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Preparation and Evaluation of Mebendazole Tablets by Using Liquisolid Technique to Enhance Its Dissolution Rate

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Abstract
Liquisolid technology has been applied to prepare water-insoluble drugs into rapid-release solid dosage forms. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties. With Liquisolid technique liquid formulations such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders by simple physical blending with selected excipients named the carrier and the coating material. The liquisolid approach has been successfully applied in release enhancement of low dose poorly soluble drugs. Liquisolid system is characterized by flow behavior, saturation solubility, drug content, Fourier transform infra-red spectroscopy, *in-vitro* release and *in vivo* evaluation. By using this technique, solubility and dissolution rate can be improved for the water soluble drugs.

Keywords
Liquisolids, Carriers, Coating materials, Water in-soluble drugs, Poorly soluble drugs.

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INTRODUCTION:
Nowadays, the synthesis of poorly soluble drug is increasing steadily. Therapeutic effectiveness of a drug depends upon the bioavailability which is dependent on the solubility and dissolution rate of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The drugs which are poorly water soluble will be inherently released at a slow rate owing to their limited solubility within the GI contents. The dissolution rate is often the rate determining step in the drug absorption. The challenge for these drugs is to enhance the rate of dissolution or solubility. This in turn subsequently improves absorption and bioavailability. Formulation methods targeted at dissolution enhancement of poorly soluble substances are continuously introduced.[1]

Almost more than 90% drugs are orally administered. Drug absorption, bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium. More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble

compounds. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity of drugs. Poorly water soluble drugs which belong to BCS class II and class IV.[2]

A frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development is solubility. There are various methods which can be adapted to improve solubilization of poorly water soluble drug and to improve its bioavailability. Bioavailability is affected by several other factors like drug solubility in aqueous environment and drug permeability through lipophilic membranes being the important ones.[3]

MATERIALS AND METHODS:

1. Drug candidate

We select Mebendazole (Gift sample from K.A. Malle pharmaceuticals LTD. ankleshwar) as a drug candidate having poorly soluble & 5-10% Bioavalability.[4-9]

2. Nonvolatile Solvent

Nonvolatile solvent should be Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilise the drugs. The nonvolatile solvent acts as a binding agent in the liquisolid formulation. In this formulation PEG400 (Research lab fine chem. industries Mumbai) is used as nonvolatile solvent.[10-13]

3. Carrier Methods

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption. The carrier & coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier's results in decreased powder flow ability. In this formulation Microcrystalline Cellulose (Vishal chem. Mumbai 400002 India) is used.[14, 15]

4. Coating Materials

Coating material should be a material possessing fine and highly adsorptive particles which contributes in covering the wet carrier particles & displaying a dry looking powder by adsorbing any excess liquid. Coating material is required to cover the surface and maintain the powders flow ability. In this formulation Aerosol 200 (Evonik industries AG Germany) is used.[16-18]

5. Disintegrant

Super disintegrate increases the rate of drug release, water solubility and wettability of liquisolid granules. In this formulation cross povidone (Ana lab fine chemicals, Mumbai) is used.[19-24]

Preparation of Liquisolid Compact

Common method of preparation of liquisolid: for all formulation batches

1) A drug was initially dispersed in the nonvolatile solvent systems termed as liquid vehicles with different drug: vehicle ratio.
2) Then a mixture of carrier or different polymers and excipients were added to the above liquid by continuous mixing in a mortar. These amounts of the carrier and excipients were enough to maintain acceptable flow and compression properties.
3) In the above binary mixture disintegrant and other remaining additives were added according to their application and mixed properly for 10 to 20 mins.
4) The blend was used for precompression parameter which listed below.
5) The final powder blend was compressed using the 12 station rotary punching machine to achieve tablet hardness.
6) Further these tablets were evaluated for weight variation, disintegration time, content uniformity, dissolution study, friability, hardness, thickness etc.

Preparation of conventional tablet (F14)

Tablet containing mebendazole was prepared by mixing 100 mg of drug with microcrystalline cellulose, lactose, aerosil200, and cross povidone mixed for 10 min. Glidant and lubricant are added and then compressed by rotary tablet punching machine. Same formulation but without nonvolatile treatment.

Table 1.1: Formulation for tablets (F1-F5)

Composition	F1	F2	F3	F4	F5
Mebendazole	100	100	100	100	100
PEG200	2	-	-	1	-
PEG400	-	2	-	-	1
Glycerine	-	-	2	-	-
Lactose	90	90	90	45	45
Microcrystalline Cellulose	-	-	-	45	45
Aerosil200	3	3	3	3	3
Crosspovidone	2	2	2	2	2
Mag.stearate	1	1	1	1	1
Talc	2	2	2	3	3
Total wt./ tablet	200	200	200	200	200

All quantities are in mg

Table 1.2: Formulation for tablets (F6-F10)

Composition	F6	F7	F8	F9	F10
Mebendazole	100	100	100	100	100
PEG200	-	-	-	1	-
PEG400	-	-	-	-	1
Glycerine	1	-	-	-	-
Lactose	45	46	60	60	60
Microcrystalline Cellulose	45	45	30	30	30
Aerosil200	3	3	2	2	2
Crosspovidone	2	2	4	4	4
Mag.stearate	1	1	1	1	1
Talc	3	3	3	2	2
Total wt./tablet	200	200	200	200	200

All quantities are in mg

Table 1.3: Formulation for tablets (F11-F15)

Composition	F11	F12	F13	F14	F15
Mebendazole	100	100	100	100	100
PEG200	-	-	-	-	-
PEG400	-	61	61	30	-
Glycerine	1	-	-	-	-
Lactose	60	37	37	55	85
MCC	30	30	30	30	30
Aerosil200	2	2	6	4	4
Crosspovidone	4	4	12	12	12
Mag.stearate	1	1	3	3	3
Talc	2	3	9	9	9
Total wt./tablet	200	238	258	243	243

All quantities are in mg

RESULTS AND DISCUSSION:

The aim of the present study was to prepare, evaluate and compare with conventional and marketed tablet. The liquisolid compacts prepared using (PEG200, PEG400 & glycerin) and mebendazole as a drug. Fifteen batches of Mebendazole tablets using PEG200, PEG400 and glycerin were prepared by liquisolid technique to study the effect of solvent on in vitro release.

- **Preformulation Study:**
- ✓ **Melting Point Determination:**

Table 1.4: Melting Point Determination

Sample	Reported	Observed
Mebendazole	295.3 ºC	294.5 ºC

- ✓ **Solubility studies of Mebendazole for selection of nonvolatile solvent:**

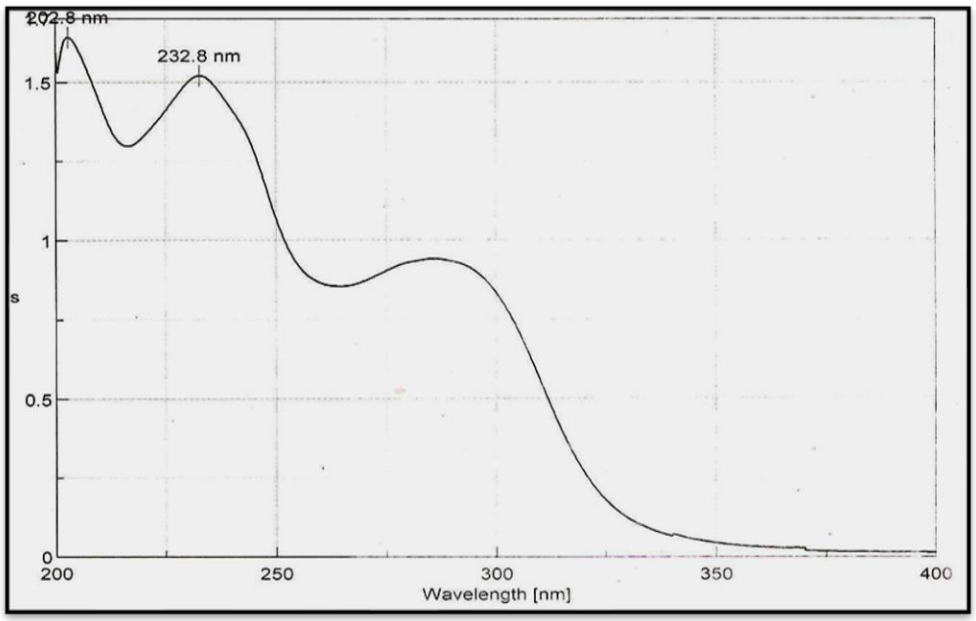
Solubility of mebendazole in PEG200, PEG400, propylene glycol, liquid paraffin, tween80, glycerine and sorbitol. As shown in the Table 1.5, its solubility is very poor in Sorbitol (0.01343 mg/ml). Mebendazole solubility is very high in PEG200 as compared to other. PEG, with a large nonpolar part and several hydroxyl groups is responsible for the enhanced solubility. Thus among the solvents tested, PEG 400 could be a better choice as a solvent.

Table 1.5: Solubility studies in different solvent

Solvent	Solubility (mg/ml)
Polyethylene Glycol 400	0.55904
Polyethylene Glycol200	0.14964
Propylene glycol	0.02044
Glycerin	0.2413
Sorbitol	0.01343
Tween80	0.5524
Liquid paraffin	0.030828

- ✓ **Calibration Curve of Drug:**
  - **Scanning of Mebendazole in 0.1N HCl**

Figure 1.1: λ_{max} observed for Mebendazole in 0.1 N HCl

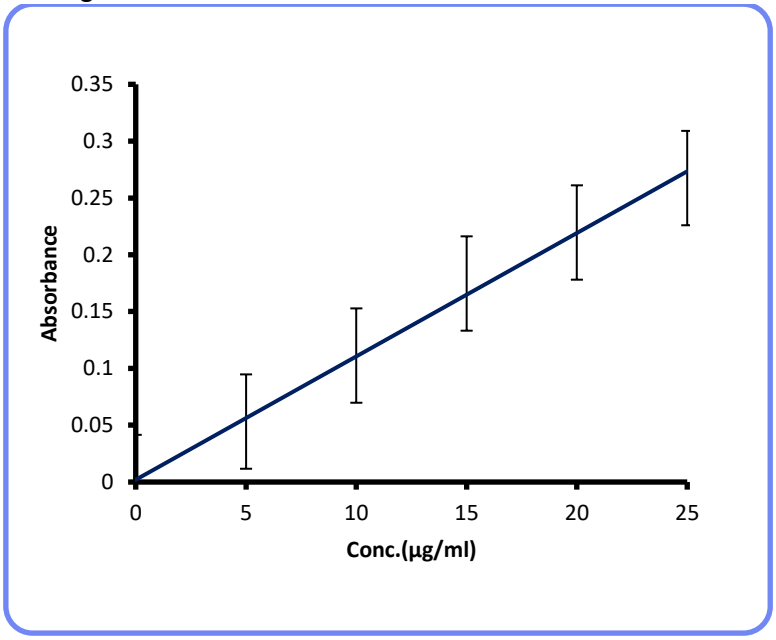


- **Calibration curve of Mebendazole in 0.1N HCl**

Table 1.6: Absorbance data for Mebendazole in 0.1 N HCl

Concentration(µg/ml)	Absorbance ± SD
0	0
5	0.0532±0.0532
10	0.1113±0.1567
15	0.1646±0.9456
20	0.2196±0.7345
25	0.2665±0.2675

Figure 1.2: Calibration curve for Mebendazole in 0.1 N HCl



Slope=0.002 coefficient of regression = 0.996 Intercept = 0.010 λmax at 232.8 nm

➢ **Preparation of Tablet:**

✓ **Preparation of Liquisolid Compact:**

To investigate the effect of type of non-volatile solvent on the dissolution rate of mebendazole from Liquisolid tablets, several formulations prepared using PEG200 (F-1), PEG 400(F-2) and glycerin (F-3) with same drug concentration in liquid medications. These tablets were stick to punches. So to overcome sticking problem MCC was added in the formulation. The liquisolid formulation F4 shows 46.95%, F5 shows 40.16%, F6 shows 30.82% and conventional formulation (F7) shows 21.65%.

The further study was performed on conventional formulation increase concentration of lactose and cross povidone ultimately increase the % CR. So used these formulas to different nonvolatile agent increasing the % CR. Cumulative releases shown in Table 6.6. From formulations only one nonvolatile agent i.e. PEG400 which shows the greater release as compared to other nonvolatile agent. (F9-F11).

Excess nonvolatile agent were used to observe its effect on release profile but due to excess addition of nonvolatile agent in formulation couldn't be proceed because formed the dummy mass. Also concentration of lactose decrease. But these tablets were stick to punches and not burst in dissolution medium hence not showing the release properly. To overcome this sticking & bursting problem further formulation was formulated with higher concentration of Aerosil200, cross povidone, mag. stearate and talc. Also for this formulation tablets were stick to punches. (F12, F13) so, avoid sticking problem further formulation formulated by using half quantity of nonvolatile agent (F14).

✓ **Preparation of Conventional Tablet (F15):**

These tablets were prepared same as optimized liquisolid tablet formulation F-14 only used drug was not treated.

➢ **Pre-compression Evaluation:**

The results for pre-compression evaluation are given below.

Table 1.7: Pre-compression evaluation for Mebendazole powder

Formulation	Bulk Density* (gm/cm^3) *	Tapped Density* (gm/cm^3) *	Carr's Index* (%)*	Hausner's Ratio*	Angle of Repose (θ^0) *
F1	1.650±0.004	1.815±0.006	9.06±0.12	1.099±0.003	22.15±0.44
F2	1.492±0.008	1.612±0.003	12.84±0.85	1.146±0.006	24.66±0.28
F3	1.523±0.002	1.692±0.008	14.96±0.35	1.166±0.001	25.89±0.65
F4	1.556±0.006	1.689±0.002	12.99±0.69	1.149±0.003	23.46±0.42
F5	1.691±0.003	1.806±0.005	6.41±0.19	1.068±0.008	21.06±0.68
F6	1.606±0.006	1.952±0.006	12.54±0.22	1.143±0.005	25.65±0.66
F6	1.853±0.002	1.965±0.003	5.66±0.18	1.060±0.006	22.64±0.32
F8	1.682±0.003	1.911±0.001	6.64±0.21	1.062±0.002	23.06±0.46
F9	1.691±0.005	1.992±0.005	15.08±0.54	1.166±0.006	26.49±0.63
F10	1.636±0.006	1.930±0.006	9.984±0.33	1.110±0.003	25.25±0.33
F11	1.601±0.004	1.998±0.003	14.85±0.86	1.164±0.006	26.98±0.55
F12	1.629±0.001	1.965±0.006	16.46±0.53	1.211±0.001	26.49±0.66
F13	1.659±0.003	1.955±0.002	15.14±0.81	1.168±0.008	26.35±0.81
F14	1.633±0.006	1.949±0.005	16.16±0.35	1.192±0.003	26.48±0.69
F15	1.646±0.005	1.993±0.002	12.38±0.64	1.141±0.005	24.10±0.42

*All values are expressed as Mean ± SD, n = 3

➢ **Evaluation of Tablets:**

Results for evaluation of tablets were as shown in table

Table 1.8: Evaluation of tablet for Mebendazole tablets

Formulation	Tablet dimensions		Hardness (kg/cm^2) *	% Friability*	Weight variation (mg) *	Content uniformity (%)*
	Thickness (mm) *	Diameter (mm) *				
F1	-	-	-	-	-	-
F2	-	-	-	-	-	-
F3	-	-	-	-	-	-
F4	3.39±0.03	8.66±0.00	5.2±0.18	1.2±0.25	196.9±2.55	60.1±0.3
F5	3.66±0.06	8.60±0.01	1.5±0.22	1.3±0.26	196.6±4.11	69.3±0.4
F6	3.80±0.02	8.63±0.02	4.5±0.31	1.16±0.31	198.1±3.34	98.4±0.2
F6	3.45±0.01	8.66±0.01	3.5±0.62	1.01±0.29	198.0±6.44	98.1±0.5
F8	3.66±0.05	8.63±0.00	3.6±0.35	0±0.00	198.9±3.46	66.4±0.4
F9	3.46±0.04	8.69±0.00	1±0.28	1±0.32	199.9±2.25	65.2±0.6
F10	3.35±0.03	8.66±0.01	3.8±0.44	1.96±0.36	200.0±5.52	99.4±0.3
F11	3.46±0.05	8.65±0.01	3.6±0.48	1.14±0.22	199.8±1.46	99.3±0.2
F12	3.65±0.04	8.64±0.02	4±0.56	0.65±0.16	238.2±3.36	100.2±0.6
F13	3.44±0.02	8.62±0.00	4.2±0.38	0.85±0.16	256.8±5.55	98.3±0.6
F14	3.53±0.01	8.68±0.00	3.8±0.36	0.48±0.19	242.9±3.32	100.2±0.1
F15	3.66±0.10	8.64±0.01	4.4±0.52	0.45±0.21	242.8±3.56	99.2±0.4

*All values are expressed as Mean ± SD, n = 3

➢ ***In-Vitro* Dissolution Studies:**

Table 1.9: *In vitro* release data of Mebendazole compacts

Formulation	%CR*±SD (at 120 min)	Formulation	%CR*±SD (at 120 min)
F1	-	F9	56.02±0.0496
F2	-	F10	46.8±0.040
F3	-	F11	40±0.0523
F4	46.95±0.0586	F12	30±0.0164
F5	40.16±0.0122	F13	56.99±0.0263
F6	30.82±0.0436	F14	92.46±0.0543
F7	21.65±0.0628	F15	40.56±0.0154
F8	50.12±0.041		

All values are expressed as mean ± SD, *n=6

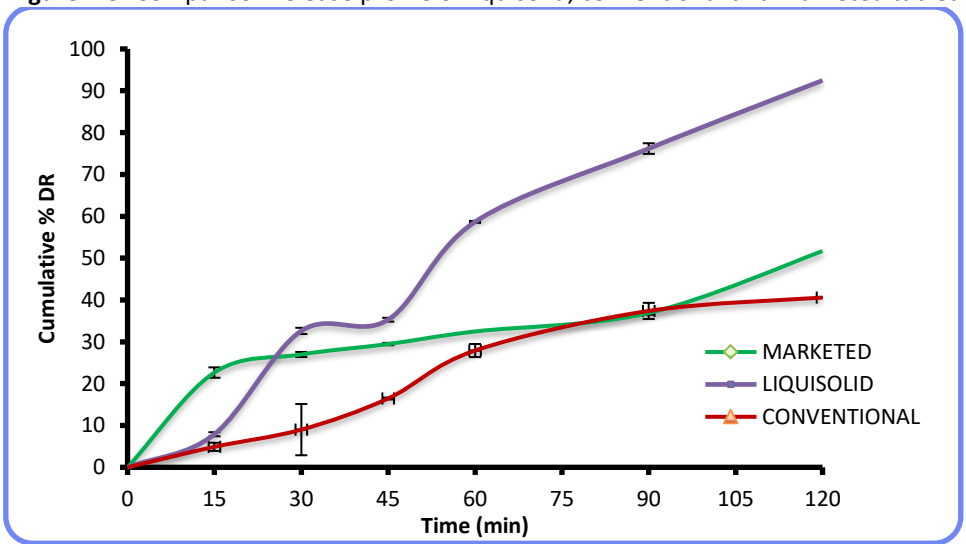
The comparison study of liquisolid, marketed and conventional tablet was studied using USP II apparatus in 0.1 N HCl. The releases were shown in Table 1.10.

Table 1.10: Comparison release data for liquisolid tablet, conventional tablet and marketed tablet of Mebendazole

Time (min)	Liquisolid tablet %CR*±SD	Conventional tablet %CR*±SD	Marketed tablet %CR*±SD
0	0	0	0
15	6.91±0.02121	4.9±1.138442	22.65±0.060611
30	32.6±0.48083	9.00±0.965806	26.96±1.244508
45	35.28±0.64246	16.45±6.123545	29.46±0.601041
60	58.66±0.45255	26.91±0.226264	32.46±0.282843
90	66.46±0.23335	36.38±1.562606	36.88±0.06364
120	92.46±1.26562	40.56±1.930402	51.69±0.403651

*Mean n = 6

Figure 1.3: Comparison release profile of liquisolid, conventional and marketed tablet



➢ **Compatibility between Drug and Excipients:**

The compatibility and interactions between drug and excipients were checked using Fourier transform infra-red (FTIR) spectroscopy and results obtained were as follow:

Figure 1.4: IR spectrum of optimized formula (F14)

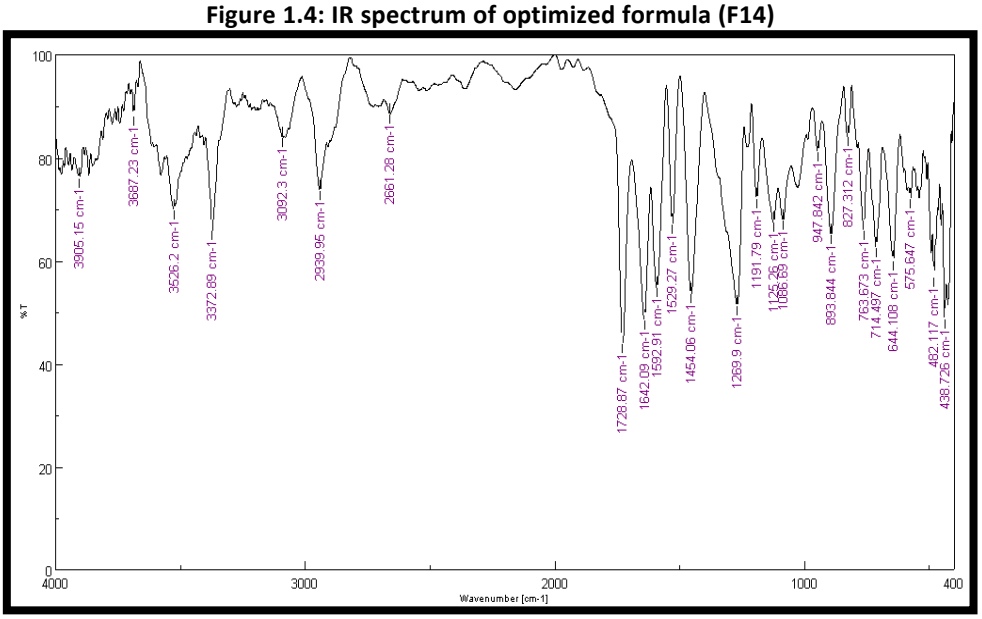


Table 1.11: Peaks observed in spectrum[25, 26]

Sr.no.	Wavenumber (cm^{-1})	Functional group	Peak observed	
			Pure Mebendazole	Blend F14
1.	1650-1635	C=O stretching	1624.05	1628.86
2.	1650-1450	C=C Stretching	1592.91	1592.91
3.	4000-3000	C-H stretching	3060.12	3092.3
4.	3500-3300	NH stretching	3406.64	3526.2
5.	1300-1050	C-O stretching	1088.62	1086.69
6.	1680-1650	C=N stretching	1648.84	1642.86

Observations of spectrum were summarized in Table 1.11. The blend showed almost the same characteristic peaks of drug indicating no interaction. In the spectra almost of the optimized formulation, N-H stretching of amide group of the mebendazole was shifted towards lower wavelength and the other peaks are almost the same. This indicated that overall symmetry of the molecule is not significantly affected.

➢ **Stability Studies:**

The batch F14 was subjected to stability study. Stability study was conducted at 40°C & 25°C to investigate the effect of temperature on physical parameter of the formulation for 3 months.

Table 1.12: Stability studies data for accelerated temperature

Batch No. & Stability Condition F14 40^0c ±2^0c/ 65%±5% RH	Hardness* kg/cm^2 ±SD	DT* Min ±SD	Friability % ±SD	Assay* % ±SD	Dissolution Study* % CR ±SD
Initial	3.6±0.49	3±0.14	0.45±0.82	99.9±0.14	92.93±0.7489
1st month	3.5±0.82	3.2±0.49	0.46±0.42	100±0.24	93.38±0.6961
3rd month	3.8±0.39	3±0.39	0.49±0.55	99.89±0.83	92.93±0.7489

*Mean n = 6

Table 1.13: Stability studies data for room temperature

Batch No. & Stability Condition F14 25^0c ±2^0c/ 60%±5% RH	Hardness* Kg/cm² ±SD	DT* Min ±SD	Friability % ±SD	Assay* % ±SD	Dissolution Study* % CR ±SD
Initial	3.6±0.55	3±0.47	0.45±0.15	99.9±0.43	92.93±0.7489
1st month	3.8±0.52	3.3±0.34	0.45±0.57	99.89±0.69	91.81±0.9226
3rd month	3.4±0.11	3.2±0.73	0.42±0.43	102.1±0.45	92.23±1.383

*Mean n = 6

To obtained information on the stability of tablet the effects of storage on the release profile and the crushing strength of tablets showed that storage at different conditions neither had an effect on the hardness nor on the release profiles of liquisolid tablets. This indicates that the technology is a promising technique to enhance the release rate without having any physical stability issues. Tablet was packed in polythene bag and kept in humidity chamber maintain it at 45°C±2% and desiccators for 25°C±2% for 3 months. Changes in parameter were investigated after 1 and 3 months. No major differences were found in evaluated parameter before and after storage at 45°C & 25°C.

CONCLUSION:

From the results obtained from executed experiments it can be concluded that:

Among the nonvolatile agent PEG 200, PEG 400 & Glycerine. PEG 400 was found to show good release. All Precompression & Post compression parameters studied were concluded that formulation F14 shows acceptable results. From the In-vitro drug release study and kinetics study of optimized formulation was concluded that enhanced the dissolution rate of mebendazole. FT-IR study concluded that no interaction between drug and excipient found. After studied the 3 months stability study were concluded that the prepared liquisolid tablets are stable. Liquisolid tablet dissolution profile shown good dissolution rate were compared to marketed & conventional preparation of the same drug.

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