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FORMULATION AND CHARACTERIZATION OF METHOTREXATE CONTROL RELEASE TABLETS

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Abstract:

The present study was aimed at the formulation and evaluation of Methotrexate controlled release matrix tablets using suitable hydrophilic polymers to achieve sustained drug release and improve therapeutic efficacy. Methotrexate is an antimetabolite and antifolate drug widely used in the treatment of various cancers and autoimmune disorders. Controlled release dosage forms can reduce dosing frequency, maintain therapeutic drug concentrations, and enhance patient compliance.Methotrexate matrix tablets were prepared by the direct compression method using Sodium Alginate and Guar Gum as release-retarding polymers. The powder blends exhibited good flow properties suitable for tablet compression.The prepared tablets were evaluated for weight variation, thickness, hardness, friability, and drug content. All formulations showed acceptable physicochemical properties and complied with pharmacopeial specifications. In vitro dissolution studies demonstrated sustained drug release from the matrix tablets over a period of 8 hours. Among the four formulations, F3 exhibited the most desirable performance with satisfactory tablet characteristics, high drug content (98.83%), and maximum cumulative drug release (98.36%).Stability studies of the optimized formulation (F3) carried out under different storage conditions showed no significant changes in physicochemical properties or drug content, indicating good stability of the formulation.The results of the present investigation demonstrate that Methotrexate controlled release matrix tablets can be successfully formulated using suitable polymers, and formulation F3 was found to be the optimized formulation for providing sustained drug release with acceptable stability and tablet characteristics.

Keywords: *Methotrexate, FTIR Studies, Polymers, Direct compression technique, In vitro drug release studies*

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INTRODUCTION:

Oral drug delivery remains the most preferred route of drug administration because of its convenience, patient compliance, cost-effectiveness, and ease of manufacturing. However, conventional oral dosage forms often require frequent administration due to rapid drug elimination, leading to fluctuations in plasma drug concentration and reduced therapeutic efficacy. Controlled release drug delivery systems have been developed to overcome these limitations by releasing the drug at a predetermined rate over an extended period, thereby maintaining consistent plasma drug levels, reducing dosing frequency, minimizing adverse effects, and improving patient compliance.Controlled release tablets are designed to deliver the drug in a sustained manner for prolonged therapeutic action. The release of the drug is regulated through the use of hydrophilic or hydrophobic polymers that control the rate of drug diffusion and matrix erosion. Such systems are particularly beneficial for drugs that require long-term therapy, possess a short biological half-life, or cause dose-related side effects when administered as conventional dosage forms.Methotrexate is a folic acid antagonist widely used as an antimetabolite and immunosuppressive agent. It inhibits the enzyme dihydrofolate reductase, thereby interfering with DNA synthesis, repair, and cellular replication. Methotrexate is extensively prescribed for the treatment of rheumatoid arthritis, psoriasis, and various malignancies, including leukemia, lymphoma, osteosarcoma, and breast cancer. Although highly effective, conventional methotrexate therapy is associated with frequent dosing, fluctuations in plasma drug concentration, gastrointestinal irritation, and systemic toxicity, which may compromise patient adherence and therapeutic outcomes.

The development of controlled release tablets of methotrexate offers a promising approach to overcome these limitations by providing prolonged drug release, maintaining therapeutic drug concentrations for an extended duration, reducing peak plasma fluctuations, minimizing adverse effects, and enhancing patient compliance. Matrix tablets prepared using suitable release-retarding polymers such as Hydroxypropyl Methylcellulose (HPMC), Carbopol, Ethyl Cellulose, or natural polymers have been widely investigated for controlled drug delivery because of their simplicity, stability, and cost-effectiveness.

MATERIALS:

Methotrexate was procured from Synpharma Research Labs, Guargum, Sodium alginate, Microcrystalline cellulose, Magnesium Stearate and Talc were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Preparation method:

Methotrexate controlled release tablets were prepared by the direct compression method. Accurately weighed quantities of Methotrexate, polymer (Sodium Alginate or Guar Gum), and Microcrystalline Cellulose were passed through a #60 sieve and blended thoroughly to obtain a uniform powder mixture. The blended powder was mixed for 10–15 minutes to ensure uniform distribution of the drug and excipients.Subsequently, Talc and Magnesium Stearate, previously passed through a #60 sieve, were added to the powder blend and mixed gently for an additional 3–5 minutes. The final lubricated blend was compressed into tablets using a rotary tablet compression machine fitted with 8 mm concave punches. The compression force was adjusted to obtain tablets with a hardness of approximately 5–6 kg/cm². The prepared tablets were collected and stored in airtight containers for further evaluation.

Table-1: Formulation table of Methotrexate controlled release tablets

S.NO.	INGREDIENTS	F1	F2	F3	F4
1	Methotrexate	10	10	10	10
2	Sodium alginate	40	80	-	-
3	Guargum	-	-	40	80
4	Microcrystalline Cellulose	143	103	143	103
5	Magnesium stearate	3	3	3	3
6	Talc	4	4	4	4
7	Total weight	200	200	200	200

EVALUATION STUDIES

a) Bulk Density

The powder were precisely weighed from all trials and was slightly shaken to breakdown any agglomerates formed. Then it was kept in the measuring cylinder of required quantity. The volume engaged by the granules was calculated. The bulk density of granules was calculated by the formula.

Bulk density = weight of sample taken /volume noted

b) Tap density

The granules were precisely weighed from all trials. It was slightly shaken to breakdown any agglomerates formed. Then it was kept in the measurable cylinder of required quantity. Then the measuring cylinder was tapped until there is no further variation in volume. This is the tapped volume. The tapped density of granules was calculated as given below.

Tapped density = weight of sample taken / tapped volume

Where,

V_o = initial volume

$V_{f=}$ final volume.

Compressibility index

Carr's index also known as compressibility index is the index which determines the flow property with small quantity. Carr's indexes of the granules was calculated as given below,

Carr's index (%) = [(TBD-LBD)/ TBD] x100

Hausner's ratio

It is used to predict the flow property and this is underarticulate friction. Hausner's ratio was calculated as given below,

Hauser's Ratio = Tapped bulk density / Loose bulk density

The value of Hauser's ratio less than 1.25 directs good flow while higher than 1.5 directs poor flow.

Angle of repose

Angle of Repose It can be determined by using classic funnel method. The prepared granules which the flow property need to be analyzed was weighed accurately. The funnel height was accustomed in the way that the lowest just touched the top of heap of granules. Granules was permitted to freely flow through the funnel orifice to the surface. The radius of heap formed was measured. The angle of repose was determined using the equation.

$$\theta = \tan^{-1} h/r$$

Where

h = height of pile

r = radius of the base of the pile

θ = angle of repose

Evaluation Of Tablet

Weight Variation

Weight variation is one of the official quality control tests for tablets. This is important because it directly relates with drug content. To do this test, minimum 20 tablets were weighed separately and average weight was calculated and compared with individual weight. The deviation gives the report of the weight variation. Usually it is expressed in percentage. Weight variation should be done in process checking and for finished products.

Thickness

The dimensions like thickness and diameter of the tablets may have important effect in the drug content and other parameters. Hence it is required to maintain the thickness and diameter in the optimum acceptable range. This can be done by means of Vernier caliper. 10 tablets prepared from each trial were used. The average values were noted.

Tablet Hardness

Monsanto hardness tester was utilized to find the tablet hardness. In each formulation, 10 tablets were taken and the hardness was measured. The tablet was kept in the perfect position in the axis in the two jaws of instrument. The measurement should be zero kg/cm^2 at this stage. The knob is rotated to apply force to the tablet, the force is continued until there is fracture in the tablet. The point at which tablet breaks is break point and it was noted in kg/cm^2.

Friability

Tablet strength can be measured by using friabilator. This is performed to know the impact of shock abrasion on tablets when on travelling and handling. The test involves keeping the tablets in a plastic chamber and allowing it to revolve at 25rpm for 4 minutes that is equivalent to 100 rotations. In this test the tablets are subjected to drop at heights of 6 inches in each revolution. The initial weight and final weight of the tablets after dedusting were noted. The limit acceptable is less than 1% weight variation. It was calculated as follows. The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

W o = Initial weight of tablet

W = weight of tablets after revolution

Drug Content

The drug content directly relates to the pharmacological efficacy, so it is mandatory to do the drug content test. It is an official quality control test. The drug content in all formulations were analyzed by triturating 20 tablets in mortar and pestle, then from the powder 75 mg equivalent of Dapagliflozin was taken and transferred to 100ml

standard volumetric flask. Then the volume was prepared to 50ml with pH 6.8 phosphate buffer. This was shaken for 15 min to mix. Then the volume was prepared to 100ml with phosphate buffer. The solution was strained by using whatmann filter paper and then it is diluted and absorbance was determined by using UV-Visible spectrophotometer at 285 nm using pH 6.8 phosphate buffer as blank.

In vitro release studies

The in vitro drug release studies of Methotrexate controlled release tablets were carried out using the USP Dissolution Apparatus II (Paddle Method). The dissolution medium consisted of 900 mL of phosphate buffer (pH 6.8), maintained at a temperature of 37 ± 0.5°C throughout the study. The paddle speed was set at 50 rpm.At predetermined time intervals, 5 mL samples were withdrawn from the dissolution medium and immediately replaced with an equal volume of fresh phosphate buffer maintained at the same temperature to maintain sink conditions. The withdrawn samples were filtered through a 0.45 µm membrane filter and suitably diluted, if necessary.The amount of Methotrexate released was determined spectrophotometrically using a UV–Visible spectrophotometer at a wavelength of 302 nm. The cumulative percentage drug release was calculated and plotted as a function of time. All dissolution studies were performed in triplicate, and the results were expressed as mean ± standard deviation.

Stability studies:

The stability studies are performed to analyze the quality of drug and drug product with exposure to different temperature and humidity conditions on estimated time. General conditions like light, environment and other general parameters are maintained and the general evaluation tests were performed at different time interval periods. It is undesirable and time consuming to do full shelf life period study. To avoid this accelerated stability studies has been adopted.

RESULTS AND DISCUSSIONS:

Pre compression Parameters

Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.599-0.620.

Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.710-0.720.

Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 27 to 30^0

Compressibility index: Compressibility index was carried out, it found between 13.15% to 14.23 % indicating the powder blend have the required flow property for compression.

Table-2: Results of Pre compression parameters

F. No	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose(0)
F1	0.620	0.710	13.15	1.14	28^0
F2	0.612	0.718	14.23	1.17	29^0
F3	0.608	0.719	13.46	1.14	30^0
F4	0.599	0.720	13.89	1.17	27^0

Post compression parameters

Table-3: Results of Evaluation parameters of tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	199	3.69	4.53	0.26	96.32
F2	198	3.75	3.29	0.30	97.24
F3	201	3.16	4.15	0.27	98.83
F4	200	3.79	3.64	0.29	89.53

1.Weight Variation

- The weight of all formulations ranged from 198–201 mg, which is within the acceptable pharmacopeial limits for tablets of this size.

- Minor variations in weight could be due to differences in powder flow properties or compression during tablet formation.
- This indicates that the tablet mass was uniform, ensuring consistent drug dosing.

2. Thickness

- Tablet thickness ranged from 3.16–3.79 mm, showing slight variation across formulations.
- Such variation is considered acceptable as tablet thickness is influenced by compression force, granule density, and formulation composition.
- Uniform thickness is essential to ensure consistent drug release and packaging convenience.

3. Hardness

- The hardness values ranged between 3.29–4.53 kg/cm², indicating adequate mechanical strength to withstand handling, transportation, and storage.
- F1 showed the highest hardness (4.53 kg/cm²), suggesting slightly higher compression force or binder effect.
- Tablets with moderate hardness are preferable for controlled release formulations to prevent cracking but still allow gradual drug release.

4. Friability

- Friability values were between 0.26–0.30%, which is well below the official limit of 1%, indicating that all tablets were resistant to abrasion and handling stress.
- This confirms that the tablet integrity was maintained during processing, and the formulations are mechanically robust.

5. Drug Content

- Drug content ranged from 89.53–98.83% across different formulations.
- Formulations F2 (97.20%) and F3 (98.83%) showed the highest drug content, indicating better drug uniformity and incorporation in the polymer matrix.
- Lower drug content in F4 (89.53%) may be due to incomplete mixing or drug loss during compression.
- Overall, the drug content is reasonably high, but optimization may be needed to improve uniformity in lower-performing formulations.

In-vitro Dissolution Study

Table-4: In vitro release data of tablet F_1 to F_4

Time (hrs)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	15.69	14.59	19.96	17.50
2	24.58	25.81	26.35	26.73
3	37.50	38.50	37.42	35.43
4	44.63	45.10	48.20	47.50
5	58.10	57.48	55.63	56.10
6	68.20	69.83	71.29	58.10
7	83.16	85.10	88.10	82.36
8	94.58	95.25	98.36	95.34

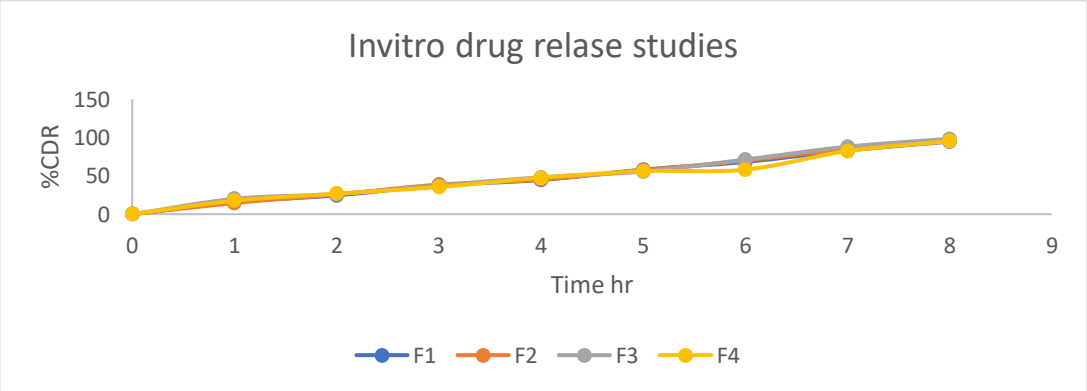


Fig-1: In vitro drug release studies of F1-F4 formulations

F3 shows highest release (98.36%) and good drug content, so F3 is the optimized formulation.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 3 months. Parameters quantified at various time intervals were shown;

Table-5: Results of stability studies of optimized formulation F3

Formulation Code	Parameters	Initial	1st Month	2nd	3rd	Limits as per Specifications
F-3	25^{0}C/60%RH	98.36	97.58	96.84	95.81	Not less than
F-3	30^{0}C/75% RH	98.36	97.53	96.35	95.83	Not less than
F-3	40^{0}C/75% RH	98.36	97.13	96.50	95.25	Not less than

SUMMARY AND CONCLUSION:

The present study was undertaken to formulate and evaluate Methotrexate controlled release matrix tablets using Sodium Alginate and Guar Gum as release-retarding polymers. Four formulations (F1–F4) were prepared by the direct compression method and evaluated for their physicochemical characteristics, drug-excipient compatibility, in vitro drug release, and stability.Preformulation studies confirmed the suitability of Methotrexate for formulation development. The drug was found to be a yellow to orange-yellow crystalline powder with a bitter taste and was odorless in nature. The melting point was found to be 198–202°C, indicating the purity of the drug. Solubility studies revealed that Methotrexate was slightly soluble in water and methanol and soluble in phosphate buffer pH 6.8.FTIR studies demonstrated the compatibility of Methotrexate with the selected excipients, as no significant changes in the characteristic peaks were observed in the physical mixtures.

The calibration curve of Methotrexate in phosphate buffer pH 6.8 at 302 nm showed good linearity and obeyed Beer-Lambert's law.The powder blends exhibited satisfactory pre-compression properties with acceptable bulk density, tapped density, compressibility index, Hausner ratio, and angle of repose, indicating good flow characteristics suitable for direct compression.The prepared tablets showed acceptable post-compression characteristics such as weight variation, thickness, hardness, friability, and drug content. The friability values were below 1%, confirming adequate mechanical strength of the tablets.

In vitro dissolution studies demonstrated sustained drug release from all formulations over a period of 8 hours. Among all formulations, F3 exhibited the highest cumulative drug release of 98.36% and satisfactory physicochemical properties, indicating its suitability as an optimized formulation.

Stability studies conducted on the optimized formulation F3 under different storage conditions showed no significant changes in drug content, indicating good stability throughout the study period.

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