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Research Article

FORMULATION, CHARACTERIZATION AND IN-VITRO DISSOLUTION STUDIES OF METADOXINE TABLETS PREPARED BY VARIOUS GRANULATION METHODS

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ABSTRACT

Pharmaceutical tablets are robust, flat, or biconvex dishes, according to the Indian Pharmacopoeia. Depending on a range of medicinal substances, they vary in shape and differ greatly in size and weight. In the era of increasing health awareness and strict standards set by regulatory authorities such as the US FDA, WHO, and globalization, it has become mandatory for the producer to launch a product cost-effectively. In the tablet dosage form, two classes of drugs are administered orally. Narrow extensions of the parietal peritoneum that suspend the diaphragm's liver are the right and left coronary ligaments. To produce an effective and reliable product, the drug must have a fine particle size and a large surface area. The tablet coating takes place inside a perforated rotating drum in a controlled atmosphere. Tablets are lifted and turned into the center of the drum from the sides. To make the tablet surface easier to swallow, every tablet surface is exposed to an even amount of deposited/sprayed coating. The purpose of the present investigation is to formulate a tablet of Metadoxine, which improves cognitive impairment and the main psychological symptoms due to occasional or prolonged alcohol abuse, such as aggressiveness, agitation, mood, and behavioral disturbances. The tablets were prepared using direct compression, dry granulation and wet granulation method and comparison of the same with an innovator's product.

Keywords: Tablets, Metadoxine, Dry granulation, direct compression, Wet granulation

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INTRODUCTION

The heaviest gland in the body is the liver. In size, the liver is second only to the skin. In the human body, the liver is inferior to the diaphragm. The visceral peritoneum almost totally covers the liver. The liver is divided by the falciform ligament into two important lobes: the large right lobe and the smaller left lobe (a fold of peritoneum). The Falciform Ligament suspends the liver in the abdominal cavity. Ligamentum teres is a remnant of the foetus's umbilical vein. Narrow extensions of the parietal peritoneum that suspend the diaphragm's liver are the right and left coronary ligaments. [1, 2, 3, 4]

The most important method of administering drugs with systemic effects is the oral route of drug administration. A tablet is a form of pharmaceutical dosage that includes a blend of active substances and excipients. Tablet costs are also lower than other forms of oral dosage.[5] Excipients include diluents, binder or granulating agents, gliders (flow aids) and lubricants. To render the tablet smoother and easier to swallow, a polymer coating is often applied. They vary in shape and differ significantly in size and weight depending on the number of medicinal substances.[6] The formulation and design of tablets can be described as how the formulator ensures that the correct amount of drug is delivered in the correct form. In tablet dosage form, two classes of drugs are administered orally. Formulation, granulation, and tableting on the material's surface properties are critical. Before finalizing the formula, must thoroughly understand the physical properties of the active ingredient. To produce an effective and reliable product, the drug must have a fine particle size and a large surface area. Several pharmaceutical adjuncts, known as excipients, are usually found in compressed tablets. The recipients determine the bulk of the final product in dosage forms such as tablets, capsules. The tablet coating takes place inside a perforated rotating drum in a controlled atmosphere. Angled baffles fitted into the drum and inside the drum, airflow provides ways to mix the tablet bed.[7] Tablets are raised and turned into the centre of the drum from the sides. An even amount of deposited/sprayed coating is exposed to each tablet

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surface. Tablet coating equipment consists of spray guns, coating pans, polishing pans, solution tanks, blenders and mixers. It has become mandatory for the producer to launch a product cost-effectively in the era of increasing health awareness and the strict standards set by regulatory authorities such as the US FDA, WHO, and globalization.[8]

Metadoxine acts on alcohol metabolism promote the conversion of alcohol into acetaldehyde and subsequently its urinary excretion. Pyrrolidone carboxylate of drug accelerates the uptake of glycine into the purine synthesis to increase the AMP concentration.[9] Pyridoxine facilitates phosphorylation of AMP to ATP. Restores the correct ratio of saturated and unsaturated fatty acids in all tissues. Inhibits fibrosis by normalizing the enzyme proline hydroxylase.[10] The drug is rapidly absorbed as such and therefore can supply the same amount of pyridoxine and Pyrrolidone carboxylate in the tissues. The bioavailability of the drug is high, between 60-80%. The half-life is 40-60 minutes. The drug is excreted mainly through urine and faeces.[11]

MATERIAL AND METHODS

MATERIALS

Metadoxine was obtained as a gift sample from Ajanta Pharma Limited, Mumbai. Microcrystalline cellulose (Avicel PH 101®) and Croscarmellose sodium (Ac-Di-Sol®) were procured from FMC Biopolymer (USA), Polyvinylpyrrolidone (Kollidon®) were procured from BASF (Germany), Opadry Pink 21K540020® were obtained as a gift sample from Colorcon, Mumbai and other chemicals were procured from Qualigens fine chemicals, Sigma Aldrich (India) and Hi-Media laboratory (India).

METHODS

Characterization of API: The API sample was subjected to pre-formulation studies such as visual appearance, micromeritics determination and API-excipient compatibility. Granules ready for compression were evaluated for flow properties, loss on drying, particle size analysis.[12]

Compatibility study: API's compatibility study with multiple commonly used excipients to understand the physical and chemical interaction between them in the proposed formulation system. The suggested excipients were mixed with the API based on their level of use in the appropriate ratio selected. As a control, the API and excipients alone were also subjected to study. The following samples were packed in glass vials and held at 30ºC. 65 per cent RH for compatibility study, which was then physically analyzed at 1-, 2-, 4- and 8-week intervals.[13]

Evaluation of Tablets: Prepared tablets were evaluated for in-process quality control test and evaluated for dissolution test using USP Type II (Paddle) Dissolution apparatus.[14]

EXPERIMENTAL STUDIES

Metadoxine is moisture sensitive, tablets needed coating. The coating was carried out using a composition involving Ethyl cellulose to provide a moisture barrier. The market sample was obtained in a blister pack since the prepared tablets were suggested to be packed in Alu-Alu blister packs. Dissolution method for prepared tablets is not mentioned in any of the pharmacopoeias. The performance of the prepared tablets should be compared with that of the marketed sample. This should be done as a discriminatory dissolution.

Preparation of tablets using direct compression method (Batch size 100 tablets)

Metadoxine and Avicel PH 101® were sifted through 40# and mixed. Magnesium stearate was sifted through 60# and used as a lubricant. The blend parameters were found to be satisfactory. Hence compression processed. Compression parameters include D tooling; punch dimension was 13 mm standard concave. The humidity of the compression area was 46% and measured using Lutron HT-305 Dew Point Humidity Meter. [15,16]
The manufacturing formula is described in table 1.

Table 1: Metadoxine Tablet by Direct Compression Method

Ingredients	DCM1 (mg/unit)	DCM2 (mg/unit)	DCM3 (mg/unit)
Metadoxine	500	500	500
Avicel PH 101®	130	140	134
Kollidon 30®	--	--	6
Mag. stearate	20	10	10
Total	**650**	**650**	**650**

DC: Direct compression, M: Metadoxine, Mag.: Magnesium

Tablets were capped during the compression process in the case of DCM1. Thus, with increased Avicel PH-101® and decreased magnesium stearate, tablet weight increases. In DCM2, the capping of the tablet was still observed, so Kollidon 30 ® in DCM3 was added as a dry binder. In DCM3, with Kollidon 30® as a dry binder, the issue of capping was noted. Therefore, the dry granulation technique for tablet preparation was favored in DCM2 using the same composition.

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Preparation of tablets using dry granulation method (Batch size 100 tablets)

Capping was observed in direct compression method in the above 3 batches, i.e., DCM1, DCM2 and DCM3, the formula was revised to dry granulation using the roller compactor process.

Metadoxine and Avicel PH 101® have been sifted and mixed through sieve 40#. At 3 metric ton pressure and 6 rpm roller speed, a prepared blend was passed through the roller compactor to form a compact mass. The compacted mass was sifted to obtain granules through 25#. Lubrication was carried out with magnesium stearate (sifted through 60 #) and allowed 3 minutes to be mixed with phase 3 granules at 15 RMP using an octagonal blender. Compared with direct compression blend, blend parameters showed that the roller compactor improved the blend flow property. The lubricated blend was thus exposed to compression. Compression parameters include D tooling; punch dimension was 13 mm standard concave. The humidity of the compression area was 43% and measured using Lutron HT-305 Dew Point Humidity Meter. The manufacturing formula is described in table 2.

Table 2: Metadoxine Tablet by Dry Granulation Method

Ingredients	DGM1 (mg/unit)	DGM2 (mg/unit)	DGM3 (mg/unit)
Metadoxine	500	500	500
Avicel PH 101®	140	138	135
Mag. stearate	10	12	15
Total	**650**	**650**	**650**

DG: Dry granulation, M: Metadoxine, Mag.: Magnesium

During the compression process, tablets were capped in the case of DGM1. Thus, tablet weight increases with increased Avicel PH-101® and reduced magnesium stearate. The problem of capping with increased hardness was observed in DGM2, so the quantity of magnesium stearate was increased in DGM3. The issue of capping was noted in DGM3 with increased amounts of magnesium stearate. Therefore, the use of a wet granulation technique for the tablet's preparation was preferred because of the capping problem in all 3 batches prepared by the dry granulation method.

Preparation of tablets using wet granulation method (Batch size 200 tablets)

Metadoxine was water-soluble, so lump formation problems occurred with water as a binder solvent during the granulation process. IPA was selected as binder solvent during the granulation process and Kollidon 30® as a binder based on such API property. [16,17]

Table 3: Metadoxine Tablet by Wet Granulation Method

Ingredients	WGM1 (mg/unit)	WGM2 (mg/unit)	WGM3 (mg/unit)
Metadoxine	500	500	500
MCC	67	61	55
Avicel PH 101®	68	61	61
Kollidon 30®	6	7	7
AcDiSol®	--	12	18
Mag. stearate	9	9	9
Total	**650**	**650**	**650**

WG: Wet granulation, MCC: Microcrystalline cellulose

Compression parameters include D tooling; punch dimension was 13 mm standard concave. The humidity of compression area was 39-40% and measured using Lutron HT-305 Dew Point Humidity Meter. The manufacturing formula is described in table 3.

WG: Wet granulation, M: Metadoxine

The drug, MCC were sifted through 40# and mixed in RMG for 5 mins. The impeller was run at 75rpm, and the chopper was off. 10% w/v Kollidon 30® in Isopropyl alcohol was prepared and used for the granulation process. Prepared binder solution was added within 2 minutes with the impeller at 75 rpm and chopper off for the granulation purpose in RMG. Further mixing was carried out for 3 mins with the impeller at 75 rpm and chopper off. The wet mass was dried at 40° C using Retsch Dryer till LOD was found 0.91% and dried mass was sifted through 25#. Dried granules were mixed with Avicel PH 101® and AcDiSol® (sifted through 40# & not used in trail WGM1) in an octagonal blender for 5 mins 15rpm. Lubrication was done with magnesium stearate (sifted through 60#) & allowing to blend with the granules of step 3 at 15 RMP using octagonal blender for 3 minutes.

In WGM1, the blend was tested for bulk density, tapped density, compressibility index, Hausner's ratio and loss on drying. The compressed tablet friability test was not successful. It was therefore decided to raise the concentration of the binder. The compressed tablet's disintegration time was found to be greater than the official limits. Therefore, it was decided to add a tablet disintegrant. [17,18,19]

In a batch prepared by WGM2, the disintegration time of tablet was found still higher; hence in the next trial, the disintegrating agent's concentration was increased, but friability of compressed tablets was found within the range. The dissolution of an uncoated tablet was carried out by UV spectrophotometry to check the drug release. The dissolution parameters are described below table 4.

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Table 4: Dissolution test parameter for tablets prepared by wet granulation method

Dissolution apparatus	:	USP Type II (Paddle) Dissolution apparatus
Medium	:	0.1N HCl
Volume	:	900 ml
Paddle speed	:	50
Temperature	:	37 ± 0.5°C
Withdrawal	:	10ml
Time	:	15, 30, 45 & 60 min.

In WGM3 batch, the Disintegration time of tablet was found higher in the previous trial; hence, the disintegrating concentration was increased from 12 mg/unit to 18 mg/unit.

Compression parameters were found satisfactory, but API was moisture-sensitive hence it was decided to perform coating on the tablets of trial 7 for moisture protection and improve physical appearance.

Tablets of trial WGM3 were divided into 2 parts as WGM3A and WGM3B and used for coating Trial WGM3A with Opadry Pink 21K540020®.

Preparation of Coating Solution

Opadry Pink 21K540020® 5 percent w/w in IPA: Methylene chloride blend (40:60) was prepared. Stirring was done and then filtered through the muslin cloth for 45 minutes. 20% of the additional coating solution was prepared to compensate for damages. Ganscoater model GHPN III-mini was used to coat using Gansons, USA coater [18-19]. The parameters of the coating are mentioned in table 5.

Table 5: Coating parameters for WGM3A and WGM3B

Coating parameters	Results
Inlet temperature	40°C-42°C
Outlet temperature	26°C-29°C
Tablet bed temperature	29°C-30°C
Pan speed	6 rpm
Spray rate	1.8 g/min
% Weight gain	3%

The dissolution profiles of the test batch WGM3A and WGM3B were performed and compared with the product of the innovator, which is a significant feature of the in vivo prediction of the formulation behavior under investigation. Two statistical factors called difference factor (f1) and similarity factor were used to compare the product and test batches of innovators (f2).

$$f_1 = \frac{\sum|R_t - T_t|}{\sum R_t} \times 100$$

Where,

f_1= Difference factor

$|R_t - T_t|$ = Absolute difference of % API released at each time points between reference Product and test product

R_t = % API release of the test product at each Time points

$$f_2 = 50.\log\left\{\left[1 + (1|n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5}.100\right\}$$

Where,

F_2 = Similarity factor

n = No. of time points

R_t = Reference profile at time point t

T_t = Test profile at time point t

The f1 and f2 values of both WGM3A and WGM3B were compared, and compared to WGM3A, it was better in the WGM3B experiment. The WGM3B formula was then chosen as an optimized formulation and therefore the WGM3B tablets multimedia dissolution profile was tested in 0.1 N HCl, Water, Buffer pH 4.5 and Buffer pH 6.8. Thus, optimized formulation as per Trial WGM3 and WGM3B as shown in Table 6.

Table 6: Optimized formula - Metadoxine coated Tablet

Ingredients	WGM3C (mg/unit)
Metadoxine	500
Microcrystalline cellulose	55
Avicel PH 101®	61
Kollidon 30®	7
AcDiSol®	18
Magnesium stearate	9
Opadry 21K540020®	20
Total	**670**

Stability study: The purpose of the stability test is to provide evidence as to how, over time, the structure of the drug material or drug product changes under the influence of a variety of environmental factors, such as temperature, humidity and light, as well as to determine the duration of the drug substance re-test or the shelf life of the drug product and the recommended storage conditions. The collection of test conditions defined in the ICH Q1A (R2) guideline focuses on the analysis of the effects of climate conditions and samples have been held for 6 months in an accelerated stability study and tested at intervals of 1 month, 2 months, 3 months and 6 months. [20-25]

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RESULTS AND DISCUSSION

Pre-formulation study

Characterization of API Metadoxine was characterized using various parameters and all the parameters complies with the standard given in Pharmacopoeia. The API had fair flow properties and compressibility index.

Table 7: Characterization of Metadoxine

Parameters	Result
Appearance	White to off white crystalline powder
Colour	Colorless
Taste	Tasteless
Odour	Odourless
Solubility	Freely soluble in water and methanol, soluble in methanol, insoluble in chloroform and diethyl ether
Bulk Density	0.608 g/ml
Tapped density	0.489 g/ml
Compressibility index	19.57 %
Hausner's ratio	1.24
Angle of repose	38.6°
LOD	0.40%

Particle size determination: Particle size determination of Metadoxine was performed by sieve analysis method using sieve shaker and is shown in table 8.

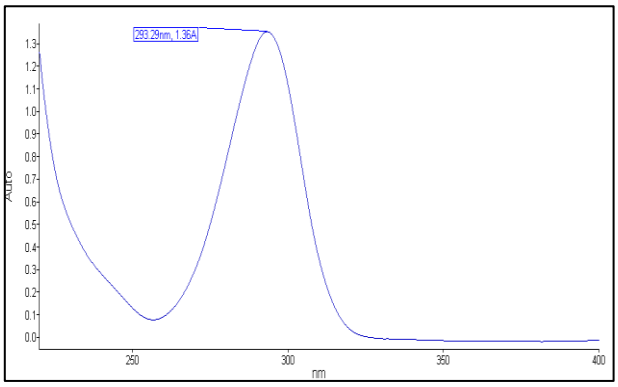
Table 8: Particle size distribution of Metadoxine

Mesh (microns)	% Retained	% Cumulative Retained
On 20 # (> 850 µ)	0	0
On 40 # (> 425 µ)	26.2	26.2
On 60 # (> 250 µ)	69.7	95.9
On 80 # (> 180 µ)	2.9	98.8
On 100 # (> 150 µ)	0.98	99.78
Below 100 # (< 150 µ)	0.22	100
Total	100	-

Identification of API: UV spectrophotometry, IR spectrometry and DSC study were used to confirmation or identification of drug.

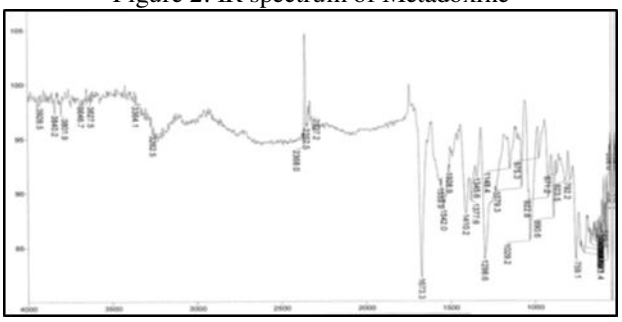
UV Spectroscopic method: UV λmax: 293nm.

Figure 1: UV spectrum of Metadoxine



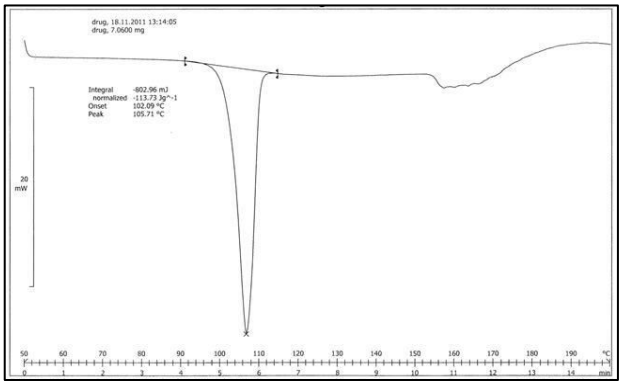
IR study: The IR spectrum of Metadoxine is shown in figure 2.

Figure 2: IR spectrum of Metadoxine



DSC study: Differential scanning colorimeter scan of API exhibits a sharp melting endotherm with onset temperature 102.09°C and peak temperature 105.71°C as shown in Figure 3.

Figure 3: DSC thermogram of Metadoxine



Compatibility study: Compatibility studies between Metadoxine and various excipients carried out in closed condition vials at 30°C / 65% RH. All the samples were evaluated for physical evaluation and no change in physical appearance at the end of 8 weeks was observed. Based on these observations, incompatibility of active with selected excipients.

Blend Analysis: Various parameters including bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose and loss on drying were performed. DCM1, DCM2, DCM3 blend (by direct compression method) and DGM1, DGM2 and DGM3 blend (by dry granulation method) showed comparatively fair flow prope66rty; but during compression of DCM1, DCM2, DCM3, DGM1, DGM2 and DGM3 blend capping was observed. Thus, with both the methods i.e., Direct compression (DCM1, DCM2 and DCM3) and Dry granulation (DGM1, DGM2 and DGM3) capping was observed. Therefore, wet granulation method was adopted. WGM1, WGM2 and

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WGM3 blend shows fair flow properties; therefore blend was used for compression.

Compression IPQC Parameters: In-process quality control parameters for trial WGM1, WGM2 and WGM3 including average weight, thickness, hardness, friability and disintegration time were performed and summarized in table 9.

Table 9: Compression IPQC Parameters

Parameter		WGM1	WGM2	WGM3
Average weight (mg)		650.2 ±0.56	650.1 ±1.0	650.4 ±0.9
Thickness (mm)		5.42 ±0.04	5.40 ±0.05	5.42 ±0.06
Hardness kPa		8.67 ±0.8	9.46 ±0.7	9.42 ±0.9
Friability %	100 revolutions	0.413 ±0.81	0.192 ±0.97	0.187 ±1.12
	300 revolutions	1.143 ±0.91	0.769 ±1.11	0.752 ±1.81
Disintegration time		15.05 ±0.65	11.00 ±1.17	8.40 ±1.02

During IPQC study of compressed tablets of WGM1 higher friability and disintegration time was observed. Hence Formula was revised as WGM2. Disintegration time of uncoated WGM3 tablets was less than Innovator coated tablets hence dissolution study was carried out to check effect of coating agent on drug release.

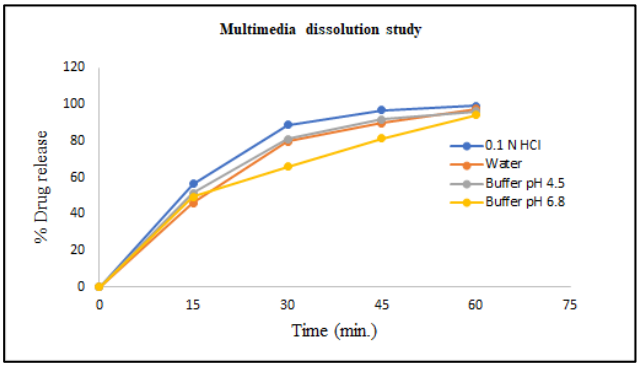
Evaluation of Coated tablets: Coated tablets were evaluated for average weight, thickness, hardness, disintegration time and dissolution test to check drug release as mentioned in table 10.

Table 10: Evaluation of coated tablets

Parameter (Unit) n=No. of samples	Observed Value (±) S.D.
Weight variation (%) n=20	Mean 669.6 mg +1.57%, -2.14% S.D. = 0.072
Thickness (mm) n=20	Mean 5.53 mm +2.17mm, -1.97mm S.D.=0.131
Hardness (kPa) n=20	Mean 15.40 kPa +1.17kPa, -1.29kPa S.D.=1.49
Disintegration time (min) n=6	Mean 9.75 min +1.12 min, -0.89min, S.D.= 1.17
Drug content (%) n=2	Mean 98.80 S.D.=1.88

Multimedia dissolution study: This study is used to mimic the *in-vivo* condition by doing *in-vitro* test and pH/buffer selection is based on the exposure of drug from stomach to intestine/colon. Multimedia dissolution study of WGM3C tablets in 0.1N HCl, Water, Buffer pH 4.5 and Buffer pH 6.8 was carried out as shown below figure 4.

Figure 4: Multimedia dissolution profile of WGM3C tablets



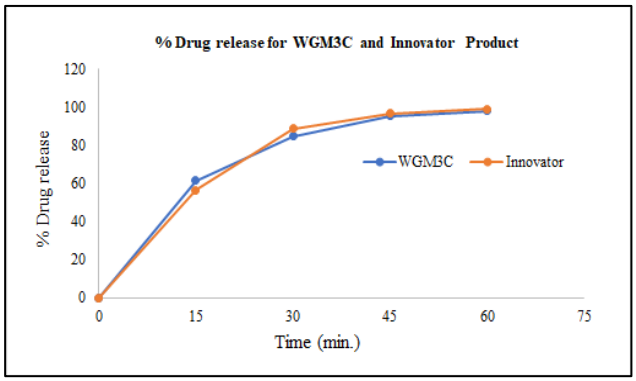
Comparison of Difference factor (f1) and Similarity factor (f2): The fit factors can be expressed by two approaches: *f*1 (the difference factor) and *f*2 (the similarity factor). Two dissolution profiles to be considered similar and bioequivalent, f1 should be between 0 and 15 whereas f2 should be between 50 and 100. Therefore, as shown in table 11, the dissolution profiles of coated tablets (WGM3C) and innovators product is given.

Table 11: Comparison of f1 and f2 using WGM3c and Innovators product

Time	Mean % Drug Release		(R-T)	$(R-T)^2$
0	0	0	0	0
15	61.5	56.5	5	25
30	84.8	88.6	3.8	14.44
45	95.3	96.7	1.4	1.96
60	98.1	99.00	0.9	0.81
Σ	**339.7**	**340.8**	**11.1**	**42.21**

The dissolution profiles of the WGM3C and innovator product have been presented in figure 6. According to the result, the WGM3C have shown superior dissolution performances over the innovator product.

Figure 5: Dissolution profile of WGM3C and innovator product



Stability study: Accelerated stability testing was carried out to provide evidence of how the quality of the manufactured tablets may change with time under the

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influence of environmental factors such as temperature and humidity. The prepared tablets were tested for accelerated stability test for 6 months in an accelerated stability chamber (Thermo lab) at 40 ± 2ºC and 75 ± 5% relative humidity. All the samples tested during 0-, 3- and 6-month interval and meet all the specified parameters as per standards.

CONCLUSION

Liver is the body's heaviest gland that performs a variety of functions, including synthesis, storage, digestion, excretion. Up to today, only Ayurvedic formulations were available for the treatment of liver disorders. Synthetic molecules were prepared using synthetic molecules for generic drug applications. Tablets were coated using Opadry Pink 21K540020® as a coating agent to enhance physical appearance, and provide moisture safety. The goal was to achieve tablets with the same disintegration time as innovator tablets to obtain f1 value less than 15, and an f2 value of more than 50. All the stability samples were prepared as per optimized formulation and kept for stability study as per ICH guideline Q1A (R2) at 40°C ± 2°C/75% RH ± 5% RH, 30°C ± 2°C/65% RH ± 5% RH and 25°C ± 2°C/60% RH ± 5% RH. Six months stability data at 40°C ± 2°C/75% RH ± 5% RH were found within specifications.

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