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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2023, Vol. 39, No.(5):
Pg. 1386-1388

Brief communication

A Practical Approach for Solubility Enhancement of Leflunomide

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http://dx.doi.org/10.13005/ojc/390537

(Received: June 09, 2023; Accepted: October 10, 2023)

ABSTRACT

Leflunomide is an anti-rheumatic medication. As it has low water solubility, it shows low absorption in gastrointestinal tract. The reported solubility of Leflunomide is approx 25.27 mcg/mL. Leflunomide comes under BCS Class II in which it has low solubility and high permeability. In this study, gel entrapment technique is used to enhance the solubility of leflunomide. In this technique Hydroxy Propyl Methyl Cellulose and Ethyl Cellulose are used which are converted to gel with the addition of different organic solvent such as Ethanol, Chloroform, Di chloro Methane etc. The analyses of the samples are done by UV Spectrophotometer at 260nm. Results shows an increment in solubility of Leflunomide drug by gel entrapment technique and are found to be 5.23, 3.80, 3.05 and 2.64 times using HPMC+Chloroform, HPMC+Ethanol+Dichloro methane, HPMC+Ethanol+Water, HPMC+Ethyl Cellulose+Dichloro methane+ Water respectively.

Keywords: Leflunomide, Anitrheumatic, Polymers, Gel entrapment technique, Solubility enhancement.

INTRODUCTION

Leflunomide is 5-Methyl-N-[4-(trifluoromethyl)phenyl]-4-isoxazole carboxamide, structure shows in Fig. 1.[1] It is a drug used to treat rheumatoid arthritis.[2] Leflunomide is practically insoluble in water. Poorly soluble drugs can be made more soluble by altering their physical and chemical characteristics, as well as by using particle size reduction, crystal engineering, salt creation, solid dispersion, and surfactants.[3] Solid dispersion is a dispersion of one or more hydrophobic active compounds that is dispersed in a hydrophilic inert carrier at the solid state using the hot melt extrusion technique, solvent evaporation, or melting (fusion).[4] The finished product consist of a hydrophilic matrix and a hydrophobic drug.[5] The promising results of solid dispersion systems in improving the solubility and dissolution rate of poorly soluble drugs can be attributed to numerous views like replacement of amorphous structure by crystalline, enhanced local solubility and wettability of drug in matrix of solid dispersion or improving ability of functional group to interact with drug.[6] This study was done by assuming that solid dispersion technique will improve the aqueous solubility of leflunomide.

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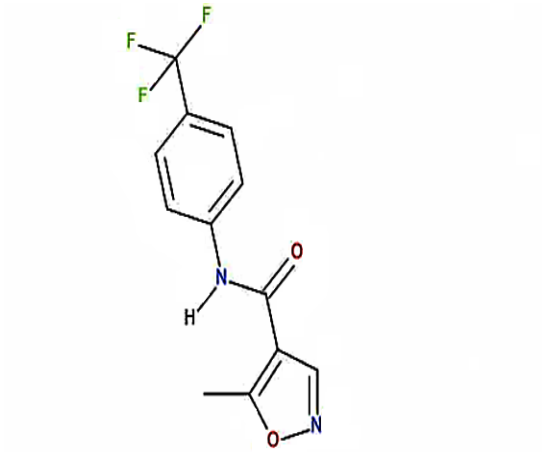

5-methyl-N-[4-(trifluoromethyl)pheny]-4H-isoxazole-4-carboxamide

Fig. 1. Structure of Leflunomide

MATERIALS AND METHOD

Leflunomide (Pure drug), Hydroxy Propyl Methyl Cellulose, Ethyl Cellulose, Ethanol, Chloroform, Dichloro Methane of analytical grade was taken from Sri Aurobindo Institute of pharmacy, Indore.

10 mg of each Hydroxy Propyl Methyl Cellulose and Ethyl Cellulose taken as carrier, was separately dissolved in 10 mL organic solvents like ethanol, chloroform, and dichloromethane in 1:1 ratio that results in formation of clear and transparent gels. Leflunomide was then incorporated into these gels and dissolved by using sonicator. The organic solvent from leflunomide gels was evaporated under vacuum that results in the formation of solid dispersion, which was then reduced to optimal size. The final powdered product obtained was used for determination of its aqueous solubility. This final product was introduced to volumetric flask and distilled water was added, and final volume was made up to 10 mL.[7-8]

RESULTS AND DISCUSSION

The purpose of this research work was to increase aqueous solubility of Leflunomide that helps to improve characteristics of dosage form. There are numerous methods exists for solubility enhancement like nanosuspension, cryogenic techniques, particle size reduction and solid dispersion. In this study, gel was prepared by adding HPMC and EC separately in different organic solvents and incorporating leflunomide to it and then dry it by using evaporator gives dried solid dispersion. This dried solid dispersion was then checked for aqueous solubility.

Results shows, an increment in solubility up to 5.23, 3.80, 3.05 and 2.64 times for Sample 1,4,5 and 6 respectively. This increased aqueous solubility of leflunomide may be due to wettability of leflunomide in solid dispersion matrix that leads to its solubilization and may be because of leflunomide bound with organic solvent results in improving functional group interaction. Incorporation of inorganic solvents disintegrates leflunomide in ionic form and makes leflunomide dissociate before incorporating it into dosage form. Also, when the dried solid dispersion of leflunomide was subjected to distilled water, it gets dissolve and the drug was released as fine colloidal particles and the ensuing increased surface area leads to an increased in solubility of leflunomide.

Table 1: Formulation of gel using HPMC and EC in different solvents

S. No	Sample	Carrier+solvent
1	Sample 1	HPMC(10 mg)+Chloroform(10 mL)
2	Sample 2	Ethyl cellulose(10 mg)+ethanol(10 mL)
3	Sample 3	Ethyl cellulose(10 mg)+Chloroform(10 mL)
4	Sample 4	HPMC (10 mg)+ethanol (10 mL)+dichloro methane (10 mL)
5	Sample 5	HPMC (10 mg)+ethanol (10 mL)+ water (10 mL)
6	Sample 6	HPMC (10 mg)+ethyl cellulose (10 mg)+ dichloro methane (10 mL)+water (10 mL)
7	Sample 7	Ethyl cellulose (10 mg)+ethanol (10 mL)+ dichloro methane (10 mL)

Table 2: Determination of solubility of solid dispersion in water

S.No.	Solid dispersion +Water	Solubility of Leflunomide (µg/mL)	Increase in solubility
1	Sample 1	132.16	5.23 times
2	Sample 2	No Change	No Change
3	Sample 3	No Change	No Change
4	Sample 4	96.21	3.80 times
5	Sample 5	77.16	3.05 times
6	Sample 6	66.62	2.64 times
7	Sample 7	No Change	No Change

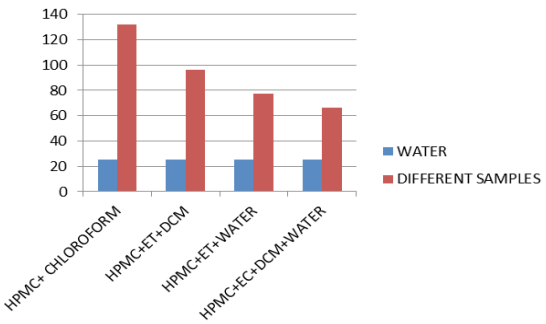

Fig. 2. Comparison of Solubility enhancement of leflunomide in different samples with water

Where, Sample 1: HPMC+CHLOROFORM, Sample 4: HPMC+Ethanol+Dichloromethane, Sample 5: HPMC+Ethanol+Water, Sample 6: HPMC+Ethyl cellulose+Dichloromethane+ water

CONCLUSION

Solid dispersions are important tools for enhancing solubility of drugs by enhancing properties of dissolution. Many of the drugs in pharma sector has low aqueous solubility which require an improvement of solubility factor. Also, many of the dosage forms are introduced to body by oral route that cause bioavailability issue. Carriers plays active role in solid dispersions. The observed solubility of Leflunomide in water was noted to be 25.27 µg/mL. Solubility of Leflunomide drug by gel entrapment technique is increased using different polymers and solvents. Solid dispersion prepared by gel entrapment technique express an enhancement in solvability of Leflunomide in water. Solid dispersion prepared by incorporating Lefunomide in gel prepared by HPMC and Chloroform, shows maximum solubility of 132.16 µg/mL.

ACKNOWLEDGEMENT

Sri Aurobindo Institute of Pharmacy, Indore, supported this work.

Conflicts of Interest

The authors declare no conflict of interest.

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