FORMULATION, DESIGN AND DEVELOPMENT OF MIFEPRISTONE IMMEDIATE RELEASE TABLET

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ABSTRACT

Mifepristone tablet is being developed for the termination of 49 days pregnancy following regulatory submissions. The proposed commercial formulation for Mifepristone tablet is an immediate release tablet, with strength (350/200 mg) is proposed for commercialization. This study presents a summary of the process optimization of Mifepristone tablet. The purpose of this research is to prepare Mifepristone immediate release tablet by wet granulation technique. In order to obtain the best, optimized product six different formulations were developed. Different filler, disintigrants and lubricants were taken as variables in different ratios. Weight variation, thickness, hardness, friability, disintegration time; *In-vitro* release and pharmaceutical assay were studied as response variables. Poor flow property was observed with the formulation containing less concentration of Colloidal silicon anhydrous during slugging. However, in the remaining four formulations containing constant concentration of Colloidal silicon anhydrous, improved flow property was observed due to absence of static charges during slugging. The formulation F-6 was selected as an optimized product. The different physical properties and *in-vitro* release profile showed F-6, best comparable with reference product. Optimization has been proven an effective tool in product development.

Keywords: Mifepristone, Optimization, Wet granulation technique, Immediate release tablet, Disintegration time, Slugging.

INTRODUCTION:

Immediate release Tablet

In pharmaceutical industries, manufacturers of generic tablets are generally concerned for optimization of the mixture of excipients to obtain a product that meets a required standards[1,2]. Now the scientists have focused their attention on the formulation immediately released tablet. The task of developing rapidly disintegrating tablet is accomplished by using suitable diluents and super disintegrants[3]. Main factor for immediate release dosage form is poor solubility of the drug and for the treatment of unwanted defect or disease[4]. There are various methods acquired by pharmaceutical industries to produce granules, but the most common and suitable method for most of the drug is wet granulation technique that offers several advantages for example high dose drugs that experience poor flow and/or poor compactibility can be granulated to obtain suitable flow and cohesion for compaction with low dose drugs, content uniformity in the tablet can be increased[5]. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1-10% by weight relative to the total weight of the dosage unit.[6]

An immediate release dosage form allows a manufacturer to extend market exclusively, while offering patients a convenient dosage form or dosage regimen. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques.[10,11]

Mifepristone

Mifepristone is a compound categorized in anti-progestin category. It is an abortifacient agent (a menstrual inducing agent). It is used for the medical termination of intrauterine pregnancy through 49 days pregnancy. Mifepristone has anti-progestational activity that results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit, and monkey) the compound inhibits the activity of endogenous or exogenous progesterone. Mifepristone is soluble in 100% ethanol. It is very soluble in methanol, chloroform and acetone and poorly soluble in water. It has absolute bioavailability of a 200mg oral dose is 69%. Mifepristone is 98% bound to plasma proteins, albumin and α_1- acid glycoprotein.

MATERIALS AND METHOD

MATERIAL

Ingredients used in the preparation of Mifepristone immediate release tablet were Mifepristone(Zhejiang Xianju Junye Pharmaceutical Co Ltd), Maize starch(Roquette, France), Microcrystalline cellulose(FMC Biopolymer, Ireland), Silica colloidal Anhydrous(Evonik Degussa GmbH, Germany), Povidone(ISP Sales Limited, UK), Magnesium stearate(Ferro Corporation, Cleveland, USA)

Equipment used in preparation of Mifepristone immediate release tablet are Analytical balance(PW214/Eagle, MS205S/A01/Mettle Toledo, Elderpan2000), Rapid mixture Granulator(HSMG/Gansons), Fluidized bed dryer(TG200/Retsch dryer), Tablet Compression machine(Cip Labpress), Octagonal Blender(GMP159/Gansons), Tablet hardness tester(EH01/Electrolab), Vernier Caliper(Absolute Digimatic), Friability test apparatus(EF-2/Electrolab, Dissolution Test apparatus(Electrolab), UV Visible spectrophotometer(Shimadzu UV Spec 1700), HPLC(Shimadzu), Moisture balance (HB43-S Halogen Mettle Toledo), Tap density tester USP-II(ETD-1020/Electrolab), Multi mill with 1.5mm screen(GMP15/Gansons), Mechanical sifter(GMP54/Gansons), Disintegration Apparatus USP(ED-2L/Electrolab), Electromagnetic sieve shaker(Electrolab), Tray dryer(Ambassador), Dehumidifier(NV20000SS/Topical nortec), Vaccume gauge oven.

METHOD

FORMULATION:- For the preparation of Mifepristone immediate release tablet wet granulation method was opted because API is hygroscopic in nature and so direct compression method cannot be applied. Other major reasons for not applying direct compression method were flow of blend was very poor and disintegration time was not matching with innovator.

The steps for manufacturing of mifepristone immediate release tablet to be taken were:

All the ingredients were accurately weighed as per formula in Table 6.9 and dispensed in clean polythene covers.

Table 1. Trial batches of developed formulation

INGREDIENTS	**F-1 mg/tab**	**F-2 mg/tab**	**F-3 mg/tab**	**F-4 mg/tab**	**F-5 mg/tab**	**F-6 mg/tab**
Mifepristone	200.00	200.00	200.00	200.00	200.00	200.00
Silica colloidal anhydrous	2.00	2.00	2.00	2.00	2.00	2.00
Maize starch	80.5	79.60	80.00	78.80	76.00	74.60
Microcrystalline cellulose	44.00	45.00	45.00	46.00	48.00	49.50
Plasdone K29/32	12.10	11.90	11.40	11.20	10.80	10.40
Purified Water	--	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Maize Starch	7.80	8.00	8.10	8.50	9.00	9.80
Magnesium Stearate	3.50	3.50	3.50	3.50	3.50	3.50
Tablet Weight	350.00	350.00	350.00	350.00	350.00	350.00

Silica colloidal anhydrous, Maize starch, Microcrystalline cellulose were sifted individually through #40 sieve using Vibro Sifter.

Mifepristone was mixed with Silica colloidal anhydrous and then sifted through #40 sieve.

Table 2: Mesh size used for sifting & mixing of ingredients

S.No	INGREDIENTS	MESH SIZE
Intragranular Part		
1.	Mifepristone	#40
2.	Silica colloidal anhydrous	#40
3.	Maize starch	#40
4.	Microcrystalline cellulose	#40
Extra Granular Part		
5.	Maize starch	#80
6.	Magnesium Stearate	# 40

After sifting all the above Intragranular Part ingredients were transferred into a big polythene cover and mixed for 30 min.

The above co-sifted blend and pre-sifted maize starch and microcrystalline cellulose were loaded in Rapid Mixer Granulator (RMG) and mixed for 10 minutes at Impeller slow speed and Chopper off.

Binder solution was prepared by dissolving weighed amount of Povidone in required amount of purified water and added to the dry mix blend to granulate. Binder was added with low impeller speed. Kneading was done for 3-10 min(s) at fast impeller speed, repeated kneading for 10-60 sec(s) with fast impeller speed and slow chopper speed.

Granules were dried in Fluidized Bed Dryer at 60°C & airflow 20 % till the LOD reaches below 2.50%

Moisture content checked at 105°C for 5min in Mettler Toledo Halogen Moisture analyzer.

Dried granules were passed through #20 sieve

The retention was milled by using multimill with 1.5 mm screen at slow speed, with knife forward configuration

Milled granules were passed through #20 sieve.

The above milled blend was mixed with pre-sifted extragranular Maize Starch (#40 sieve) in an Octagonal Blender for 15 min at 12 rpm.

Pre-sifted Magnesium Stearate (# 80 sieve) was added to the blend and mixed for 5 minutes at 12 rpm.

The above lubricated blend loaded in Hopper and take 10.40 mm round, standard concave punches embossed with “J02” on upper punch and plain on lower punch, and dies for the corresponding punches.

The average weight of tablets was also set according to the finished product specification. It should be 350mg limit ±5%

The weight, thickness and friability were adjusted at the beginning of the preparation and then, monitored every 15-minute during whole process of compression.

Now Lubricated blend were compressed into tablets to meet the required standard physical parameters as given in Table and the compression was continued of the lubricated granules

Table 3: Required Parameters during compression of optimize batch

S.No	Parameters	Specification
1.	Appearance	Light yellow powder
2.	Weight (mg)	350.0 mg
3.	Hardness (N)	70.0-100.0 N
4.	Thickness (mm)	4.76-4.84 mm
5.	Diameter (mm)	10.38-10.42 mm
6.	Disintegration Test (without disc) (min.)	1minute 30 second
7.	Friability (%) at 100 rpm	0.11 %

- The tablets de-dusted by blowing air or by means of sieving to remove the excess powders. The tablets were inspected for chipping, black spot etc.
- The appearance, group weight variation, individual weight variation, thickness, hardness, friability, Disintegration time parameters were checked before proceeding for compression of the batch.
- The in-process checks were carried out as follows:
  - 30 Tablets were weighed and average thickness was measured at an interval of 15 minutes to ensure that the weights and thickness of tablets are within the limits.
  - The mean hardness of 6 tablets, friability of 30 tablets and Disintegration Time of 6 tablets twice a shift was measured.

The individual weight of 30 tablets were checked every 15 minutes

EVALUATION: Granules of different batches were evaluated for flow properties that are follows:

Pre-compression tests

Angle of repose

The Angle of repose of blend was determined by funnel method. The accurately weighed powder blend was taken in funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touches the apex of the powder of the blend. The powder blend was allowed to flow through the funnel freely to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following formula:

$\tan \theta = h/r$

Where,

h = height of the powder cone and

r = radius of the powder cone

Table 4: Effect of angle of repose θ on flow property

Angle of repose	**Type of flow**
< 25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk Density

Density is defined as the weight per unit volume. Bulk density (ρb), is defined as the mass of powder divided by the bulk volume and expressed as gm/cm^3.

Bulk density(ρb) = $(M)/V_b$

Where, M = Mass of test sample

V_b = Bulk volume

Tapped Density

Tapped density is defined as the weight of powder per unit tapped volume. Tapped density was determined by powder mass into 25ml of measuring cylinder and 100 tappings were done using tapped density apparatus. This method was repeated three times and the mean value is calculated as result of tapped volume. It is also expressed as gm/cm^3.[7]

Tapped density (ρt) = M/ V_t

Where, M = Mass of test sample

V_t = Tapped volume

Compressibility Index (Carr's Index)

The simplest way of measurement of free flow properties of powder is compressibility, an indication of ease with which a material can be induced to flow given by % compressibility index(%CI), which is calculated as follows:

$$\% CI = \frac{(\text{Tapped density} - \text{Bulk density}) \times 100}{\text{Tapped density}}$$

Hausner's Ratio

Hausner's ratio is an index of ease of powder flow, it is related to inter-particulate friction as such, could be used to predict powder flow properties. It is calculated by the following formula:[8]

$$HR = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post-compression tests

Weight variation test

According to the official test, 20 tablets were weighed individually and collectively. Average weight per tablet was calculated from the collective weight. Then the weights of the individual tablets were compared with the average weight to determine weight variation.

Batch F-1: Tablet was made by direct compression method and compression was not done because mifepristone is a floppy powder and has very poor flow.

Batch F-2: During granulation lumps were formed suddenly because the wet ability of API was very less, compression was not done.

Thickness

The thickness of the tablets was determined using a vernier caliper. 20 tablets from each batch were used and mean ± SD was calculated.

Hardness

For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester.

Friability

In The Roche friabilator the weight of tablets was noted initially (W1) and placed in a friabilator and rotated at speed of 25rpm for 4 min(s) or upto 100 revolutions. The tablets were dropped from a distance of 6 inches in each revolution reweighed and noted as (W2). The difference in the weight is noted and expressed as percentage.

$$\%\ \text{friability} = \left[1 - \frac{\text{weight of tablets after test}}{\text{weight of tablets before test}}\right] \times 100$$

The mean ± SD of 6 tablets were calculated.

Disintegration Time

The disintegration time of a tablet was determined using disintegration test apparatus as per I.P. A tablet was placed in each of the 6 tubes of the basket. Added a disk to each tube and the apparatus was operated using 0.01N HCl maintained at 37°±2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in 0.01N HCl maintained at 37°±2°C. The time in sec(s) taken for complete disintegration of tablet with no palpable mass remaining in the apparatus was measured and recorded.

Drug content uniformity

10 tablets were weighed and crushed in a mortar. Then weighed powder containing equivalent to 10mg of drug transferred into 100ml of 0.01N HCl to give concentration 100 µg /ml. 10ml from this stock solution was taken and diluted to 100ml of 0.01N HCl to give 10 µg /ml. Then 0.6ml from this solution was diluted to 10ml. The absorbance was measured at 304nm by UV-visible spectrophotometer.

Table 5: Evaluation of Physical parameters of finished product of trial batches

Test	**Acceptance criteria**	**F-3**	**F-4**	**F-5**	**F-6**
Thickness (mm)	**4.76-4.84mm**	4.78 ± 0.05	4.82 ± 0.02	4.76 ± 0.02	4.88 ± 0.04
Hardness (N)	**70-100 N**	98.8 ± 1.86	97.3 ± 1.72	100.0 ± 1.75	96.5 ± 1.12
Friability (%w/w)	**NMT 1.0% w/w**	0.96±0.03	0.85±0.05	0.75±0.05	0.70±0.02
Disintegration time (min.)	**NMT 15 minutes**	1.36±0.045	1.26±0.030	1.22±0.026	1.02±0.040

All values are expressed as Mean ± SD, n=6 for Thickness, Hardness and Disintegration time, and for friability n=3

***In-vitro* drug Release (Dissolution by UV)**[9]

In vitro drug release done under the conditions mentioned below:

Apparatus- USP Type II dissolution apparatus(paddle method)

Dissolution medium- 0.01N HCl 900ml at 75 rpm with temperature 37°C ± 0.5°C Wavelength-304nm

- **Standard solution**

Weighed accurately about 55mg of mifepristone and transfered into 100ml volumetric flask then added 50ml of Acetonitrile sonicate for 5 min to dissolved and make up the volume with diluents. Pipette out 5ml of ths stock solution into 250 ml volumetric flask and make up the volume with diluents and mixed well.

- **Test solution prepration**

Parameters which used for dissolution apparatus as described in the general monograph of USP for apparatus II. Degas the dissolution media by sonication for 10 min. Placed 900 ml of dissolution media into each vessel and equilibrate to 37±0.5 c with the paddles rotating. Placed 1 tablet in the apparatus taking care to exclude the air bubble from the dosage form and immediately operate the apparatus. Replenished the dissolution media into the each vessel after sampling. Filtered the solution through 0.45 µm filter. Further diluted 5 ml of the filtered solution into 100 ml volumetric flask and maked up the volume with diluents and measured the standard and sample. The % Drug release was calculated by formula:

$$\%\ DR = \frac{A_T}{A_S} \times \frac{W_S}{100} \times \frac{5}{250} \times \frac{900}{LC} \times \frac{100}{5} \times \frac{P}{100} \times 100$$

Where[;/'p

A_T = Absorbance of mifepristone from test prepration

A_S= Average absorbance of mifepristone from standard prepration

W_S= Weight of mifepristone taken in mg

P= Purity of mifepristone working standard taken in % on as such basis

LC= Labelled amount of mifepristone in mg per tablet

%DR= % Drug Release

Assay of Drug for HPLC

- **Mobile phase**

Water and acetonitrile were mixed in the ratio of 150:850 v/v respictevel. Filtered through 0.45 µm membrane filter and degas it.

- **Diluent**

Mixed HPLC grade water and acetonitrile in the ratio of 150:850 v/v respectively

- **Chromatographic system**

Column used was InertsilONS-3V.25λ, 4.6mm, 0.5µm, with ambient temperature, detector wavelength was 304nm, flow rate of sample 1.0ml/min., injection volume 10µl, run time 12 min., retention time about 3.6min(s)

- **Standard solution**

Weighed accurately about 60mg of mifepristone working slandered and transfered into 100ml volumetric flask, then added 10ml of diluent, sonicate for 5 min to dissolve and make up the volume with diluent. Pipetted out 5ml of this stock solution into a 50ml volumetric flask and make up the volume with diluents and mixed well.

- **Test solution prepration (prepare in duplicate)**

Weighed accurately not less than 20 tablets and note down the weight and then calculated the average weight. Crushed the tablets into fine powder with motar and pestle then weighted {accurately tablets powder equivalent to 600 mg of mifepristone approx 1050mg tablet powder} and transfer into a 250ml volumetric flask, added 160ml of diluents, sonicate for 20 min with occasional shaking and make up the volume with diluents. Centrifuged above solution at 2500 rpm about 5 min and Pipetted out 5 ml of this centrifuged solution into a 100ml volumetric flask and make up the volume with diluents.

- **Procedure**

Injected 10µl of diluents as blank, standard preparation and test prepration into the chromatogram record the chromatogram and measured the mifepristone peak response. The following sequence is followed for assay.

- **System suitability**

The relative standard deviation of peak areas of mifepristone from six replicate injections of standard prepration should NMT 2.0%

$$\% \text{ Mifepristone dissolved} = \frac{A_T}{A_S} \times \frac{W_S}{100} \times \frac{2}{100} \times \frac{900}{LC} \times \frac{P}{100} \times 100$$

Where

A_T = Absorbance of mifepristone from test prepration

A_S= Average absorbance of mifepristone from standard prepration

W_S= Weight of mifepristone taken in mg

P= Purity of mifepristone working standard taken in % on as such basis

LC= Labelled amount of mifepristone in mg per tablet

Table 6: Drug content of finished product of Trials batches

Formulations	**Drug content (%) w/w**
	Acceptance criteria NLT 90% & NMT 110%
F-3	99.8 ± 1.23
F-4	100.0 ± 1.37
F-5	104.5 ± 2.30
F-6	100.0 ± 1.08

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

A. Related substance of mifepristone (by HPLC method)

- **Mobile phase**

HPLC grade methanol, water and triethylamine were mixed in the ratio of 750:250:0.5v/v respectively. Filtered through 0.45µmmembrane filter and degas it.

- **Diluents**

HPLC grade water and methanol were mixed in the ratio of 2:8v/v respectively

- **Chromatographic conditions**

  Column used was Thermo hypersil BDS, 4.6×250mm, 5µm with temperature 30°C, Detectoe wavelength 304nm, Flow rate of sample 1.0ml/min, injection volume 10µl, run time 30 min(s), retention time about 7.3 min(s).

- **Diluted standard solution**

Weighed accurately about 100 mg of mifepristone standard and transfered into 200ml volumetric flask, then added 140 ml of diluents and sonicated for 5 min to dissolve and volume make up with diluents. Pipette out 5 ml of this stock solution into 250 ml volumetric flask and make up the volume with diluents. Further dilute 5 ml of it into a 50ml volumetric flask and make up the volume with diluents and mixed well.

- **Test solution prepration**

Weighed accurately not less than 20 tablets and note down the weight then calculate the average weight. Crushed the tablets into fine powder with motar pestle then weighted accurately a weight 175mg of tablet powder and transfer into 200ml volumetric flask then added 140 ml of diluents sonicate for 30 min with occasionally shaking and make up the volume with diluents. Centrifuge the sample at 2500 rpm for 5 min.

- **Procedure**

Injected 10µl of diluents as blank diluted standard preparation and test preparation into chromatogram and recorded the chromatogram and measured the peak responses.

The following sequence is followed for related substance:

- **Calculation**

% of known impurities of mifepristone

$$= \frac{A_{KI}}{A_{MSP}} \times \frac{W_S}{200} \times \frac{5}{250} \times \frac{5}{50} \times \frac{200}{W_T} \times \frac{P}{100} \times \frac{\text{Avg wt in mg}}{LC} \times 100$$

% of single maximum unknown impurities of mifepristone

$$= \frac{A_{TUI}}{A_{MSP}} \times \frac{W_S}{200} \times \frac{5}{250} \times \frac{5}{50} \times \frac{200}{W_T} \times \frac{P}{100} \times \frac{\text{Avg. wt in mg}}{LC} \times 100$$

Total impurities =

Sum of known impurities + Sum of total unknown impurities $= \frac{A_{SI} - A_{BKT}}{A_{SI}} \times 100$

Where

A_{KI}- Area of known impurity obtained in test prepration

A_{MSP}- Area of mifepristone peak in diluted standard

A_{UKI}- Area of unknown impurity obtained in test prepration

A_{TUI}- Area of total unknown impurity including single maximum unknown impurity

W_S- Weight of mifepristone working standard taken in prepration of diluted standard solution.

P- Purity of mifepristone working standard in %on as such basis

LC- Label claim of mifepristone in mg per tablet

R_{RF}- Relative response factor

A_{SI}- Average area of standard injection

A_{BKT}- Area of bracketing standard injected from the standard prepration

RESULTS

Table 7: Evaluation of Optimized Tablets

Batch no.	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose	Inference
F-1	ND	ND	ND	ND	ND	ND
F-2	ND	ND	ND	ND	ND	ND
F-3	0.522± 0.005	0.712± 0.006	26.68± 0.10	1.36± 0.010	27.22± 0.12	Good flow
F-4	0.508± 0.002	0.692± 0.004	26.58± 0.15	1.36± 0.020	27.03± 0.15	Good flow
F-5	0.494± 0.002	0.648± 0.005	22.44± 0.12	1.28± 0.023	23.92± 0.12	Excellent flow
F-6	0.486± 0.004	0.637± 0.005	23.61± 0.11	1.31± 0.010	24.80± 0.10	Excellent flow

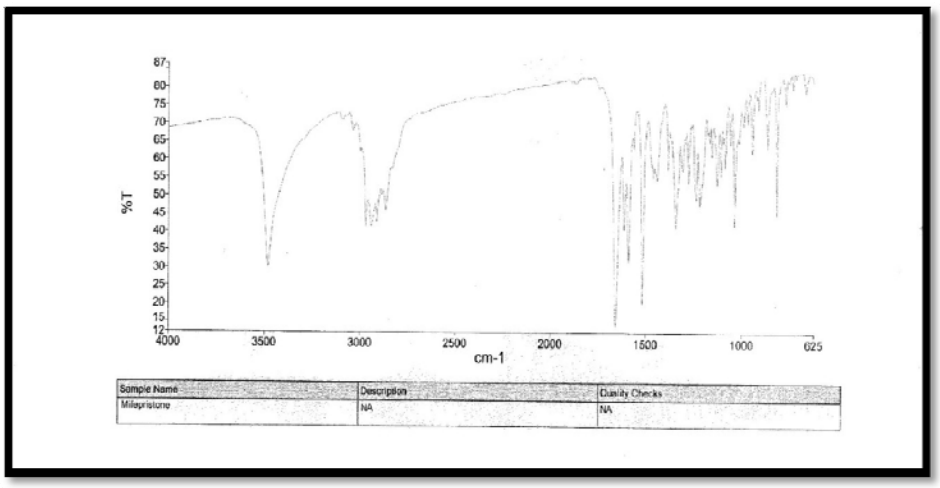

Fig 1: FT-IR Spectra of Mifepristone

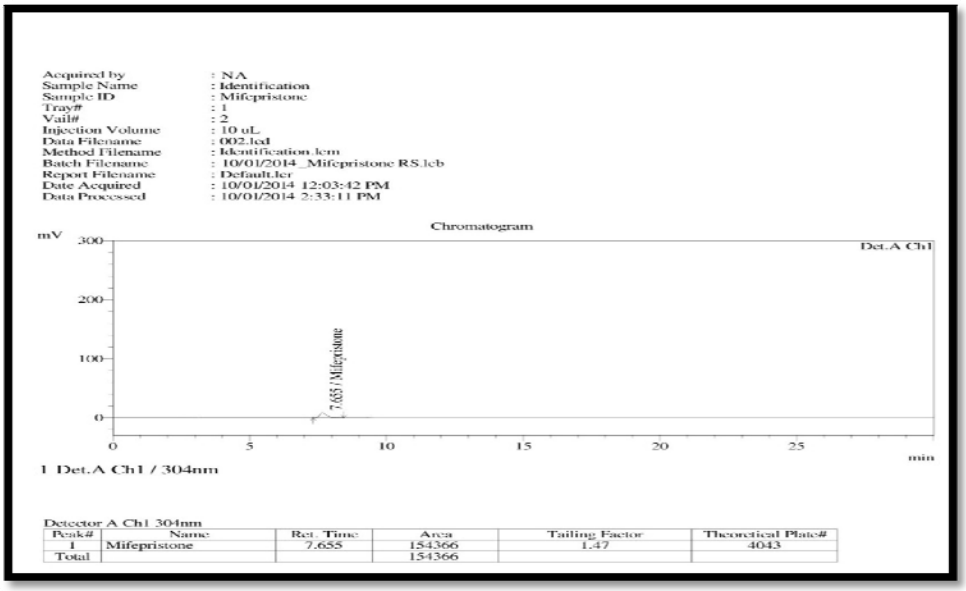

Fig 2: HPLC chromatogram of Mifepristone

Table 8: % Drug release Comparison of Innovator tablet with Trial batches tablets

Dissolution 75 RPM , USP II (% Drug release in w/w) 0.01N Hydrochloric acid					
Time (mins)	**Innovator (%)**	**F-3 (%)**	**F-4 (%)**	**F-5 (%)**	**F-6 (%)**
0	0	0	0	0	0
5	87	72	75	80	85
10	98	76	81	88	97
15	101	82	86	94	100
20	101	86	88	95	101
30	102	90	92	97	102

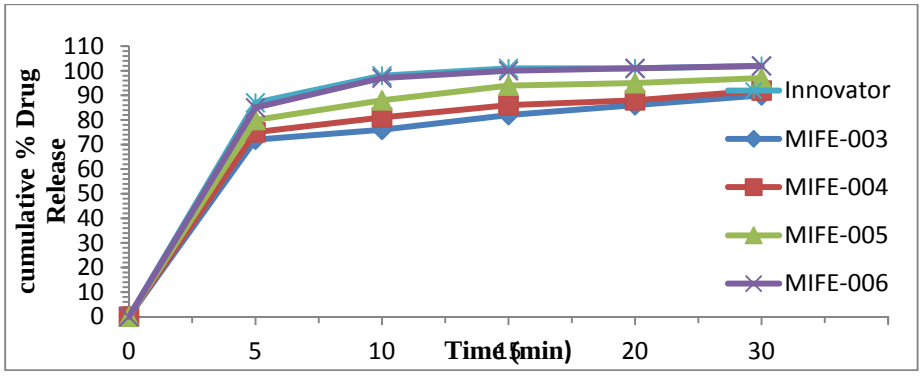

Fig 3: Graph showing % drug release of finished products of trial batches

DISCUSSION

The present study was an attempt to develop a stable immediate release tablet formulation of mifepristone. The physical and chemical evaluation of mifepristone was done. Further the identification test confirmed the mifepristone as an authentic batch. The Pre-formulation studies confirmed that there was no interaction between the drug and the proposed excipients. The objective was to develop a tablet, which has a similar dissolution pattern in official media as that of innovator.

By using same ingredients as used by innovator we have better chance of clearing the bioavailability and bioequivalence test, therefore we were using the same ingredients as used by the innovator. The quantities of the ingredients used should not be infringing the already approved patents for the same drug. The type of ingredients used in the innovators tablet was taken from the physician desk reference book.

The best possible grades of the ingredients were then optimized. After optimizing the grade of ingredients, the quantity and distribution of these ingredients were optimized to get the final optimized product, which gave similar dissolution and disintegration time as that of innovator tablet. The similar dissolution profile was confirmed at 75 rpm in media i.e. 0.01N Hydrochloric Acid.

The stability studies done for final optimized batch no. F-6 according to the ICH guidelines. Evaluation of stability data indicated that there is no significant change at the end of three months at 40°C/75% RH, 30°C/65% RH, 25°C/60% RH with respect to all parameters as compared to the initial data.

The immediate release tablet was prepared by Wet Granulation method.

- The ingredients used in the formulation are not infringing any present patents for the same drug.
- The ingredients used in the formulation showed no interaction with the drug.
- The *in vitro* release was carried out in 0.01N Hydrochloric acid.
- The *in vitro* release at 75 rpm showed similar dissolution profile when compared with the innovator tablet
- The stability studies were carried out and there was no significant change in the drug content, assay, and disintegrstion and dissolution rate.
- The tablet ingredients and process were not infringing the present patents.

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