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Formulation and Evaluation of Comparative Study on Natural and Synthetic Polymer to Matrix Tablet (Methotrexate)

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ABSTRACT

Objective: The basic goal is to optimize formulation which favors of body susceptibility and minimize the side effect by synthetics polymer. Sustained-release drug delivery systems, with an aim of improved patient compliance, better therapeutic efficacy, fewer side effects, and reduced dosage regimen with less toxicity for treatment for many acute and chronic diseases. The objective of the proposed work is to formulate and compare sustained release matrix tablet of Methotrexate, insuring sustained delivery of drug with body suitable polymer. The broad objective of the present study is: To select suitable natural and synthetic polymer for the formulation of matrix tablet of Methotrexate to ensure the sustained release of the drug. **Methods:** Preformulation may be defined as the stage of formulation development during which the physical pharmacist characterizes the physicochemical properties of the drug substance which are considered important in the formulation of a stable, effective, and safe dosage form. During this evaluation, possible interactions with various inert ingredients intended for use in the final dosage form are also considered. In the present work, preformulation studies such as solubility, determination of melting point, development of calibration curve, compatibility studies were carried out. FT-IR spectroscopy study was carried to assess the compatibility between Methotrexate and polymer Hydroxy Propyl Methyl Cellulose, Xanthan gum, Crude cashew gum. The pure drug and drug with polymers were separately scanned. The pellets were prepared with potassium bromide. Both the individual and mixture spectra were compared for confirmation of peaks. **Result & Conclusion**: In the present investigation an attempt has been made to design and develop some Methotrexate matrix tablets using Xanthan gum, Crude cashew gum, Hydroxypropyl methyl cellulose, and their combination as release retarding polymers. The release exponent 'n' determined was between 0.45 and 0.89 thus the drug is released through anomalous or non – Fickian diffusion.

INTRODUCTION:

The oral route for drug delivery is the most popular, desirable, and most preferred method for administrating therapeutically agents for systemic effects because it is natural, convenient, and cost-effective to the manufacturing process. One of the most common approaches used for prolonging and controlling the rate of drug release is incorporating the drug in a hydrophilic colloidal matrix such as Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, carbopols, chitosan, alginates, and gelatin, etc. The mechanism and kinetics of the release of drugs incorporated in these polymer matrices have depended on the type and amount of polymer as well as on the physicochemical properties of drug substance[1]. Generally, the drug release from these matrices includes penetration of fluid, followed by dissolution of drug particles and diffusion through fluid-filled pores (Collette and Morten, 2002). The diffusion of the drug through a matrix is a rate-limiting step.[2-3]

Present sustained release drug delivery systems are for a maximum of 10 hours of clinical effectiveness. Such systems are primarily used for drugs with short elimination half-life.

The oral route is the most commonly used route for drug administration. The oral dosage form is flexible to design. The treatment of acute disease or chronic illness has been achieved by the delivery of drugs to the patient for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids, aerosols, etc. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity, and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges.[4]

Historically, the most popular drug delivery system has been the matrix because of its low cost and eases of fabrication. Methods of altering the kinetics of drug release from the inherent first-order behavior especially to achieve a constant rate of drug release from matrix devices have involved several factors[5-6].

There are three types of matrix tablets i.e.

1. Hydrophilic matrices
2. Fat-wax matrices

3. Plastic matrices

Table No. 1: Types of matrices

Types of matrices	Examples
Hydrophilic matrices	Methylcellulose, Hydroxyethylcellulose, Sodiumcarboxy-methylcellulose, Carboxypolymethylene, Hydroxypropylmethylcellulose (HPMC).
Fat-wax matrices	Stearyl alcohol, Stearic acid, Triglycerides, Carnauba wax, Polyethylene glycol.
Plastic matrices	Polyvinylchloride, Ethylcellulose, Methyl acrylate-methyl acrylate copolymer, Polyethylene

NEED FOR THE STUDY:

Oral delivery of drugs is the most convenient route of drug delivery systems due to

- Ease of administration
- Patient compliance
- Flexibility in formulation

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic absorption. Such immediate-release products result in relatively rapid drug absorption and the onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations[7-8] fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. In recent years, various modified–release drug products have been developed to control the release rate of the drug and/or the time for drug release[9-10].

CRITERIA FOR SELECTION OF SUSTAIN DRUG RELEASE:

A. PHYSICAL-CHEMICAL FACTORS:

- Dose
- Aqueous solubility
- Partition coefficient
- Drug stability

B. PHARMACOLOGICAL FACTORS:

- Absorption
- Distribution
- Metabolism
- Duration of action
- Therapeutic

C. PHARMACEUTICAL FACTORS:

- Route of administration
- Total dose

D. PATIENT /DISEASE FACTORS:

- Age
- Physiological state
- Acute/chronic therapy
- Degree of mobility of the patient

To perform the preformulation study of Drug:

- Solubility studies of the drug.
- Melting Point determination.
- Drug-excipient compatibility (FTIR) study.

- Determination of λ max.
- Preparation of Standard curve of Methotrexate using UV-visible spectroscopy.

To perform the preformulation study of Physical mixture of formulation:

- Angle of repose
- Bulk density
- Tapped density
- Hausner; ratio
- Carr index
- Content uniformity

To prepare different batches of sustained release matrix tablet of Methotrexate.

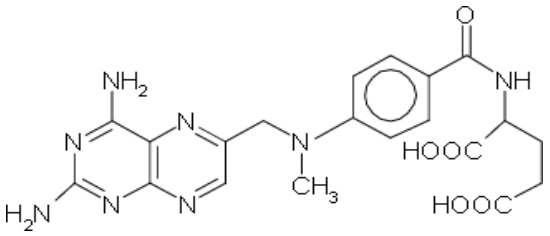
To evaluate the formulated matrix tablet of Methotrexate:

- Shape of tablet
- Tablet dimension
- Weight variation
- Friability
- Drug content
- In vitro drug release[11]

METHOTREXATE:

Category: Antineoplastic, antirheumatic.

Methotrexate is an antimetabolite, antineoplastic that inhibits folate metabolism by its inhibiting effects on dihydrofolate reductase.



Synonyms: Amethopterin, α-methopterin, 4-Amino-10-methylfolic acid.

Molecular weight: 454.45

Molecular formula: $C_{20}H_{22}N_8O_5$

IUPAC Name: N-[4-{(2, 4-Diamino-6-pteridinyl) methyl} methyl amino) benzoyl]-L-glutamic acid.

It is a mixture of 4-amino-10-methyl pteroyl-L- glutamic acid and related substances and contains not less than 97% of C20H22N8O5. BP specifies not less than 97% and the USP not less than 98% of C20H22N8O5 calculated on an anhydrous basis.

Description: Yellow to orange-brown crystalline powder**.**

Melting point: 182º to 189ºC**.**

Solubility: Practically insoluble in water, alcohol, chloroform, and ether, but dissolved in dilute solutions of mineral acids and alkali hydroxides and carbonates.

Stability to light: Methotrexate undergoes photodegradation when stored in the light in dilute solutions although undiluted commercial preparations are reported to show negligible photodegradation.

Storage: Store in air-tight containers, protected from light and moisture.

Colour tests:

Mandelins test - red color,

Mercurous nitrate - black colour,

Nessler's reagent - orange colour.

UV Spectrum:

Light absorption in the range of 230-380 nm of a 0.001 % w/v solution in 0.1 M sodium

hydroxide exhibits three maximum at about 258, 303, and 371 nm; the ratio of the absorbance at the maximum at about 303 nm to that at the maximum at about 371 nm[12]

2.8 to 3.3.

Quantification:

High-Pressure Liquid Chromatography.

In serum or urine: methotrexate and 3 metabolites, detection limit 12.5 ng/ml for methotrexate in serum.

In plasma, urine, or cerebrospinal fluid: methotrexate and 2 metabolites, sensitivity 50 ng/ml.

In serum: methotrexate and 7- hydroxy methotrexate, sensitivity 100 ng/ml for methotrexate.

Pharmacokinetics:

When given in low doses, methotrexate is rapidly absorbed from the gastrointestinal tract, but higher doses are less absorbed. It is also rapidly and completely absorbed following intramuscular absorption.

Half-life: Plasma half-life is about 4 to 10 hrs; a longer terminal elimination phase of 10 to 70 hours (mean 27 hours has also been reported).

Protein binding: In plasma variously reported as 50 to 95%.

The volume of distribution: About 0.4 to 0.8 lt/Kg. Distribution in blood: Plasma: whole blood ratio, 0.9

Disposition in the body:

When given in low doses, it is rapidly absorbed after oral administration to give plasma concentration equivalent to those obtained by i.v. administration; higher doses may be well absorbed. It is distributed mainly in the extracellular spaces but a proportion penetrates cell membranes and is strongly bound to dihydrofolate reductase. Small amounts of methotrexate diffuse into the cerebrospinal fluid, higher concentrations being achieved with high doses. Distribution into body spaces such as the pleural or peritoneal cavities occurs slowly.

Mechanism of action:

It acts as an antimetabolite of folic acid. Within the cell, folic acid is reduced to dihydrofolic acid and then to tetrahydrofolic acid. Methotrexate competitively inhibits the enzyme

dihydrofolate reductase and prevents the formation of tetrahydrofolate which is necessary for purine and pyrimidine synthesis and consequently the formation of DNA and RNA[13].

Therapeutic uses:

Acute lymphoblastic leukemia, meningeal leukemia, burkitts lymphoma, non-Hodgkin's lymphomas, osteosarcoma, tumors of the bladder, brain, breast, g.i.t, head, and neck, lung, pancreas and prostate, retinoblastoma, mycosis fungoides, psoriasis, rheumatoid arthritis, primary biliary cirrhosis, polymyositis, Wegener's granulomatosis. It is an effective immunosuppressive agent used for the prevention of graft-versus-host reaction in bone-marrow transplantation.

Dosage and administration:

Methotrexate may be given orally as the base or sodium salt, or by injection as methotrexate sodium. Doses larger than 100 mg are usually given partly or wholly by intravenous infusion over not more than 24 hrs[14].

Acute lymphoblastic leukemia - 2.5 to 5 mg for children by mouth/i.m. inj

2.5 to 10 mg for adults by mouth/i.m, once or twice weekly.

Meningeal Leukemia - 12-mg/m^2 body-surface or 15 mg whichever is less, Once, or twice weekly, by intrathecal injection.

Choriocarcinoma - 1 mg /Kg by i.m, daily for four doses, at intervals of 1 to 2 weeks, for 3 to 5 courses.

Lymphosarcoma - 3 to 30 mg/Kg or about 90-900 mg /m^2 with folinic acid.

Mycosis fungoides - 50 mg once weekly or 25 mg twice weekly.

Psoriasis - 10-25 mg once weekly by i.m or i.v or per oral.

Rheumatoid arthritis - 7.5 mg once weekly by mouth.

Burkitt's lymphoma - 0.625 – 2.5 mg/kg/day for 1-2 weeks, by i.m., i.v., or peroral, then off the drug for 7-10 days.

Breast cancer - (combined with cyclophosphamide and fluorouracil) 40 mg/m2 on days 1 and 8, then repeat monthly by i.m or i.v.

Osteogenic sarcoma - 12- 15 g/m2 by intravenous infusion, followed by Folinic acid.

If over doses occur, the antidote is calcium leucovorin (citrovorum factor) which can be given i.v. or i.m. in methotrexate equivalent doses up to 75 mg every 6 hr for 4 doses. A delay of greater than 36 hr lessens the chance of rescue.

Dosage forms:

Tablet -2.5 mg

Injection (As sodium) - 2.5 mg/ml (Preserved solution)

- 25 mg/ml (non-preserved solution)

- 20, 25, 50, 100, 250 mg, 500 mg and 1g (non-preserved solution) The minimum therapeutic concentration: 0.4 µg/ml[15]

LD50 (Rat, i.v): 14 mg/Kg.

MATERIALS AND METHODS:

Table No. 2: List of Chemicals and Reagents

Materials	**Source**
Xanthan gum	Vikram Thermo, India.
Crude cashew gum	Prepared in college Laboratory.
Hydroxypropyl Methylcellulose	Vikram Thermo, India.
Microcrystalline Cellulose	SD Fine chemical Ltd, Mumbai.
Magnesium Stearate	SD Fine chemical Ltd, Mumbai.
Talc	Cabot sanmar.
Alcohol	SD Fine chemical Ltd, Mumbai.
Methanol	SD Fine chemical Ltd, Mumbai.
Phosphate buffer pH 6.8	Prepared in college Laboratory.
D. Water	Prepared in college Laboratory.
KBr	SD Fine chemical Ltd, Mumbai.

All other chemicals and reagents were of analytical grade and were used as they were procured. Distilled water was used in all experiments.

Methotrexate was a gift sample from Sun Pharma, East Sikkim, India.

RESULTS AND DISCUSSION:

RESULTS:

PREFORMULATION STUDIES OF DRUG

Preformulation may be defined as the stage of formulation development during which the physical pharmacist characterizes the physicochemical properties of the drug substance which are considered important in the formulation of a stable, effective, and safe dosage form. During this evaluation, possible interactions with various inert ingredients intended for use in the final dosage form are also considered. In the present work, preformulation studies such as solubility, determination of melting point, development of calibration curve, compatibility studies were carried out.

Table No. 3: Different terminologies of solubility

Descriptive term	Parts of solvent required for part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 or more

PREFORMULATION STUDIES OF DRUG

Preformulation studies are necessary to understand the physicochemical properties of the drug and the compatibility of the polymers used in the formulation. The results of the various preformulation characterizations are given below.

A. Solubility studies

Methotrexate is practically insoluble in water, alcohol, chloroform, and ether; freely soluble in dilute solutions of alkaline hydroxides and carbonates; soluble in dilute hydrochloric acid.

B. Determination of Melting Point

The melting point of Methotrexate was found to be 185^{o}C.

C. Determination of λmax

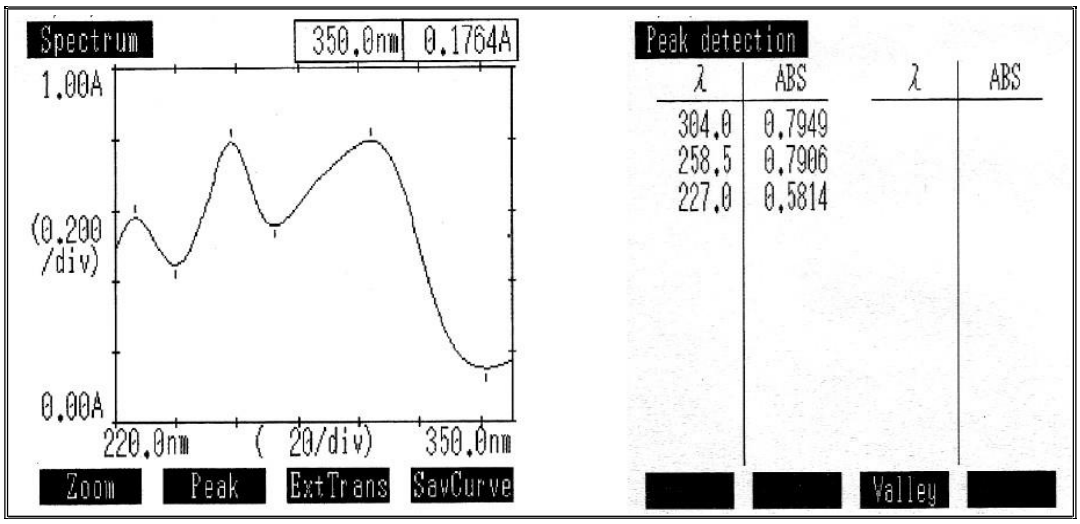


Figure No. 1: λmax of Methotrexate

The absorption maximum (λ_{max}) was found to be 304 nm.

A. Development of Calibration Curve for Methotrexate

The concentration ranges and data are reported in **Table 4**. The calibration curve of Methotrexate was plotted using this data and shown in **Figure 2.**

Table No. 4: Calibration Curve for Methotrexate in 0.1 (N) NaOH Solutions

Sl. No.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	3	0.191 ± 0.007
3.	6	0.333 ± 0.014
4.	9	0.526 ± 0.010
5.	12	0.686 ± 0.018
6.	15	0.855 ± 0.020

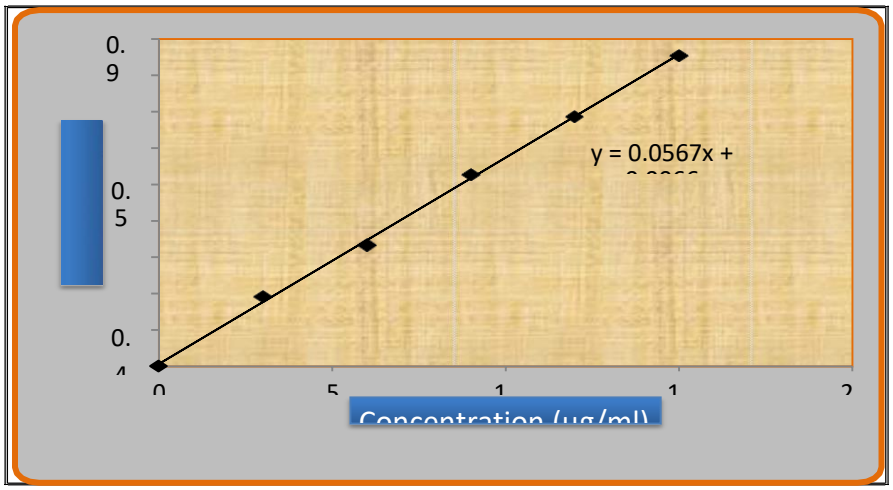


Figure No. 2: Calibration curve of Methotrexate in 0.1 (N) NaOH Solution at 304 nm

D. FT-IR study

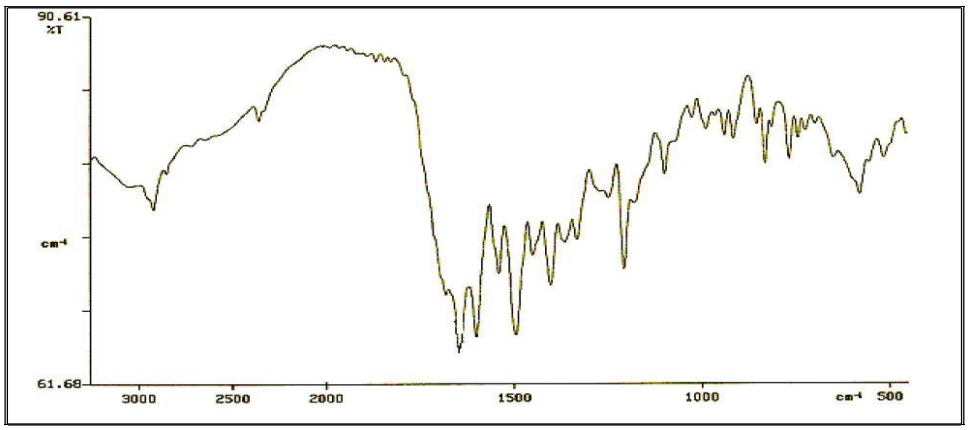


Figure No. 3: FTIR Spectra of Methotrexate

FT-IR study was employed to ascertain the compatibility of the drug Methotrexate with Xanthan gum, Crude cashew gum, and HPMC. Both the spectra were compared for confirmation of common peaks. Specific peaks of pure drug and drug with polymers showed no significant variation in height, intensity, and positions of peaks. This proved that drugs and polymers were compatible. There is no interaction between drug and polymer. The FT-IR spectra are shown in **Figure 3, 4** and **Table 5**.

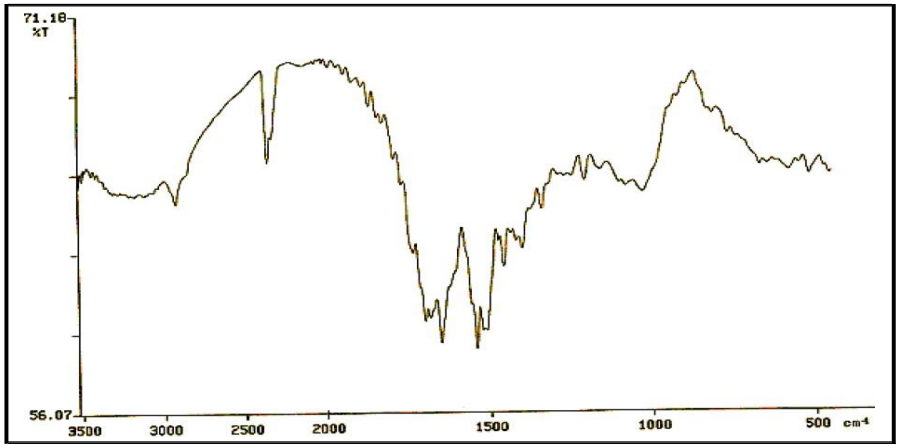


Figure No. 4: FTIR spectra of Methotrexate with Polymers

Table No. 5: FTIR spectra data of Methotrexate and Methotrexate with Polymers

Assignment	**Drug (cm^{-1})**	**Drug With Polymers (cm^{-1})**
C-H Stretching (Aromatic)	2923	2927
C=O Stretching	1647	1649.8
C-C Stretching (Aromatic)	1540	1541.6
C-H deformation (CH_3)	1451	1457.9
C=C Stretching (Aromatic)	1403	1397.9
C-O Stretching	1206	1204.1
C-H deformation (Aromatic)	830	831

Table No. 6: Physical Properties of all Formulations

Formulation Code	Diameter* (mm)	Thickness* (mm)	Weight variation* (mg)	Hardness* (kg/cm2)	Friability# %
F1	10.04±0.03	5.70 ± 0.400	441 ±4.833	4.4 ± 1.11	0.998
F2	10.06±0.04	5.75 ± 0.403	433 ±2.977	6.8 ± 1.60	0.159
F3	10.04±0.03	6.50 ± 0.387	417 ±4.893	3.8 ± 0.75	0.64
F4	10.04±0.04	6.30 ± 0.510	428 ±4.021	4.0 ± 0.81	1.10
F5	10.02±0.05	6.30 ± 0.400	428 ± 4.52	4.0 ± 0.77	0.79
F6	10.05±0.06	6.75 ± 0.403	425 ±4.372	4.1 ± 1.22	0.47
F7	10.05±0.03	6.85 ± 0.391	419 ±3.672	4.1 ± 0.65	0.16
F8	10.03±0.02	7.10 ± 0.374	424 ±4.689	4.3 ± 0.64	0.80
F9	10.04±0.05	6.95 ± 0.415	428 ±4.139	5.2 ± 1.18	0.63
F10	10.04±0.02	6.90 ± 0.436	417 ±4.363	4.1 ± 0.83	1.30
F11	10.07±0.02	6.20 ± 0.400	416 ±3.175	5.3 ± 1.91	0.81
F12	10.05±0.03	6.55 ± 0.415	418 ±4.335	4.0 ± 0.63	0.16
F13	10.04±0.02	5.85 ± 0.391	431 ±3.617	4.1 ± 0.70	0.16
F14	10.02±0.03	6.15 ± 0.450	408 ±3.137	6.6 ± 1.85	0.65
F15	10.03±0.03	6.30 ± 0.458	417 ±3.209	5.7 ± 1.72	0.66

*** mean ±SD, n=6. # mean ±SD, n=20.**

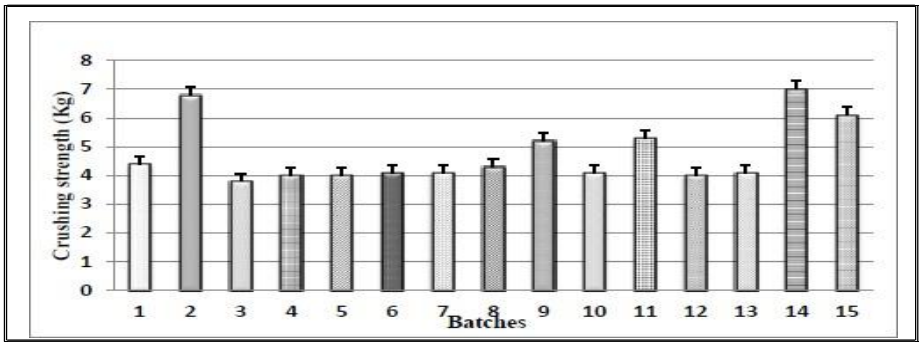


Figure No. 5: Hardness of the Methotrexate matrix tablets

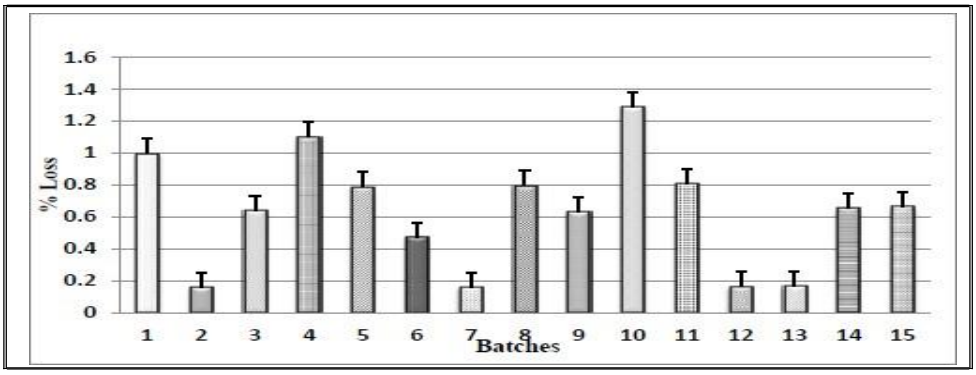


Figure No. 6: Friability of the Methotrexate matrix tablets

D. Swelling study:

After determining the Swelling study of the prepared formulation, the results which were found are given below------

Table No. 7: Swelling Index Behavior Study of Prepared Formulations

Code	Percentage Water Absorbed (Time in Hours)										
	0.25	0.50	1	2	4	6	8	10	12	15	18
1	11.6	4.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	54.8	85.7	92.9	116.7	150.0	190.5	242.9	269.0	285.7	288	285
3	7.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
4	11.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	6.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
6	11.4	11.4	2.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
7	38.1	57.1	66.7	90.5	111.9	140.5	159.5	178.6	223.8	231	235
8	32.5	57.5	60.0	67.5	77.5	62.5	55.0	35.0	0.0	0.0	0.0
9	23.8	26.2	19.0	9.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10	61.4	79.5	93.2	118.2	152.3	184.1	197.7	211.4	236.4	250	250
11	67.4	144.2	167.4	195.3	200	218.6	218.6	216.3	214	221	218
12	25	47.7	81.8	97.7	106.8	90.9	81.8	52.3	18.2	0.0	0.0
13	46.5	74.4	79.1	81.4	69.8	62.8	27.9	0.0	0.0	0.0	0.0
14	28.6	50	66.7	59.5	40.5	28.6	16.7	0.0	0.0	0.0	0.0
15	60.5	104.7	123.3	151.2	139.5	114	72.1	65.1	18.6	0.0	0.0

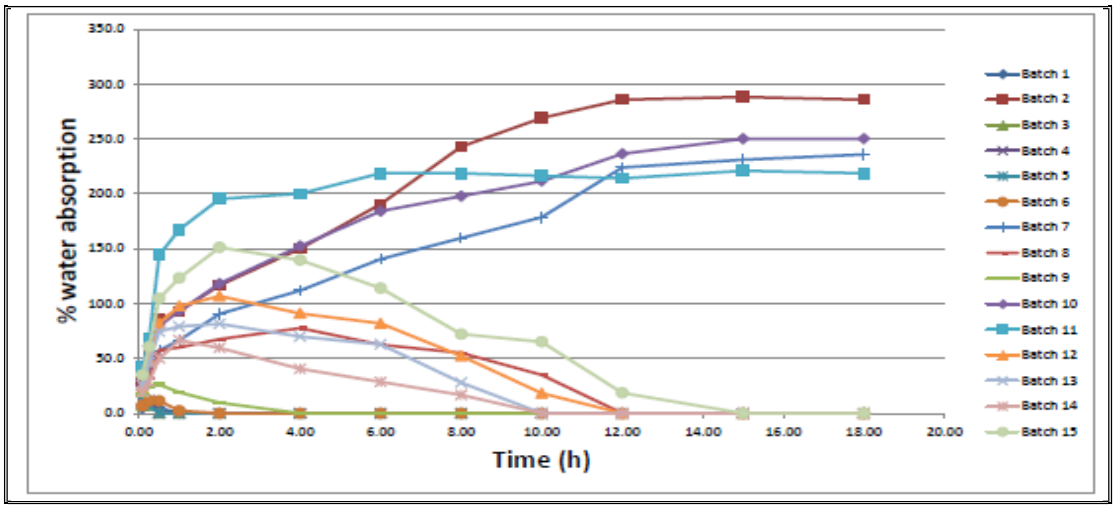


Figure No. 7: Swelling Index of Prepared Formulations

E. *In-vitro* drug release Study:

After an *in-vitro* drug release study of prepared formulation, the below-given result was found.

Table No. 8: *In-vitro* drug release of prepared formulation (Batch 1)

Time/hr	Mean Absorbance	Concentration (%w/v)	Percentage Release
0.25	0.121	0.00512	5.19 ± 0.005
0.5	0.187	0.00703	7.03 ± 0.003
1	0.209	0.00770	7.70 ± 0.010
2	0.392	0.01269	12.69 ± 0.003
4	0.651	0.01983	19.83 ± 0.007
6	0.861	0.02574	25.74 ± 0.035
8	1.109	0.03266	32.66 ± 0.056
10	1.274	0.03745	37.45 ± 0.062
12	1.372	0.04051	40.51 ± 0.034
15	1.358	0.04061	40.61 ± 0.030
18	1.368	0.04124	41.24 ± 0.034
21	1.350	0.04122	41.22 ± 0.027
24	1.322	0.40890	40.89 ± 0.030

Table No. 9: *In-vitro* drug release of prepared formulation (Batch 2)

Time/hr	Mean Absorbance	Concentration (%w/v)	Percentage Release
0.25	0.000	0.00188	1.88 ± 0.000
0.5	0.134	0.00551	5.50 ± 0.028
1	0.041	0.00307	3.06 ± 0.004
2	0.122	0.00529	5.29 ± 0.005
4	0.274	0.00943	9.43 ± 0.019
6	0.378	0.01230	12.30 ± 0.012
8	0.510	0.01603	16.03 ± 0.011
10	0.612	0.01900	19.00 ± 0.012
12	0.771	0.02331	23.31 ± 0.051
15	1.003	0.02986	29.86 ± 0.012
18	1.140	0.03398	33.98 ± 0.019
21	1.204	0.03604	36.04 ± 0.009
24	1.328	0.03976	39.76 ± 0.009

Table No. 10: Drug release profile of Batch 3

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.423	0.01338	13.38 ± 0.051
0.5	0.542	0.01673	16.73 ± 0.098
1	0.716	0.02156	21.56 ± 0.084
2	0.962	0.02843	28.43 ± 0.045
4	1.456	0.04209	42.09 ± 0.054
6	1.545	0.04492	44.92 ± 0.003
8	2.019	0.0582	58.20 ± 0.365
10	1.555	0.04633	46.33 ± 0.020
12	1.538	0.04631	46.31 ± 0.014
15	1.574	0.04776	47.76 ± 0.023
18	1.480	0.04573	45.73 ± 0.002
21	1.528	0.04745	47.45 ± 0.026
24	1.621	0.05043	50.43 ± 0.055

Table No. 11: *In-vitro* drug release of prepared formulation (Batch 4)

Time/hr	Mean absorbance	Concentration (%w/v)	% Release
0.25	0.198	0.00726	7.26 ± 0.055
0.5	0.266	0.00917	9.17 ± 0.014
1	0.554	0.01704	17.04 ± 0.023
2	0.882	0.02602	26.02 ± 0.051
4	1.373	0.03957	39.57 ± 0.029
6	1.645	0.04734	47.34 ± 0.028
8	1.675	0.04863	48.63 ± 0.032
10	1.641	0.04828	48.28 ± 0.038
12	1.672	0.04959	49.59 ± 0.017
15	1.684	0.05041	50.41 ± 0.051
18	1.631	0.04953	49.53 ± 0.007
21	1.615	0.04964	49.64 ± 0.025
24	1.684	0.05195	51.95 ± 0.052

Table No. 12: Drug release profile of Batch 5

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.238	0.00836	8.36 ± 0.019
0.5	0.295	0.00998	9.98 ± 0.011
1	0.465	0.01469	14.69 ± 0.035
2	0.716	0.02165	21.65 ± 0.032
4	1.132	0.03309	33.09 ± 0.041
6	1.492	0.04315	43.15 ± 0.032
8	1.471	0.04302	43.02 ± 0.032
10	1.513	0.04458	44.58 ± 0.005
12	1.524	0.04535	45.35 ± 0.014
15	1.517	0.04562	45.62 ± 0.012
18	1.508	0.04590	45.90 ± 0.015
21	1.501	0.04617	46.17 ± 0.013
24	1.487	0.04624	46.24 ± 0.012

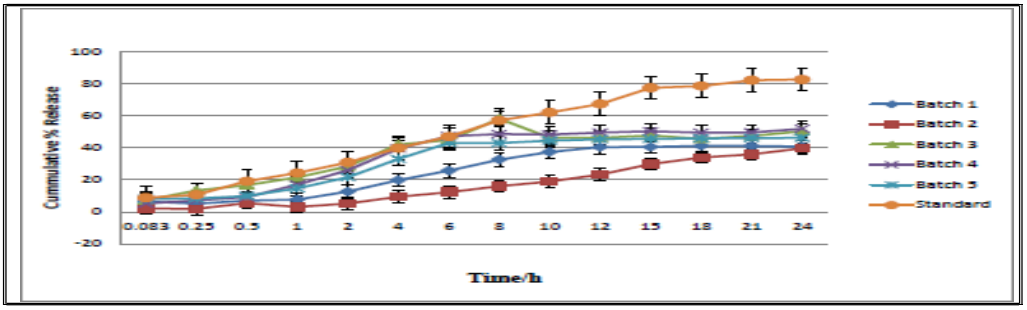


Figure No. 8: Dissolution profiles of tablets in Batches 1 to 5

Table No. 13: *In-vitro* drug release of prepared formulation (Batch 6)

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.278	0.00946	9.46 ± 0.062
0.5	0.447	0.01411	14.11 ± 0.065
1	0.544	0.01687	16.87 ± 0.028
2	1.038	0.03035	30.35 ± 0.059
4	1.530	0.04398	43.98 ± 0.031
6	1.620	0.04686	46.86 ± 0.010
8	1.607	0.04707	47.07 ± 0.022
10	1.628	0.04807	48.07 ± 0.025
12	1.589	0.04758	47.58 ± 0.020
15	1.616	0.04878	48.78 ± 0.016
18	1.567	0.04798	47.98 ± 0.016
21	1.592	0.04917	49.17 ± 0.018
24	1.599	0.04977	49.77 ± 0.028

Table No. 14: Drug release profile of Batch 7

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.199	0.00728	7.28 ± 0.005
0.5	0.335	0.01106	11.06 ± 0.017
1	0.568	0.01748	17.48 ± 0.144
2	0.892	0.02637	26.37 ± 0.072
4	1.507	0.04326	43.26 ± 0.175
6	1.638	0.04723	47.23 ± 0.171
8	2.214	0.06324	63.24 ± 0.165
10	2.253	0.06502	65.02 ± 0.119
12	2.541	0.07342	73.42 ± 0.067
15	2.555	0.07460	74.60 ± 0.056
18	2.435	0.07219	72.19 ± 0.027
21	2.422	0.07254	72.54 ± 0.017
24	2.463	0.07439	74.39 ± 0.014

Table No. 15: *In-vitro* drug release of prepared formulation (Batch 8)

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.203	0.00742	7.42 ± 0.014
0.5	0.227	0.00815	8.15 ± 0.015
1	0.326	0.01086	10.86 ± 0.019
2	0.599	0.01838	18.38 ± 0.039
4	1.225	0.03548	35.48 ± 0.033
6	1.743	0.04977	49.77 ± 0.038
8	1.891	0.05527	55.27 ± 0.034
10	2.353	0.06836	68.36 ± 0.039
12	2.581	0.07519	75.19 ± 0.030
15	2.598	0.07648	76.48 ± 0.026
18	2.625	0.07798	77.98 ± 0.050
21	2.610	0.07818	78.18 ± 0.052
24	2.643	0.07998	79.98 ± 0.039

Table No. 16: Drug release profile of Batch 9

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.285	0.00960	9.60 ± 0.004
0.5	0.402	0.01290	12.90 ± 0.037
1	0.659	0.01994	19.94 ± 0.012
2	1.056	0.03086	30.86 ± 0.034
4	1.842	0.05240	52.40 ± 0.027
6	2.003	0.05727	57.27 ± 0.010
8	2.664	0.07569	75.69 ± 0.011
10	2.734	0.07841	78.41 ± 0.017
12	2.743	0.07955	79.55 ± 0.012
15	2.689	0.07889	78.89 ± 0.033
18	2.638	0.07832	78.32 ± 0.031
21	2.623	0.07873	78.73 ± 0.014
24	2.572	0.07824	78.24 ± 0.014

Table No. 17: *In-vitro* drug release of prepared formulation (Batch 10)

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.219	0.00784	7.84 ± 0.008
0.5	0.422	0.01336	13.36 ± 0.011
1	0.657	0.01991	19.91 ± 0.014
2	0.804	0.02403	24.03 ± 0.014
4	1.098	0.03219	32.19 ± 0.006
6	1.505	0.04354	43.54 ± 0.016
8	1.929	0.05561	55.61 ± 0.022
10	2.233	0.06431	64.31 ± 0.036
12	2.317	0.06720	67.20 ± 0.051
15	2.525	0.07351	73.51 ± 0.049
18	2.629	0.07729	77.29 ± 0.047
21	2.646	0.07840	78.40 ± 0.011
24	2.675	0.07991	79.91 ± 0.043

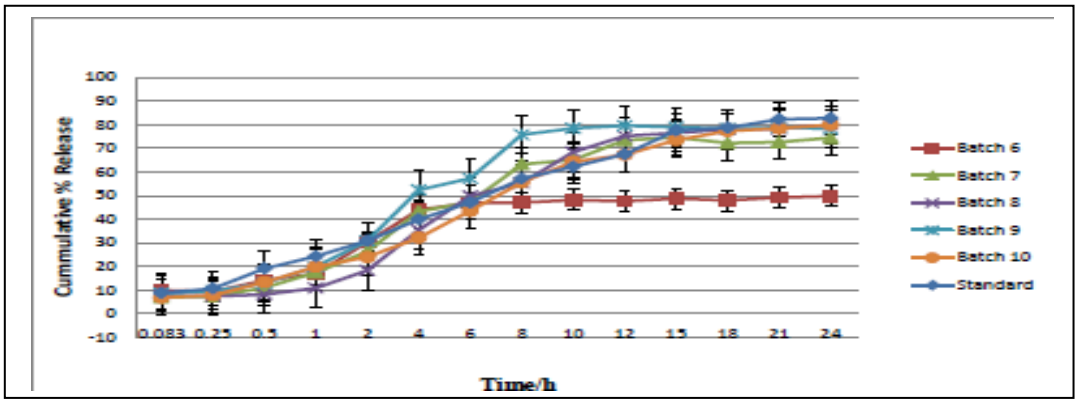


Figure No. 9: Dissolution profiles of tablets in Batches 6 to 10

Table No. 18: Drug release profile of Batch 11

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.694	0.02067	20.67 ± 0.007
0.5	0.995	0.02904	29.04 ± 0.009
1	1.250	0.03616	36.16 ± 0.006
2	1.382	0.04005	40.05 ± 0.003
4	1.694	0.04898	48.98 ± 0.001
6	1.893	0.05491	54.91 ± 0.002
8	1.995	0.05820	58.20 ± 0.001
10	2.229	0.06512	65.12 ± 0.006
12	2.239	0.06591	65.91 ± 0.006
15	2.425	0.07180	71.80 ± 0.005
18	2.442	0.07305	73.05 ± 0.007
21	2.481	0.07480	74.80 ± 0.018
24	2.505	0.07630	76.30 ± 0.010

Table No. 19: *In-vitro* drug release of prepared formulation (Batch 12)

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.420	0.01310	13.10 ± 0.009
0.5	0.771	0.02284	22.84 ± 0.010
1	1.381	0.03959	39.59 ± 0.024
2	1.590	0.04562	45.62 ± 0.051
4	1.621	0.04692	46.92 ± 0.045
6	1.650	0.04823	48.23 ± 0.020
8	1.797	0.05274	52.74 ± 0.019
10	2.112	0.06180	61.80 ± 0.001
12	2.456	0.07165	71.65 ± 0.010
15	2.653	0.07771	77.71 ± 0.018
18	2.657	0.07872	78.72 ± 0.012
21	2.682	0.08014	80.14 ± 0.012
24	2.694	0.08136	81.36 ± 0.019

Table No. 20: Drug release profile of Batch 13

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.274	0.00928	9.28 ± 0.007
0.5	0.454	0.01428	14.28 ± 0.001
1	0.773	0.02304	23.04 ± 0.039
2	1.359	0.03909	39.09 ± 0.008
4	1.632	0.04682	46.82 ± 0.011
6	1.668	0.04831	48.31 ± 0.017
8	2.189	0.06283	62.83 ± 0.096
10	2.336	0.06751	67.51 ± 0.040
12	2.553	0.07413	74.13 ± 0.026
15	2.632	0.07702	77.02 ± 0.039
18	2.634	0.07783	77.83 ± 0.016
21	2.755	0.08184	81.84 ± 0.015
24	2.696	0.08118	81.18 ± 0.020

Table No. 21: *In-vitro* drug release of prepared formulation (Batch 14)

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.268	0.00911	9.11 ± 0.012
0.5	0.381	0.01223	12.23 ± 0.005
1	0.708	0.02126	21.26 ± 0.029
2	0.892	0.02649	26.49 ± 0.028
4	1.195	0.03494	34.94 ± 0.032
6	1.225	0.03615	36.15 ± 0.061
8	1.346	0.03974	39.74 ± 0.012
10	1.851	0.05376	53.76 ± 0.066
12	1.982	0.05793	57.93 ± 0.031
15	2.154	0.06314	63.14 ± 0.032
18	2.371	0.06961	69.61 ± 0.028
21	2.463	0.07284	72.84 ± 0.033
24	2.482	0.07410	74.10 ± 0.002

Table No. 22: *In-vitro* drug release of prepared formulation (Batch 15)

Time/hr	Mean absorbance	Concentration (%w/v)	Percentage release
0.25	0.406	0.01290	12.90 ± 0.011
0.5	0.742	0.02212	22.12 ± 0.002
1	1.114	0.03236	32.36 ± 0.004
2	1.456	0.04191	41.91 ± 0.015
4	1.648	0.04757	47.57 ± 0.033
6	1.861	0.05378	53.78 ± 0.037
8	2.099	0.06076	60.76 ± 0.053
10	2.413	0.07291	72.91 ± 0.020
12	2.632	0.07659	76.59 ± 0.026
15	2.639	0.07760	77.60 ± 0.029
18	2.644	0.07841	78.41 ± 0.041
21	2.681	0.08022	80.22 ± 0.021
24	2.677	0.08104	81.04 ± 0.033

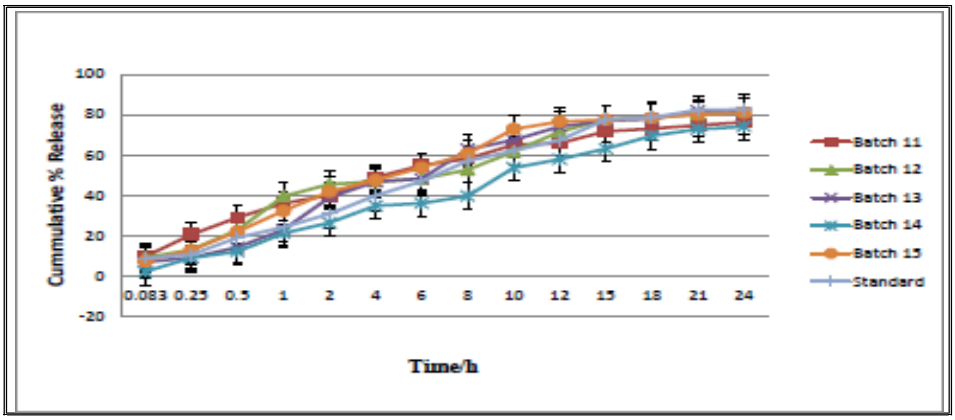


Figure No. 10: Dissolution profiles of tablets in batches 11 to15

F. Mechanism and Release Kinetics of the Methotrexate Matrix Tablet

Table No. 23: Mechanism and release kinetics of matrix tablet

Batch No	Zero Order		First Order		Higuchi Model		Hixson-Crowell Model	
	K_o	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2
1	0.0278	0.8107	0.0006	0.7088	1.2050	0.9325	0.0012	0.748
2	0.0273	0.9880	0.0009	0.8257	1.0842	0.9563	0.0015	0.909
3	0.0237	0.5265	0.0004	0.4700	1.1279	0.7310	0.0009	0.498
4	0.0298	0.6313	0.0005	0.5209	1.3794	0.8308	0.0011	0.562
5	0.0268	0.6664	0.0005	0.5854	1.2228	0.8542	0.0010	0.615
6	0.0257	0.5913	0.0004	0.5221	1.2023	0.7952	0.0009	0.547
7	0.0493	0.7735	0.0006	0.6305	2.1720	0.9231	0.0015	0.687
8	0.0568	0.8392	0.0007	0.7080	2.4360	0.9493	0.0017	0.757
9	0.0507	0.6997	0.0006	0.5969	2.2861	0.8753	0.0015	0.637
10	0.0535	0.8816	0.0006	0.7068	2.2722	0.9750	0.0016	0.779
11	0.0391	0.7951	0.0004	0.5752	1.7170	0.9404	0.0010	0.659
12	0.0465	0.8247	0.0005	0.5978	1.9622	0.9373	0.0012	0.682
13	0.0513	0.8119	0.0006	0.6147	2.2378	0.9497	0.0015	0.689
14	0.0479	0.9147	0.0007	0.5975	2.0062	0.9873	0.0015	0.741
15	0.0475	0.7863	0.0005	0.5748	2.0901	0.9363	0.0013	0.657

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