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Formulation and Evaluation of Liquid-Solid Compact of Mebendazole for Better Dissolution Rate

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ABSTRACT

Mebendazole is a poorly soluble, highly permeable drug and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal. The poor dissolution rate of water-insoluble drugs is still a major problem confronting the pharmaceutical industry. There are several techniques to enhance the dissolution of poorly soluble drugs. Among them, the technique of Liquisolid compacts is a promising technique towards such a novel aim. In this study, the dissolution behaviour of mebendazole from liquisolid compacts was investigated in 0.1 N HCl. Liquisolid compacts were prepared by using PEG 400 as the liquid vehicle or non-volatile solvent. Avicel PH 102 as absorbing carrier and Aerosil 200 as adsorbing coating material. The ratio of carrier to coating powder material were kept different in formulations. The prepared liquisolid compacts were evaluated for their micromeritic properties and possible excipients interactions. The tableting properties were falling within acceptable limits. The in vitro dissolution study confirmed increase in drug release from liquisolid compacts compared to marketed preparation. This was due to an increase in wetting properties and surface of drug available for dissolution.

Keywords: Mebendazole, Liquisolid compacts, Dissolution rate, Liquid medication, Solubility.

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INTRODUCTION

The oral Route is the most preferred route of drug administration because of high patient compliance (or) acceptance and drug development. Oral bioavailability of poorly water-soluble hydrophobic drugs is limited by their solubility and dissolution rate. Development of solid dosage forms for poorly water soluble drugs has been a major challenge for pharmaceutical scientists[1].

Liquisolid Systems is a promising and novel technique to improve the dissolution rates of the poorly water soluble drugs. The concept of powder solution technology is to convert the liquid drug into free flowing readily compressible powder. Here the liquid drug (or) liquid medication is the water insoluble drug and dissolved in a non-volatile solvent. These liquid drugs are converted to free flowable & compressible powder by the addition of suitable excipients like carriers, coating materials, lubricants, disintegrants & glidants etc. The compression can be proceeded by direct compression and slugging method[2].

Mebendazole is poorly water soluble. Low water solubility of mebendazole is considered the main cause in implying low oral bioavailability. Mebendazole, whatever its classification, it is characterised by low bioavailability and high variability, leading to the necessity to increase its solubility and dissolution rate in the gastrointestinal fluid[3].

In this work, an attempt was made to formulate liquisolid compact of mebendazole by mathematical model -factorial design for enhancement of dissolution rate and bioavailability of the drug. Calculation of optimum amounts of carrier, coat materials and composition of liquid medication was done based on new fundamental powder properties called flowable liquid retention potential (Φ-value) and compressible liquid retention potential (Ψ-number).

MATERIALS AND METHOD

Materials

Mebendazole was kindly gifted by Erica health care pvt ltd. Jejuri, Pune. Avicel PH 102, and Aerosil 200 were kindly gifted by Macleod Pharmaceuticals, Mumbai (India). Sodium starch glycolate, Polyethylene glycol 400 chemicals were of analytical grade.

Drug Authentication:

Melting Point Determination

Melting points of Mebendazole was checked for drug authentication by conventional capillary method and reported. Capillary was sealed at one end and filled with tapping with sufficient drug powder. Thieles tube was heated and capillary was inserted into the sample holder/capillary holder.

The temperature at which the column of the substance collapses was recorded as a melting point of the substance.

FTIR Spectra

FTIR absorption spectrum of drug was recorded using a spectrometer. KBr disks of Mebendazole were prepared and scanned over a range of 400-4000 cm^{-1}.

Determination of Solubility

Solubility of MBZ in distilled water and PEG 400 was determined by Higuchi-Connor's method[5]. Excess quantity of MBZ was added to 5 ml of solvents under study in screw capped vials and shaken on rotary shaker for 48 hr at 25°C. After equilibration for 24 hr, the solutions were filtered through a 0.45 µm filter and analyzed by UV-spectrophotometry (Systronics Double Beam Spectrophotometer- 2201) at 234 nm. For solubility determination in PEG 400, the solution containing same concentration of PEG without drug was taken as blank sample.

Preparation of standard calibration curve for Mebendazole in 0.1N HCl

Various drug concentrations (2-10µg/ml) in 0.1N HCl were prepared and the absorbance's were measured at 234nm. Using Double beam UV visible spectrophotometer (Systronics 2201).

Mathematical Model for Design of Liquisolid Formulation

The formulation design of liquisolid systems was done according to mathematical model described by Spireas[2].

In the present work, Polyethylene Glycol 400 was used as non-volatile liquid vehicle. Avicel PH 102 (Microcrystalline cellulose) was incorporated as carrier materials. Aerosil 200 (Colloidal silica) was selected as the coating material.

To attain optimal MBZ solubility in liquisolid formulations, concentration of drug in liquid vehicle PEG 400 (%D) was taken as 50, 60 and 70 gm%. Depending on the literature review, the carrier: coat ratio (R) was varied from 3, 6 and 9. According to theories, the carrier and coating powder materials can retain only certain amount of liquid while maintaining acceptable flowability and compressibility. Hence carrier material as well as liquid content must be optimum to elicit good drug solubility without affecting flowability and compressibility as well as to avoid "liquid squeeze out" phenomenon.

The compositions of various batches for the understanding of individual and combined effect of each variable on the performance of final dosage form were decided by applying 3^2-full factorial design. Drug percentage in the liquid medication and carrier to coat ratio were taken as independent variables.

After R is taken as variable in the factorial design, to calculate the quantities of each excipient, the mathematical model developed by Spireas was used. Mathematical model equation for Avicel PH 102 and Aerosil 200 in PEG 400 can be given according to Φ -values given by Spireas et al.

$Lf = 0.005 + 3.26 (1 / R)$

Based on this equation, Lf is calculated by using different R values.

Table 2: Translation of Coded Values in Factorial Design

Variable levels	Low (-1)	Medium (0)	High (+1)
X1= Carrier: Coat ratio (R)	3	6	9
X2= % Drug in liquid medication	50	60	70

Table 3: Composition of Liquisolid System

Batch Code	R (X1)	%D (w/v) (X2)	Lf	Avicel PH 102 (mg) (Q = W/Lf)	Aerosil 200 (mg)(Q= Q/R)
A1	3	50	1.092	325.4	108.5
A2	3	60	1.092	271.2	90.4
A3	3	70	1.092	232.4	77.5
A4	6	50	0.548	449.8	75.0
A5	6	60	0.548	374.8	62.5
A6	6	70	0.548	321.3	53.5
A7	9	50	0.367	595.2	66.1
A8	9	60	0.367	496.0	55.1
A9	9	70	0.367	425.2	47.2

Preparation of Liquisolid Tablets

Preparation of liquisolid formulation was done in a step wise manner as per the method described by Spireas. The steps involved preparation of liquid medication, incorporation of liquid on solid phase for subsequent adsorption of drug on carrier and addition of excipients for better pharmaceutical performance.

Calculated quantities of Mebendazole and non-volatile solvent Polyethylene Glycol 400 (PEG 400) were accurately weighed in 20 ml glass beaker and to produce a homogenous solution of desired %D. The medication was incorporated into a calculated quantity of carrier and coating material. Mixing process was carried out in three steps as described by Spireas.

In the first stage, system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in powder.

In second stage, the liquid and powder admixture was evenly spread as uniform layer on the surfaces of mortar and left standing for about 5 min to allow sorption of drug solution in the interior of powder particles.

Lastly, powder was scraped off the surfaces with aluminum spatula and blended uniformly with 5% sodium starch glycolate used as super-disintegrant, for another 30 seconds. After pre

compression study, formulations were compressed by 16 station single rotary compression machine.

Precompression Study

The precompression study of liquisolid mixture was done by several micromeritic techniques as per Indian Pharmacopoeia 2007. Angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio were employed to study the flow properties as well as compressibility of liquisolid formulations[6].

Thermal Analysis

DSC can be used to study the thermal behaviour and chemical compatibility between drug and excipients. It is also helpful to predict the crystallinity of solids.

DSC was performed using Detector DSC-60 to assess thermal behaviours of MBZ, and liquisolid systems. Samples (1 mg) were placed in aluminum pans and lids at constant heating range of 10°C/min in an atmosphere of nitrogen gas flow at a rate of 50 ml/min using the range of 40-400°C.

Fourier Transform Infra-Red Spectroscopy

FTIR absorption spectra of MBZ, Avicel, Aerosil, physical mixtures and the formulations were recorded for determination of compatibility between the drug and excipients using a FTIR equipment. KBr disks were prepared (2 mg sample in 200 mg KCl) and scanned over a range of 400- 4000 cm-1 with a resolution of 4 cm-1.

EVALUATION OF LIQUISOLID TABLETS[7]

Assay

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder containing about 50 mg of Mebendazole, add 50 ml of 0.5 M methanolic hydrochloric acid shake for 30 minutes and dilute to 100.0 ml with 0.5 M methanolic hydrochloric acid. Filter and discard the first 10 ml of the filtrate. Dilute 10.0 ml of the filtrate to 100.0 ml with *0.5 M methanolic hydrochloric* acid and mix. Further dilute 5.0 ml to 50.0 ml with the same solvent and mix. Measure the absorbance of the resulting solution at the maximum at 234 nm. Calculate the content of $C_{13}H_{13}N_3O_3$ from the absorbance obtained by repeating the operation using mebendazole *RS* in place of the substance under examination.

Hardness

The hardness of liquisolid tablets was determined by using Monsanto Hardness tester in terms of Kg/cm^2.

Friability:

Method: For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets.

The friability of prepared liquisolid tablets was determined using Roche‟s tablet friability tester. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

The difference in the two weights is used to calculate friability (F).

$$F = [1 – W_O / W]$$

Where, W_O – Initial weight

W – Final weight

A maximum loss of weight (from a single test or from the mean of the three tests) not greater than 1.0 per cent is acceptable for most tablets.

Disintegration Time

The disintegration time was measured using USP disintegration tester (Electrolab).

***In vitro* Dissolution Study:**

The *in vitro* dissolution study of liquisolid formulations was performed using USP-XXIII Type-II paddle Apparatus-II (Electrolab TDT- 06T). 900 ml 0.1N hydrochloric acid containing 1.0% Sodium lauryl sulfate maintained at 37±0.5°C was used as dissolution medium stirred at 75 rpm. 5 ml aliquots were periodically collected maintaining sink condition. After filtration through 0.45 µm membrane filter, MBZ was estimated spectrophotometrically at 234 nm.

Dissolution profiles of liquisolid tablets and marketed formulation were statistically compared. The comparison between dissolution of formulations was made by model independent approach, model dependent approach.

RESULTS AND DISCUSSION

DRUG AUTHENTICATION

Melting Point:

Melting point of MBZ was found to be 285-289°C. The result was in good agreement with the literature.

FTIR Spectra:

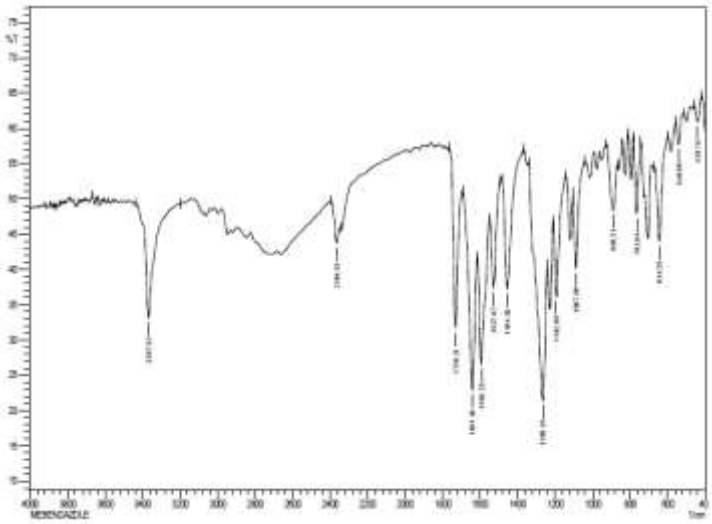

Figure 1: FTIR Spectra of Mebenbazole

Solubility Study:

Solubility of mebendazole in distilled water was found to be 0.083 µg/ml, which shows that the drug is poorly water-soluble. Determination of drug solubility in non-volatile vehicle is done to ensure formation of molecular dispersion of the drug. The solubility of MBZ in PEG 400 was found to be 510 µg/ml. Thus good solubility of MBZ in PEG 400 indicates that PEG 400 can be used as vehicle for preparation of liquid medication.

Precompression Study:

Flow properties are the important parameters in the formulation and industrial application of tablet dosage form. Results of angle of repose, Carr's index and Hausner's ratio are depicted in the Table no. 4. In general, values of angle of repose more than 40° indicate powders with poor flowability; while angle of repose less than 20° is considered to be excellent. Thus the liquisolid formulations exhibit a good to excellent flow. Also Carr's index and Hausner's ratio indicate good flowability and compressibility.

Table 4: Precompression Study of Liquisolid Formulations

Batch Code	Angle of Repose	Carr's Index	Hausner's Ratio
A1	16.69	16.66	1.24
A2	16.72	16.66	1.21
A3	15.69	16.66	1.20
A4	17.23	18.51	1.22
A5	18.26	13.33	1.15
A6	16.69	16.12	1.19
A7	18.22	14.28	1.16
A8	18.26	10.34	1.11
A9	18.30	11.11	1.12

Thermal Analysis:

Differential Scanning Calorimetry (DSC) study was carried out to determine interaction between drug and excipients and stability of dosage form. Thermograms of drug, liquisolid systems are represented in Figure.

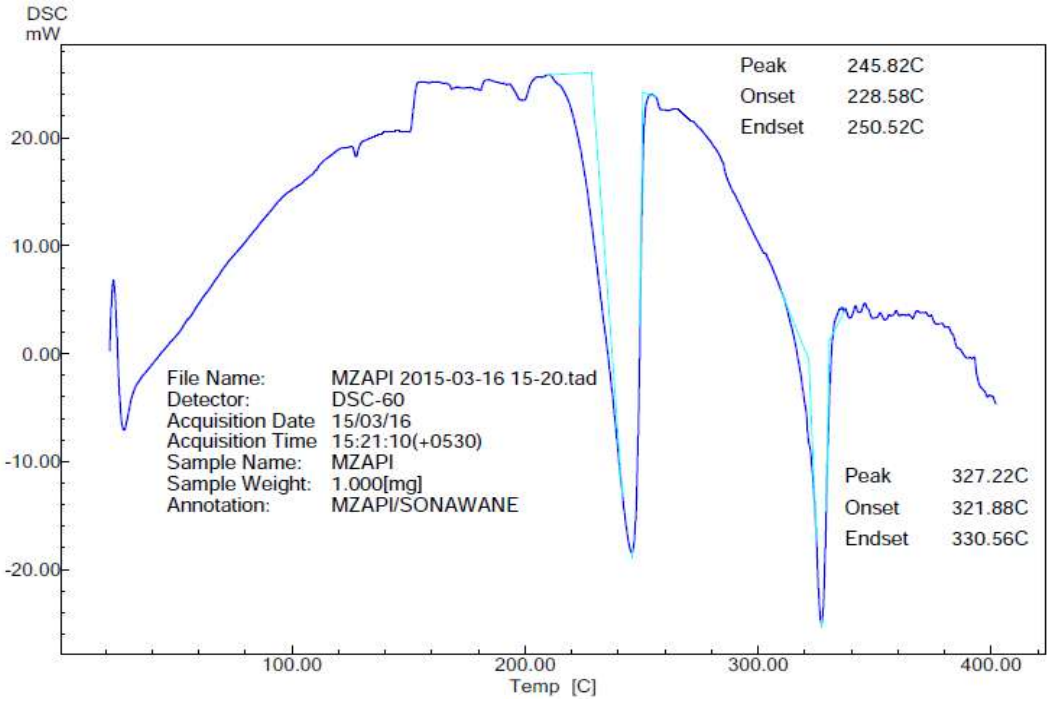

Figure 2: DSC study of MBZ API

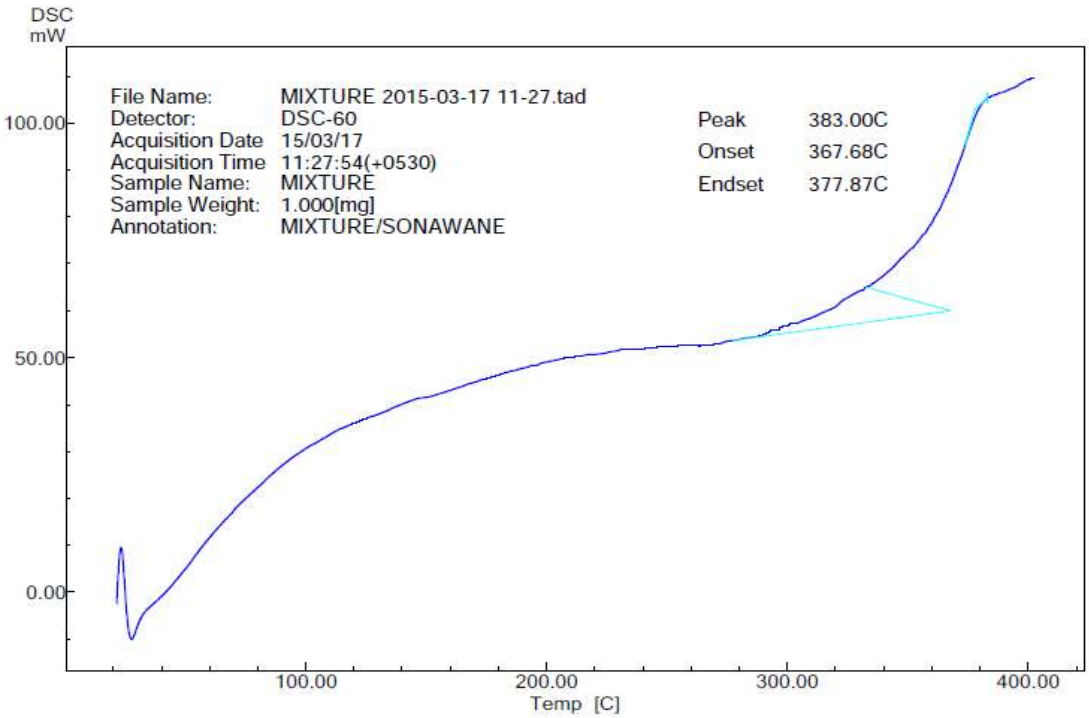

Figure 3: DSC study of Liquisolid formulation

EVALUATION OF LIQUISOLID TABLETS

Assay

As represented in Table 7.2, the drug content in the liquisolid formulations was found to be in a range of 95.62% to 102.28%, thus prepared tablets comply with the pharmacopoeial limits for the drug content.

Hardness

Tablet hardness is one of the important dosage form related factors that affects quality and performance of the dosage form. In general less hardness leads to fragile and brittle tablets resulting in poor friability and hence considered non-acceptable. On the other hand, harder tablets show slowdown of the disintegration process and ultimately dissolution. Hence, hardness must be critically monitored in the tablet manufacturing.

Considering this, the hardness of liquisolid tablets was critically controlled during the compression step of each batch and was found in the range from 6 to 8 kg/cm^2. Good compactness of tablet may be due to hydrogen bonding between Avicel molecules. As PEG 400 is an alcoholic compound, it may show hydrogen bonding due to presence of hydroxyl groups and contributes to compressibility.

Friability

Friability are in the range of 0.24% to 0.9% which ensures acceptable resistance by tablets to withstand mechanical shocks.

Disintegration Time:

Disintegration time was ranging between 3 min to 7 min. Addition of sodium starch glycolate in the formulation gives faster disintegration which helps rapid release.

Table 5: Tablet characteristics of liquisolid system

Batch Code	Hardness	% Friability	Disintegration time (min)	Assay
A1	6	0.45	3	100.10
A2	7	0.64	5	95.65
A3	6	0.34	7	98.30
A4	8	0.74	7	96.74
A5	6	0.24	3	100.24
A6	6	0.30	4	102.28
A7	8	0.9	6	97.55
A8	7	0.8	7	98.38
A9	7	0.6	5	99.47

In vitro Dissolution Study:

Dissolution rates of liquisolid formulations were compared with MBZ alone and marketed formulations (Fig. 4.).

From the dissolution profile of mebendazole, it can be seen that only 32.26 % drug is dissolved after 60 min. The percent dissolution efficiency at 60 min of MBZ was found to be 26.55. Thus the dissolution was poor as well as incomplete suggesting the need of solubility enhancement.

The dissolution parameters of the liquisolid systems compared to the drug alone. All the liquisolid batches were found to increase the drug dissolution rate compared to mebendazole alone as well as marketed formulation. It can be seen that the initial drug release within first 15 min. from some liquisolid formulation was remarkably increased compared to the drug alone. The fastest drug release was obtained from the batch A4, where complete drug was dissolved within 60 min. The mean dissolution time and percent dissolution efficiency of batch A4 at 60 min were 20.08 and 56.49 respectively. In comparison to the dissolution parameters of drug alone, this result shows a significant dissolution enhancement.

The initial rapid drug release from liquisolid formulation may be due to the use of super-disintegrant which causes a faster de-aggregation process leaving the liquisolid particles in the aqueous environment. This step may be followed by the rapid mass transfer from the carrier particles to the bulk of the solvent. During this step, the liquisolid technique brings about a faster dissolution by different proposed mechanisms of solubility enhancement which include phenomenon of drug being in the dissolved or molecularly dispersed state as well as absorption and adsorption of liquid medication in the internal structures of hydrophilic carrier material providing a greater effective surface area required for the mass transfer of drug molecules from adsorbed and absorbed liquid medication phase to the bulk of dissolution medium. The second mechanism is the co-solvency between the non-volatile hydrophilic solvent and water.

To determine the effect of independent variables on the dissolution, 3^2-factorial design was applied. The carrier: coat concentration is positively influencing the solubilization as it provides a surface area for dissolution. It can be observed that more is the carrier: coat ration, better is the solubilization. The reasons behind the effect may be the availability of greater effective surface area due to more concentration of carrier. Less coat concentration imparts less hydrophobic characters to dosage form.

Drug concentration in the liquid medication shows negative effect on the dissolution property. This may be because of availability of more amount of solvent for better solubilization of drug.

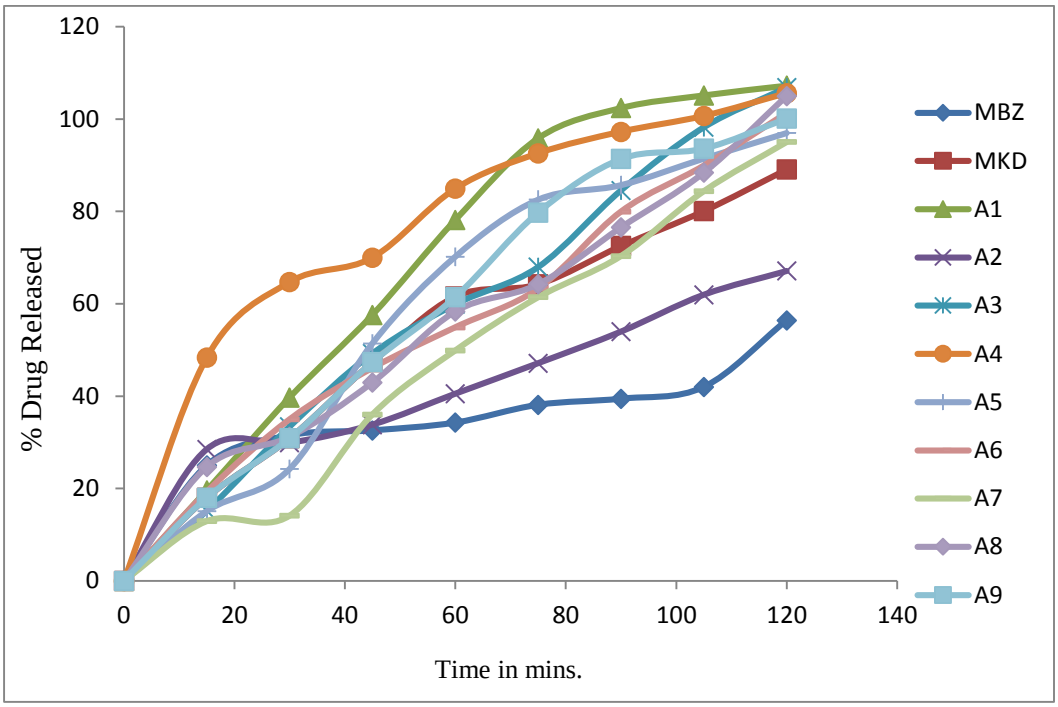

Figure 4: Dissolution Profiles of Liquisolid Tablets

CONCLUSION

The purpose of the present study was to formulate the liquisolid system of mebendazole for better dissolution rate accompanied by acceptable flow and compression characteristics. In this investigation, preformulation study was performed for authentication of drug and determination of drug solubility. Hence, from preformulation study following points were concluded.

Based on the information of melting point and FTIR spectra, the drug was confirmed to be authentic. The solubility of MBZ in distilled water is found to be 0.083µg/ml; also Dissolution of MBZ alone was very slow and also, incomplete up to 120 min. According to the findings, only 34.26 % of drug was dissolved after 1 hr. Hence, as the intrinsic solubility as well as rate of drug dissolution is poor, there is strong need to enhance its solubility and dissolution rate.

The solubility of MBZ in PEG 400 was 510µg/ml., PEG 400 shows higher drug solubility hence can be considered as the acceptable solvent for the preparation of liquid medication portion of the system.

Liquisolid systems were formulated by the technique described Spireas et al. The systems were formulated with Avicel PH102 as carrier material. Aerosil 200 was used as coating material. Sodium starch glycolate was incorporated as super-disintegrant.

Chemical compatibility between drug and excipients was checked and confirmed by DSC. A 3^2-full factorial study design was utilized for the statistical comparison of the individual and

combined effect of independent variables on dependent parameter like dissolution. The two variables were carrier to coat ratio and drug content in the liquid medication.

Liquisolid preparations were initially characterized by precompression study for flowability and compressibility. The formulations were found to possess good flow characteristics as well as satisfactory compressibility. The presence of PEG 400 can be considered to enhance the compactibility of the formulation.

Drug release rate was studied 0.1N HCL and found to be enhanced in case of some liquisolid formulations. The factorial equation shows that the drug release is dependent on both the factors under consideration. Increased carrier to coat ratio and decreased drug concentration in the liquid medication demonstrated increased drug release rates.

Finally, it can be concluded that, liquisolid formulation containing MBZ with Avicel PH 102 as carrier and Aerosil as coating material is efficient to enhance the drug dissolution rate with acceptable flow and compression characteristics. Thus, liquisolid approach has potential application for formulation research in improvement of dissolution rate of MBZ.

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