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Original Article

IMPROVING SOLUBILITY OF METHOTREXATE BY SOLID DISPERSION

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ABSTRACT

Objective: Methotrexate (MTX) is a folate antimetabolite used for the management of neoplastic diseases like leukemia and breast cancer, Methotrexate is also used in the treatment of psoriasis as well as rheumatoid arthritis. The goal of this research was to improving the solubility and dissolution profile of methotrexate solid dispersion by using different polymers.

Methods: A total six formulas were prepared as solid dispersion of methotrexate by solvent evaporation method by using polyethylene glycol (PEG-4000) and poly Vinyl pyrolidone (PVP-K30) as polymeric solubilizer in ratio (1:1,1:2,1:4), Then the solid dispersion of methotrexate were evaluated by solubility test, permeability test and FTIR study.

Results: All six solid dispersion formulas showed a significant improvement in the solubility of methotrexate, and the formulations demonstrated improved in the rate of drug release of approximately 99.8±0.9 within 60 min. FTIR study for F3 and F6 show no drug-excipients interaction.

Conclusion: Methotrexate was successfully enhanced its water solubility by using solid dispersion.

Keywords: Solid, Methotrexate, PVP, PEG

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INTRODUCTION

A folate antimetabolite called methotrexate (MTX) is used to treat multiple sclerosis and psoriasis as well as neoplastic illnesses such leukemia, breast, lung, bone, and cervical cancer. MTX is utilized in the treatment of rheumatoid arthritis since it is a member of the therapeutic class known as disease-modifying antirheumatic medicines (DMARDs) [1]. Due to its poor bioavailability (18% for doses>40 mg/m2) and poor aqueous solubility (0.01 mg/ml at 20 °C), its therapeutic importance is constrained. The Biopharmaceutical Classification System classifies MTX as a class IV molecule because of its hydrophobic properties and limited permeability (BCS). Additionally, MTX is chemically unstable; it quickly breaks down when exposed to extremes of pH or temperature, light, or both. These factors make it difficult to produce suitable oral dose formulations for medications like MTX, which are highly lipophilic and photo-unstable [2, 3]. The limited bioavailability is the main obstacle to the development of different dosage formulations. Oral bioavailability is influenced by a number of variables, including aqueous solubility, drug permeability, dissolving rate, first-pass metabolism, pre-systemic metabolism, and sensitivity to efflux mechanisms [4, 5]. Poor solubility and constrained permeability account for the majority of cases of insufficient oral bioavailability [6]. Drugs that dissolve slowly in water can be effectively prepared as solid dispersion to increase their bioavailability. Solid dispersion (SD) is a popular and well-respected technique for improving solubility and dissolution. With SD, the hydrophilic carriers dissolve the hydrophobic drug and release it to the dissolving medium as tiny particles (in the micro-nano size range) to increase their surface area, which promotes solubility and, consequently, oral bioavailability. The drug and carrier(s) must first be dissolved using large volumes of an organic solvent or mixtures of organic solvents in common SD methods. The solvents must then be removed using one of several methods, including spray drying, freeze drying, spray-freeze drying, spray congealing, rotary evaporation, or hot-plate drying. The use of organic solvents is difficult, though, as safety and regulatory issues have been raised in light of the solvents' high toxicity and potential environmental risks [7-9]. The carrier disintegrates when the solid dispersion is exposed to watery solutions and the medication releases as tiny colloidal particles. This enhances the rate of surface area dissolution and, as a result, the bioavailability of medications that are weakly water soluble [10].

The aim of this work focused on improving methotrexate solubility using a solid dispersion method. Because the stable dispersion are quick and simple to prepare, and also the carriers utilized here are affordable and widely accessible.

MATERIALS AND METHODS

Methotrrexate was pruches from yibi biotechnology Co. ltd, china, PEG was obtained from BASF, Mumbai; PVP K-30was obtained from Dow chemicals, USA; ethanol (Sigma Aldrich, USA); Electronic Balance (WF 1401096, PFB 200-3, Germany), Digital pH meter (Tlll-02303, BP 3001, Singapore), UV-Vis. Spectro-photometer(Shimadzu, Japan), Fourier Transformed Infrared Spectroscopy (FTIR) Shimadzu, Japan.

Methods

Determination of MTX maximum UV absorbance (λ max)

Maximum absorbance (λmax) of MTX was detected in phosphate buffer (pH 7). The sample was scanned at an ultraviolet (UV) range of 200-400 nm using UV-Visible spectrophotometer and the λ max of MTX was detected. The experiment was performed in triplicate [11].

Determination of MTX calibration curves

Calibration curves of MTX were constructed in phosphate buffer pH 7. In which 100 µg/ml stock solutions of MTX in each medium were prepared, then serial dilutions of 2-20 µg/ml in phosphate buffer (pH=7) as solvent were prepared. Samples were then analyzed spectrophotometrically using a UV-Visible spectrophotometer at the previously detected λ max of MTX in each medium, and calibration curves were constructed by plotting the measured absorbance values of each diluted solution against related concentrations [12].

Formulation of methotrexate solid dispersion

By using the solvent evaporation method, six formulas (F1-F6) of solid dispersions of MTX with PVP k-30 and PEG-4000 were created as shown in table (1). The physical mixes of MTX with carriers (PVP and PEG-4000) in the different ratio were introduced to the common solvents (ethanol and phosphate buffer (pH=7) in 1:1 ratio). At 40°C, the solvent was evaporating while being continuously stirred in a water bath. The residue left behind was dry. The dried substance was processed via sieve no. 40 after being ground [13].

Table 1: Composition of MTX solid dispersion

Formula no. material (mg)	F1 (1:1)	F2 (1:2)	F3 (1:4)	F4 (1:1)	F5 (1:2)	F6 (1:4)
MTX	100	100	100	100	100	100
PEG 4000	100	200	400	-	-	-
PVP K-30	-	-	-	100	200	400
solvent	q. s	q. s	q. s	q. s	q. s	q. s

Evaluation of methotrexate solid dispersion

Physical appearance

Using a basic microscope, the obtained solid dispersions were examined for color and appearance [14].

Solubility study

Saturation solubility of MTX solid dispersion was studied. Conical flasks were filled with extra solid dispersions, and they were shaken mechanically for 24 h until equilibrium was established. After that, the solubility was examined with a UV-spectrophotometer at a maximum wavelength of 302 nm using the appropriate dilutions [15, 16]. The tests were carried out in triplicate.

Permeability study

MTX solid dispersions and pure powder release were studied using a Franz diffusion cell with a 1.7 cm2 diffusion area. A semipermeable membrane was used to separate the donor and acceptor chambers. Phosphate buffer served as the diffusion medium in the donor and acceptor chambers (pH 7). The receiver chamber was filled with pure buffer, and the donor chamber was loaded with either 20 mg of MTX solid dispersion powder or 10 mg of MTX pure powder. A UV spectrophotometer was used to assess the samples that were withheld [17, 18]. The test was carried out three times.

Drug polymer compatibility study by FTIR

Fourier-transformed infrared spectroscopy (FTIR) was used to investigate the purity of methotrexate as well as the possible interactions between MTX and PEG 4000 and PVP K-30 [19].

The samples were all properly put into the sample disk, and the Spectra Manager II program was used to analyze the peaks in the 4000-400 cm^{-1} spectral band.

Statistical analysis

In this study, the data were analyzed using a T-test with a significance level of (P 0.05). Three tests on average, were used to study the data.

RESULTS AND DISCUSSION

Maximum UV absorbance (λ max) determination of MTX

One peak for the highest absorbance was visible after scanning MTX solutions in a UV spectrophotometer at 305 nm in phosphate buffer pH 7 [20].

Calibration curves of MTX

MTX calibration curve in phosphate buffer pH7 was obtained by plotting the UV absorbance of MTX (at λ max 302 nm) versus concentrations used of a series of standard solutions. Curve with straight line was achieved with a regression coefficient near 1, indicating that the curves obey Beers-Lambert law within the range of used concentrations. As shown in fig. 1.

Physical appearance

As can be seen in table 2, different solid dispersions were examined for their physical characteristics. The result show that formula (F1-F3) show waxy and yellow in appearance, while formulas (F4-F6) show glassy and yellow in appearance [21].

Table 2: Physical appearance of solid dispersion

Solid dispersion	Appearance
F1	Waxy and yellow in appearance
F2	Waxy and yellow in appearance
F3	Waxy and yellow in appearance
F4	glassy and yellow in appearance
F5	glassy and yellow in appearance
F6	glassy and yellow in appearance

Solubility study of MTX solid dispersion

The results of MTX aqueous solubility was shown by table 3.

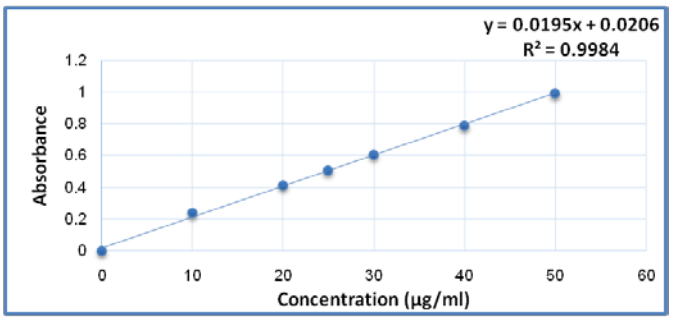

Fig. 1: Calibration curve of MTX in buffer solution (pH=7)

Table 3: Solubility data for different MTX solid dispersion

Materials	Solubility (µg/ml)
MTX	20.8±0.95
F1	86.53±0.97
F2	228.8±0.98
F3	478.4±0.96
F4	112.32±0.98
F5	374.4±0.97
F6	624.4±0.98

*Result expressed as a means of±SD, n=3

Table 3 shows the solid dispersion formulas for MTX and its intrinsic solubility data. The outcomes demonstrated that solid dispersion significantly increased the solubility of MTX. As the concentration of polymer increases, water solubility gradually rises. When comparing 1:4 ratios to 1:2 and 1:1 ratio, there is an increase in water solubility, which may be because more MTX was not integrated into the carrier at the lower carrier concentration.

However, when the carrier was present in higher concentrations, more MTX dispersed and increased the wettability of the PEG-4000 and PVPK-30. It showed the unusual effect of reducing in water solubility less than the pure medication at a 1:1 ratio. This can be

explained by the creation of a viscous layer and the glass suspension of the solid dispersion, which hinder the MTX particle's hydration [22].

Permeability study

Table 4 shows the results of the permeability study of MTX solid dispersion; it was observed that SDs released MTX more quickly than the actual medication did. Poor wettability and particle aggregation may be the cause of the pure drug's poor dissolution. Most likely, in the case of SDs, the hydrophilic inert carriers' attraction for the dissolution fluid allows for quick penetration into the particles, speeding up the dissolution process [23].

Both polymers (PEG-4000, PVP K-30) showed a faster rate of MTX solid dispersion dissolution than the pure drug, which might be explained by the fact that the presence of highly hydrophilic polymers improved the wettability of the MTX particles and preventing of drug aggregation by each polymer [24].

Table 4: Permeability data for different formulas of MTX solid dispersion

Time (min)	Formula code						
	MTX	F1(1:1)	F2(1:2)	F3(1:4)	F4(1:1)	F5(1:2)	F6(1:4)
10	18.6±1	45.5±0.9	60.5±0.93	80.6±0.9	84.6±0.9	87.6±0.9	86.6±0.9
20	25.7±0.9	65.76±0.8	79.9±.0.97	92.4±0.9	91.2±0.9	94.5±0.9	87.8±0.9
30	38.1±1.4	87.04±0.9	91.9±0.97	97.6±0.9	97±0.97	98.9±0.9	97.8±0.9
40	6.8±1.8	94.25±0.9	97.8±0.99	99.2±0.9	99.3±0.9	99.4±0.9	99.5±0.9
50	56.9±0.9	98.6±0.94	99.7±0.98	99.3±0.9	99.4±0.9	99.8±0.9	99.7±0.9
60	70.6±1.2	99.8±0.97	99.8±0.99	99.4±0.9	99.8±0.9	99.6±0.9	99.8±0.9

*Result expressed as a means of ±SD, n=3

Drug polymer compatibility study by FTIR

Fig. 2, 3, and 4 show the FTIR spectra of pure MTX, F3, and F6, respectively. Fig. 3 and fig. 4 shows that there were no appreciable changes in the positions of the drug's distinctive peaks when combined with carriers, indicating that the excipients and the drug were not incompatible [25, 26].

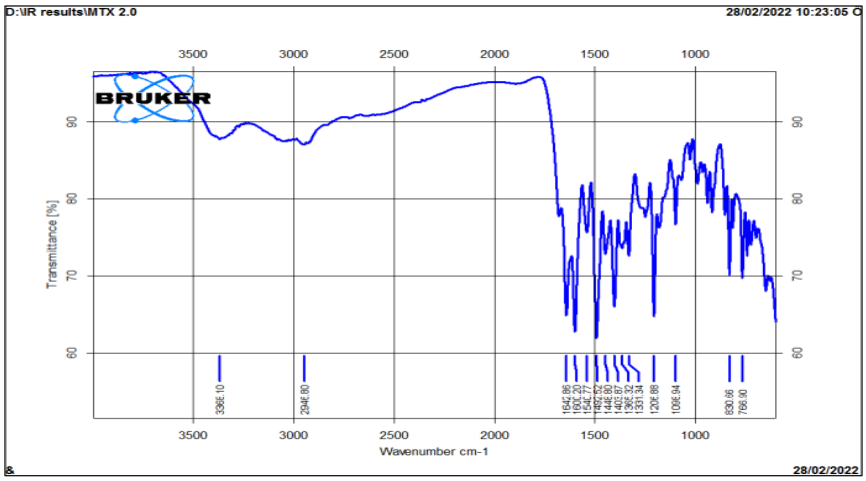

Fig. 2: FTIR spectra of pure MTX

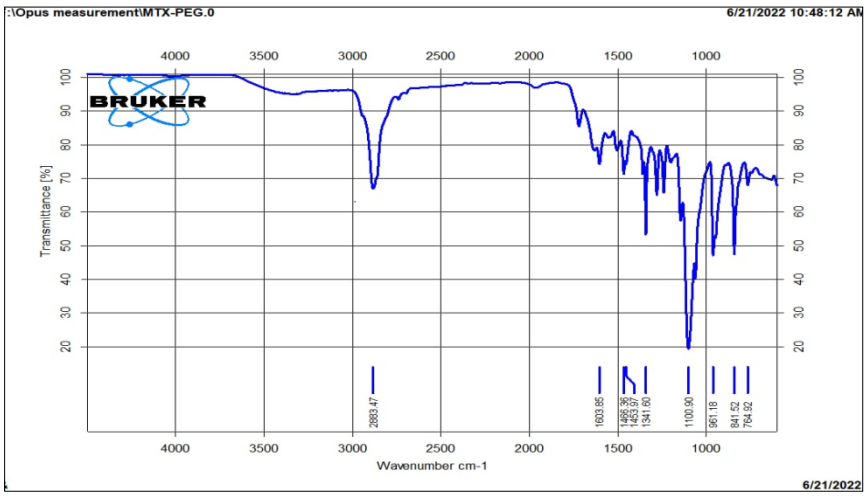

Fig. 3: FTIR spectra of F3

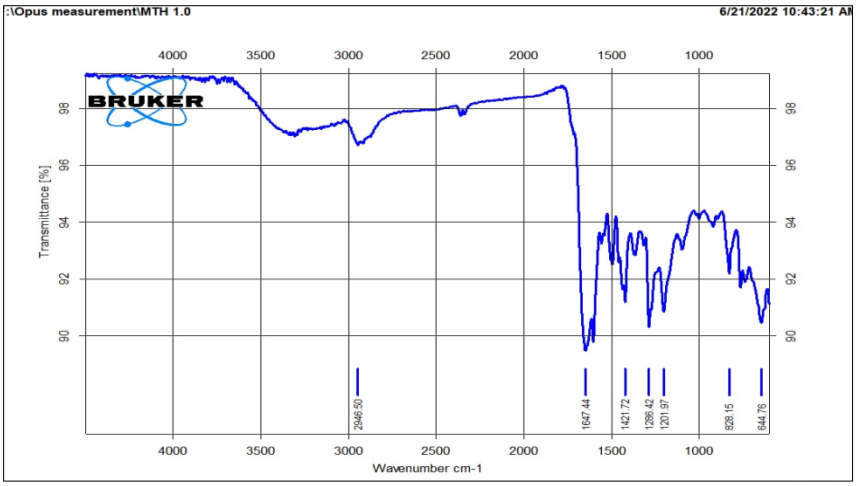

Fig. 4: FTIR of F6

CONCLUSION

Based on the aforementioned study, methotrexate was successfully prepared as solid dispersion to improve the solubility of MTX by using water-soluble carriers PEG-4000and PVP K-30. Ratio of drug to polymer (1:4) was found to be major cause of improving the permeability of methotrexate.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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