



Research Article

FORMULATION, DEVELOPMENT AND EVALUTION OF AN IMMEDIATE RELEASE TABLET OF METHOTREXATE

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ABSTRACT

Methotrexate is a Folic Acid Antagonist and used as an Antineoplastic agent. In this study Methotrexate immediate release tablet is developed, which was stable and bioequivalent generic tablet formulation equivalent to innovator's product. The developed tablet formulation shows similar dissolution and disintegration profile as that of innovator tablet. The immediate release tablet was prepared by Wet Granulation method. The *in vitro* release was carried out in 0.1N Hydrochloric Acid. The *in-vitro* release at 50 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 DT and dissolution rate.

Keywords: Methotrexate, Antineoplastic agent, innovator tablet.

INTRODUCTION

From the times immemorial, drugs have been an inseparable part of mankind's history since they fulfill one of our most basic necessities. To administer these drugs in an appealing and palatable form and in the required amount and rate, they have to be developed into an acceptable dosage form. Thus the concept of formulation development evolved to alleviate sufferings of the mankind.^{3, 4, 6}

Pros and cons compared to other dosage forms

Because oral administration of drugs is simple, convenient and safe, it is the most frequently used route. Over 80% of the drugs formulated to produce systemic effects in the United States are produced as oral dosage forms. In the past, it was even thought in some cultures (e.g. China) that the drug effect could only be achieved via the oral route and therefore other dosage forms, such as ointments, were considered ineffective. The oral tablet has a relatively short

history, however, and was introduced as late as 1843 by the Englishman Brockedon, who invented the first hand-operated device for compressed pills. Nonetheless, for a long time the tableting machine was not available at pharmacies, and pills, divided powders and capsules, which were made by hand, were more common. With the development of the modern pharmaceutical industry and effective production methods, mass production of tablets became possible and their popularity increased worldwide. The European Pharmacopoeia (2002) defines tablets as "solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth

where the active substance is liberated.” Despite the long and continuing history of the development of new technologies for administration of drugs, the tablet form remains the most commonly used dosage form. However, advantages and disadvantages associated with this well-established form could be discussed, in order to form the basis for the development of new improved systems for tablet administration.^{6,7,8}

The oral route of drug administration is the most important method of administering drugs. It is probable that 90 % of drugs are administered by oral route. Oral dosage form comprises of tablets, capsules, granules, pills, pellets etc. Because oral administration of drugs is simple, convenient and safe, it is the most frequently used route. Over 80% of the drugs formulated to produce systemic effects in the United States are produced as oral dosage forms.

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to dysphagic patients, especially the elderly and bedridden, and new business opportunities. Immediate release dosage forms are those for which $\geq 85\%$ of labelled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour. Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. Therefore for the quick onset of action The immediate release tablet of Methotrexate was prepared by wet granulation method.

MATERIALS AND METHODS

Methotrexate, Lactose Pharmatose 200 M (DHE Pharma), Supertab 21 AN (DHE Pharma), Microcrystalline Cellulose 101 (FMC Biopolymer), Microcrystalline Cellulose 102 (FMC Biopolymer), Plasdone K29/32 (ISP Technologies), Starch 1500 (Colorcon), Starch unipure F (National starch), Magnesium Stearate (Peter Greven). All the chemicals were

of commercial purity grade.

Aqueous Wet Granulation

Granulation was done in Rapid Mixer Granulator, weighed premix was added followed by addition of Plasdone K29/32 in purified water (Binder solution), impeller and chopper were operated at slow speed. Drying was performed in FBD with target LOD $< 2.0\%$ w/w. Sifting and milling was done in multimill. Finally milled granules were sifted through # 20 mesh ASTM. Blending was done in octagonal blender, extragranular materials were sifted through #40 mesh ASTM. Prelubrication blend was mixed in a blender for 15 mins with a speed of 12 rpm. Magnesium Stearate was added as a lubricant, post lubrication was done for 5mins with a speed of 12 rpm.

GRANULES ANALYSIS

Particle size analysis of final blend was done using Electromagnetic sieve shaker.

Formulation of Methotrexate IR Tablets

Various batches were prepared to optimise the excipient concentration, F1-F2 was optimized for lactose monohydrate, using two grades i.e Pharmatose 200M & Supertab 21 AN were optimized, batch prepared by using Pharmatose 200M showed most favourable result. Batches F3-F5 was optimized for starch / lactose ratio distribution, F5 was having concentration 45:15 ratio of Pharmatose 200M, Starch unipure F was found to be optimum. Batches F6-F9 was optimized for microcrystalline cellulose concentration, batch F9 that is having 25% 102 was considered best. Batch F10-F13 was optimized for pregelatinized starch concentration. Batch F10 consists of 15% pregelatinized starch intragranularly & 5% extragranularly was considered to be the best for further formulation, batch F14-F17 was optimized for Plasdone K 29/32, batch F16 was finally optimized batch.

DRUG CONTENT

The content of Methotrexate tablets was determined on HPLC. The liquid chromatograph is equipped with a 302-nm detector and a 4.6-mm $\times$ 25-cm column that contains packing L1. The flow rate is about 1.2 mL per minute. Chromatograph the Standard preparation, and record the peak responses as directed.

Procedure: relative retention times are about 0.35 for folic acid and 1.04 for drug X, the resolution R, between the folic acid and drug peaks is not less than 8.0 and the relative

standard deviation for replicate injection is not more than 2.5%. Good uniformity in drug 23 to 102.12 $\pm$ 0.8

DISSOLUTION STUDY

In-vitro dissolution studies of innovator and in-house tablets was carried out using USP Type II Paddle (model TDT-08L, Electrolab, India) at 37 $\pm$ 0.5 $^{\circ}$ C and 50 rpm using 900 ml of 0.1N Hydrochloric acid. Samples were withdrawn after 5, 10, 15, 30, 45 minutes, with sampling quantity is 10ml and subjected to comparative studies of innovator product and in-house product.

RESULTS AND DISCUSSION:

Particle size analysis by sieve shaker was carried out depicted in (Table 1). The appropriate diluents and binder were included in the formulation. Various excipient optimization has been done which result in the Prototype

optimized formula depicted in (Table 2).

The evaluation of granules of batches F1-F17 was done like angle of repose, bulk density, tapped density, hausner's ratio, compressibility index, and drug Content was evaluated which results that the flow of granules is good, depicted in Table (3). Evaluation of In-house tablet properties with different excipients & concentration from batch F1-F16 was done for friability, hardness, thickness, weight & drug content depicted in (Table 4). Formulation F16 Dissolution compared with Reference product, the dissolution profile of formulations F16 and Reference product was matched depicted in (Fig 1) therefore F16 was considered the final optimized formula for the formulation of an immediate release tablet of Methotrexate depicted in (Table 6).

Table 1: Particle size distribution of Methotrexate

Sieves	Initial wt (Empty sieves)	Final wt (Drug+Sieve)	Difference (Drug Retained)	%Retained	Cum % Retained
30	124.10	124.12	0.02	0.17	0.17
40	117.24	117.26	0.02	0.17	0.34
60	108.60	108.61	0.01	0.06	0.40
80	109.16	109.17	0.01	0.10	0.50
100	105.82	105.82	0.01	0.04	0.54
140	106.22	106.23	0.02	0.18	0.69
170	105.63	105.66	0.03	0.33	1.02
200	107.34	107.62	0.29	2.87	3.87
Pan	69.23	78.83	9.59	96.04	99.96

Table 2: Prototype formulation formula

Ingredients	Quantity (mg / tab)	% w/w
Intragranular		
API	2.5	2.5
Lactose	50	50
Starch	20	20
Pregelatinized Starch	10	10
Granulation		
Plasdone K29/32	0.5	0.5
Purified Water	q.s.	q.s.
Extra granular		
Cellulose Microcrystalline	16	16
Magnesium Stearate	1	1

Table 3: Evaluation of granules

Formulation	Angle of Repose	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index	Hausner's Ratio	Drug Content
F1	26.00 ± 0.03	0.675	0.884	23.66	1.31	100 ± 0.05
F2	27.52 ± 0.03	0.656	0.826	30.06	1.26	100.5 ± 0.03
F3	23.87 ± 0.09	0.645	0.870	25.92	1.35	98.54 ± 0.02
F4	28.47 ± 0.02	0.678	0.996	31.97	1.47	99.45 ± 0.05
F5	24.93 ± 0.03	0.632	0.897	29.57	1.42	102 ± 0.01
F6	25.29 ± 0.06	0.652	0.873	25.37	1.34	100 ± 0.05
F7	27.52 ± 0.03	0.659	0.869	24.24	1.32	99.61 ± 0.03
F8	23.87 ± 0.09	0.668	0.921	27.53	1.38	101.02 ± 0.01
F9	32.47 ± 0.02	0.654	0.869	24.81	1.33	98.21 ± 0.02
F10	24.93 ± 0.03	0.657	0.867	22.24	1.32	98.03 ± 0.03
F11	24.29 ± 0.06	0.621	0.875	29.07	1.41	101 ± 0.04
F12	26.52 ± 0.03	0.658	0.934	29.57	1.42	99 ± 0.02
F13	25.87 ± 0.09	0.689	0.1005	31.50	1.46	100 ± 0.05
F14	30.47 ± 0.02	0.673	0.915	26.47	1.36	99.87 ± 0.05
F15	25.93 ± 0.03	0.683	0.860	20.63	1.26	98.10 ± 0.06
F16	26.52 ± 0.03	0.667	0.853	21.87	1.28	99 ± 0.02
F17	25.87 ± 0.09	0.674	0.869	22.48	1.29	99.61 ± 0.03

Table 5. Dissolution Comparison of Innovator tablet with In-house tablet of Methotrexate

Time	%Drug Release Media-0.1N Hydrochloric Acid RPM- 50	
	Reference	F16
0	0	0
5	97	96.4
10	98	99.5
15	99	101
30	100	106
45	100	108

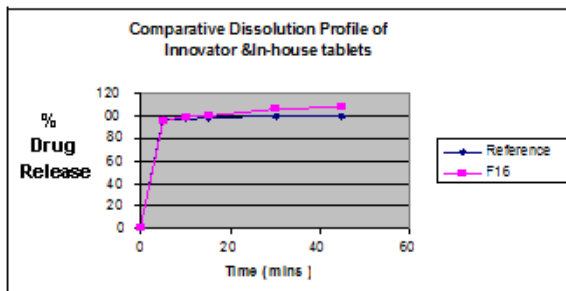
Table 4. Properties of in-house tablets with different excipients and concentrations

Formulations	Thickness* (mm)	Weight# (Gm)	Drug content* (%)	Hardness* (kg/cm ²)	Friability*** (%)
F1	3.30±0.1	2.0024±0.02	98.5±0.25	4.5±0.25	0.07
F2	3.30±0.1	2.0112±0.02	97.5±0.25	4.2±0.25	0.07
F3	3.29±0.1	2.0012±0.02	98.5±0.25	5.2±0.25	0.09
F4	2.96±0.1	2.0014±0.02	99.4±0.25	6.±0.25	0.11
F5	2.9±0.1	2.0025±0.02	96.5±0.25	4.2±0.25	0.15
F6	2.79±0.1	2.0024±0.02	98.5±0.25	6.2±0.25	0.14
F7	2.91±0.17	2.0045±0.02	98.7±0.25	6.2±0.25	0.14
F8	2.87±0.1	2.0056±0.02	98.5±0.25	5.8±0.25	0.15
F9	2.89±0.1	2.0046±0.02	98.5±0.25	4.6±0.25	0.17
F10	2.90±0.1	2.0032±0.02	98.5±0.25	5.6±0.25	0.12
F11	3.40±0.1	2.0124±0.02	98.5±0.25	5.2±0.25	0.11
F12	3.12±0.1	2.0024±0.02	98.9±0.25	7.0±0.25	0.15
F13	3.17±0.1	2.0147±0.02	98.3±0.25	6.1±0.25	0.16
F14	2.92±0.1	2.0145±0.02	97.5±0.25	4.2±0.25	0.10
F15	2.80±0.1	2.00.11±0.02	99.5±0.25	6.0±0.25	0.13
F16	3.25±0.1	2.0024±0.02	99.4±0.25	3.9±0.25	0.16

Table 6: Final Formula

Batch no:F16	Quantity (mg / tab)	%(w/w)
Intragranular		
API	2.5	2.5
Lactose Monohydrate (Pharmatose 200 M)	49.00	49.00
Starch(Unipure F)	13	13
Pregelatinized Starch (1500 LM)	5	5
Granulation		
Plasdone K 29/32	2.0	0.01
Purified Water	q.s.	q.s.
Extragranular		
Pregelatinized Starch(1500 LM)	5	5
Microcrystalline Cellulose (Avicel pH 102)	23	23
Magnesium Stearate	0.5	0.5

Fig 1. Graph showing percentage drug release of Innovator & In-house tablets in 0.1N hydrochloric acid.



CONCLUSION

The present study was an attempt to develop a stable immediate release tablet formulation of anti neoplastic drug Methotrexate. The physical and chemical evaluation of drug Methotrexate was done. Further the identification test confirmed the drug Methotrexate as an authentic batch. The Preformulation studies (physical) confirmed that there was no interaction between the drug Methotrexate 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 50 rpm in media i.e. 0.1N Hydrochloric Acid.

The accelerated stability studies done for final optimized batch no.F17 according to the ICH guidelines Evaluation of stability data indicates that there is no significant change at the end 3 Months at 40°C/75% RH with respect to all parameters as compared to the initial data. Hence the product was assumed to be stable, though the results of 6-months data will confirm its overall stability

- 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 Methotrexate.
- The ingredients used in the formulation showed no interaction with the drug.
- The *in vitro* release was carried out in 0.1N Hydrochloric Acid.

- The *in vitro* release at 50 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 DT and dissolution rate.
- The tablet ingredients and process were not infringing the present patents.

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