Total weight (mg)	1000	1000	1000

Tablet thickness is consistent from batch to batch or within a batch only if the tablet granulation or powder blends is adequately consistent in particle size and particle size distribution, Consistent length of punch tooling, Tablet press and good working conditions Thickness and diameter of the tablets were measured using digital vernier caliper. The values of thickness were used to adjust the initial stages of compression. Tablet thickness should be controlled within a ±5% variation of a standard value. Also the thickness must be controlled to facilitate packaging (Lachman et al, 1991).

Hardness

The hardness test is performed to provide a measure of tablet strength. Tablets should be hard enough to withstand packaging and shipping but not so hard as to create undue difficulty upon chewing. Tablet hardness is determined using equipment from various suppliers that measure the force needed to break up the tablets. The Pfizer tester is commonly used. This tester operates on the same mechanism principle as a pair of pliers. As the plier's handles are squeezed, the tablet is compressed between a holding anvil and a piston connected to a direct force reading gauge. The dial indicator remains at the reading where the tablet breaks and is returned to zero by depressing a reset button (Lachman et al, 1991).

Friability test

Friability is the loss of weight of tablet in the container or package, due to removal of fine particles from the surface. This parameter was conducted to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Permitted friability limit is 1.0%. Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 min.) the tablets were taken out from the friabilator and intact tablets were again weighed collectively (Nandgude *et al*, 2007., Subhramanyam et al, 2006).

Disintegration

This test initially may not appear appropriate for chewable tablets as these tablets are to be chewed before being swallowed. However, patients, especially pediatric and geriatric, have been known to swallow these chewable dosage forms. This test would thus indicate the ability of tablet to disintegrate and still provide the benefit of the drug if it is accidentally swallowed. Tablets should preferably pass the USP disintegration test for uncoated tablets.

Weight Uniformity test

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits. The percent deviation was calculated using the following formula (Nandgude *et al*, 2007., Subhramanyam et al, 2006).

Percentage deviation = [(Individual weight-Average weight) /Average weight]×100

***In vitro* dissolution test**

Dissolution measurements were carried out in a USP dissolution test apparatus. The dissolution profiles of mebendazole from chewable tablets were studied in 0.1 N HCl (pH 1.2). The chewable tablets containing 300 mg of mebendazole were placed in a rotating basket (50 rpm) filled with 900 ml of the dissolution medium, thermo stated at 37 ± 0.5 ^{O}C. At scheduled time intervals (2 hour), the samples (5 ml) were withdrawn and replaced immediately with fresh dissolution medium. The samples were assayed spectrophotometrically at 254 nm for the dissolved drug, where samples were automatically filtered before measuring the absorbance against 0.1 N HCl as blank. The amount of mebendazole released was calculated from the standard graph (Khokra et al, 2012).

Drug content

Five tablets were powdered and the blended equivalent to 300 mg of mebendazole was weighed and dissolved in suitable quantity of water. The solution was filtered, suitably diluted and drug content was analysed spectrophotometrically at 254 nm. Each sample was analyzed in triplicate (Khokra et al, 2012).

RESULTS AND DISCUSSION

All the prepared formulas of tablets were within the range. Using Monsanto hardness tester, the strength of the tablets was tested. All the tablets showed good hardness. Batch F_2 had minimum hardness (15,99 ± 0,1747) while F_1 and F_3 had maximum hardness 16,56 ± 0,2307 and 16,05 ± 0,0723, respectively. The friability was carried out for all the formulas of tablets. The friability was less than 0.2% for all the blends and was satisfactory. Assay value of all prepared formulas of mebendazole tablets were within the range of 90% to 110% of stated amount of mebendazole. From the data obtained it was found that 98,46% of drug was released for F_1 at 120 min while other tablets F_2 and F_3 had shown 86,50% and 88,28 % drug release at 120 min respectively. The variation in

the dissolution rate of mebendazole tablets was in the following order F_1 more superior to F_2 and F_3.

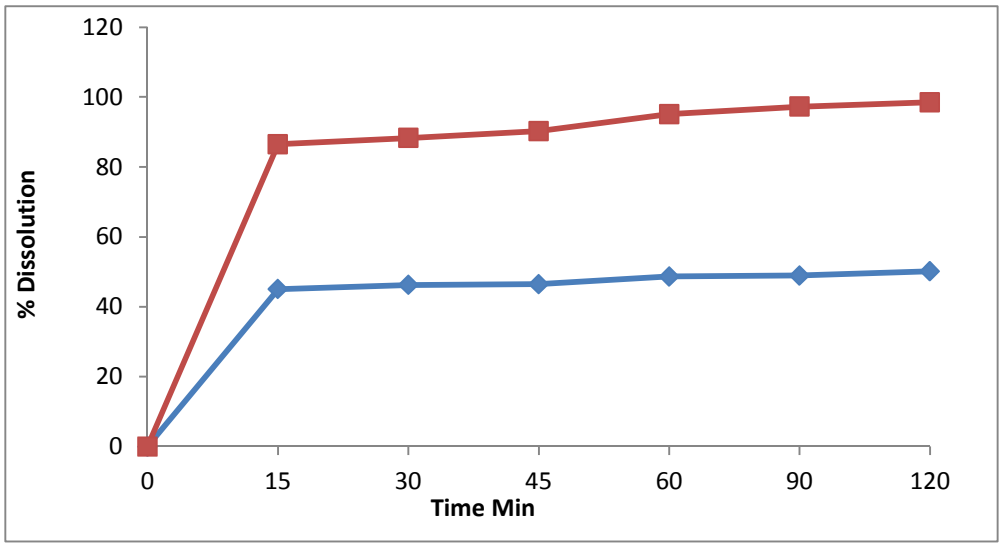

Figure 2. Comparison of dissolution profiles of tablet F_1 (■) and tablet mebendazole microparticle (◆).

Table 2: Comparative evaluation of tablets

Parameters	Tablets code		
	F_1	F_2	F_3
Weight of tablet (mg)	996,73 ± 3,0	995,82 ± 2,5	995,91 ± 2,0
Hardness (kg/cm2)	16,56 ± 0,230	15,99 ± 0,174	16,05 ± 0,07
Friability test (%)	0,03 ± 0,0058	0,05 ± 0,0116	0,06 ± 0,005
Disintegration time (min)	5	4	3,5
Dissolution (%)	98,46	86,50	88,28
Drug content (mg)	297	291	285
Assay (%)	99	97	95

The dissolution profile of tablets F_1 has shown had better results compared to the tablets as well as marketed product mebendazole microparticle as showed in fig 2.

CONCLUSION

All the tablets showed satisfactory results with respect to hardness, friability, assay and *in vitro* dissolution studies. Tablets F_1 more superior than F_2 and F_3. Tablet prepared by direct compression F_1 had the better dissolution rate when compared F_2, F_3 and marketed product mebendazole microparticle, respectively.

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