Formulation and *In-Vitro* Evaluation of Leflunomide Oral Tablet with Enhanced Dissolution

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Abstract: Leflunomide is a pyrimidine synthesis inhibitor belonging to the DMARD (Disease-Modifying Antirheumatic Drug) used in pain management associated with rheumatoid arthritis, which shows its maximum effects during morning hours. It is practically insoluble in water, so in turn showing slow dissolution pattern. The aim of this study is to enhance the solubility and dissolution rate of leflunomide by solid dispersion techniques. This is achieved by using different hydrophilic polymers at different ratios such as poloxamer 407, polyvinylpyrrolidone K30 (PVP K30), sodium laurayl sulfate (SLS), urea and polyethelenglycol 4000 (PEG 4000) at different ratios {(1:4), (1:6) and (1:8)} drug: carrier and beta-cyclodextrine (β-CD) at different molar ratios {(1:1), (1:2) and (1:3)} drug: carrier at one dose 20 mg of leflunomide. The study shows all used carriers (poloxamer 407, PVP K30, S.L.S, urea, PEG 4000 and β-CD) increased the solubility and the dissolution rate of leflunomide. IR spectroscopy and DSC techniques obviate that all the used carriers are physically compatible with leflunomide. After one way analysis of variance (ANOVA) of leflunomide formulae with respect to their % released (greater than 80%) at 15 minute followed by Tukey-Kramer multiple comparisons test, the following formulae: P_4, P_{12}, P_{15}, P_{16}, P_{21}, P_{24}, P_{25}, P_{33}, P_{40}, P_{47} andP_{49} were selected. These selected formulae were used to prepare leflunomide tablets by direct compression technique. All the prepared leflunomide tablets complied with the pharmacopieal requirements for uniformity of drug content and disintegration time.C_{24}, C_{33} and C_{49} were selected as the best formulae after one way analysis of variance (ANOVA) of lefluonamide tablets with respect to their % released (greater than 85%) at 15 minute followed by Tukey-Kramer multiple comparisons test. The release kinetics of leflunomide from solid dispersion formulae, the prepared tablets and commercial tablet were evaluated by employing the Korsmeyer peppa's equation.
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1. Introduction

The number of sparingly soluble active pharmaceutical materials has risen sharply in recent years, and the formulation of such entities presents greater challenges to industrial pharmacists. Along with other factors, solubility of active pharmaceutical materials is a key determinant of its oral bioavailability.

Solid dispersion (SD) is one of the most promising approaches for solubility enhancement. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. Solid dispersion can be prepared by various methods such as solvent evaporation, complexation and fusion methods [(1)].

The mechanisms by which the solubility and dissolution rate of the drug is increased are, firstly, the particle size of a drug is reduced to submicron size or to molecular size in the case where the solid solution is obtained. The particle size reduction generally increases the rate of dissolution; secondly, the drug is changed from crystalline to amorphous form, the high energetic state which is highly soluble; finally, the wettability of the particle is improved by the dissolved carrier [(2)].

Leflunomide is a pyrimidine synthesis inhibitor belonging to the DMARD (disease-modifying antirheumatic drug) used in pain management associated with rheumatoid arthritis, which shows its maximum effects during morning hours. It is practically insoluble in water.

2. Material and Methods

Leflunomide, Polyvinylpyrrolidone (PVP K30) and Poloxamer 407 powder were kindly provided by Hekma Pharm Company, Cairo (Egypt). Sodium lauryl sulfate (SLS), Urea, Methanol and Hydrochloric acid were supplied from El-Nasr Pharmaceutical chemicals, Cairo (Egypt). Polyethelenglycol 4000 (PEG 4000) was supplied from El-Gomhorya

Company, Cairo (Egypt). Beta-cyclodextrine (β-CD) was kindly provided by El-Kahira Company, Cairo (Egypt).

2.1.Solubility study of leflunomide in different ratios of carriers

An excess amount of leflunomide was added to 25 ml of 0.1 N HCl solution having different ratios of poloxamer 407, PVP K30, S.L.S, urea, PEG 4000 andβ-CD in stoppered conical flasks. The samples were sonicated for one hour at room temperature. The stoppered conical flasks were shaken for 24 hours at 37^{o}C to achieve equilibrium in a shaking water bath. The obtained suspensions were filtered and the filtrate was diluted properly with 0.1 N HCl solutions. The diluted solutions were measured spectrophotometrically at wavelength of maximum absorption 260 nm using the same medium as a blank. Each experiment was performed in triplicate [(3)].

2.2. Preparation of leflunomide solid dispersions

2.2.1. Microwave induced fusion method (MIF)

Microwave induced fusion method was used to prepare solid dispersions of leflunomide with different carriers (poloxamer 407, PVP K30, S.L.S, urea and PEG 4000) at ratios of 1:4, 1:6 and 1:8 drug to carrier (Table 1) as follow:

Leflunomide and carriers (poloxamer 407, PVP K30, S.L.S, urea and PEG 4000) were weighed in the previous ratios and mixed gently for 5 minutes using a mortar and pestle. A fixed amount of the mixture was subjected to microwave radiation for 3 minutes at a constant power of 590 W in a microwave reactor. Only one beaker was placed at a time inside the microwave oven. Then, the beakers containing the samples were maintained at room temperature for the samples to solidify. The solid dispersions were collected and placed in a desiccator for 24 hours, and then the product was pulverized using a mortar and pestle. The pulverized powder was sieved into defined particle size fraction of 150-200 micrometer for study [(4)].

2.2.2. Solvent evaporation method (SE)

The solvent evaporation method was used to prepare solid dispersions of leflunomide with different carriers (poloxamer 407, PVP K30, S.L.S, urea and PEG 4000) at weight ratios of 1:4, 1:6 and 1:8drug to carrier as follow (Table 1):

Leflunomide and carriers (poloxamer 407, PVP K30, S.L.S, urea and PEG 4000) were dissolved in minimum volume of organic solvent (methanol) and the solvent was allowed to evaporate in hot air oven at 45°C±10°C. Then, solid dispersion formulation was crushed, pulverized using a mortar and pestle. The pulverized powder was sieved into defined particle size fraction of 150-200 micrometer for study [(5)].

2.2.3. Mixed-grinding method (MG)

For mixed-grinding product as shown in Table (1), an appropriate amount of lefluonamide with different carriers (poloxamer 407, PVP K30, S.L.S, urea and PEG 4000) at weight ratios of 1:4, 1:6 and 1:8drug to carrier were mixing thoroughly until a homogenous mixture was obtained. Triturating was carried in a mortar for 10 -15 min to form a homogenous mixture which sieved into defined particle size fraction of 150-200 micrometer for study [(6)].

2.2.4.Physical mixture method (PM)

The physical mixture of leflunomide with β-CD was prepared in 1:1, 1:2 and 1:3 molar ratio by means of spatula for 5 minutes and was sieved into defined particle size fraction of 150-200 micrometer for study (Table 1).

2.2.5.Co-grinding method (CG)

For co-grinding products (CG), leflunomide with β-CD in 1:1, 1:2 and 1:3 molar ratio were mixed and triturated in a mortar and pestle for 20 minutes and was sieved into defined particle size fraction of 150-200 micrometer for study (Table 1)**.**

2.3. Evaluation of leflunomide solid dispersions

2.3.1. Content uniformity analysis

SD (with different carriers) equivalent to 20 mg of leflunomide were weighed and dissolved in 50 ml methanol which added to 500 ml volumetric flask, then complete to the final volume with 0.1N HCl and then were shaken for 10 minutes. The obtained solution was filtered and 3ml of the filtrate were taken and diluted separately to 10 ml with 0.1 N HCl. These diluted samples were measured using UV-Scanning spectrophotometer at 260 nm. The blank was carried out using 0.1 N HCl [(7)].

2.3.2. *In-vitro* release study

The dissolution rates of pure leflunomide and different formulae that is equivalent to 20 mg of leflunomide were determined in 900 ml of dissolution medium (0.1 N HCl) at 37 °C ± 0.5 °C with a stirrer rotation speed of 75 rpm using the USP Dissolution Apparatus II (paddle type). Aliquots (5 ml) of the sample were withdrawn from dissolution medium at time intervals of 15, 30, 45, 60, 75, 90, 105, and 120 minutes using a pipette. The same volume of 0.1 N HCl was used to replace the samples withdrawn to maintain the sink condition. The samples were suitably filtered, diluted and assayed spectrophotometrically at 260 nm.

Table (1): The suggested formulae of leflunomide solid dispersions

Formulae	Method of preparation	leflunomide (mg)	Carrier (mg)						Drug: carrier ratio
			Poloxamer 407	PVP K30	S.L.S	urea	PEG 4000	β-CD	
P_1	S.E	20	80						1:4
P_2	S.E	20	120						1:6
P_3	S.E	20	160						1:8
P_4	MG	20	80						1:4
P_5	MG	20	120						1:6
P_6	MG	20	160						1:8
P_7	MIF	20	80						1:4
P_8	MIF	20	120						1:6
P_9	MIF	20	160						1:8
P_{10}	S.E	20		80					1:4
P_{11}	S.E	20		120					1:6
P_{12}	S.E	20		160					1:8
P_{13}	MG	20		80					1:4
P_{14}	MG	20		120					1:6
P_{15}	MG	20		160					1:8
P_{16}	MIF	20		80					1:4
P_{17}	MIF	20		120					1:6
P_{18}	MIF	20		160					1:8
P_{19}	S.E	20			80				1:4
P_{20}	S.E	20			120				1:6
P_{21}	S.E	20			160				1:8
P_{22}	MG	20			80				1:4
P_{23}	MG	20			120				1:6
P_{24}	MG	20			160				1:8
P_{25}	MIF	20			80				1:4
P_{26}	MIF	20			120				1:6
P_{27}	MIF	20			160				1:8
P_{28}	S.E	20				80			1:4
P_{29}	S.E	20				120			1:6
P_{30}	S.E	20				160			1:8
P_{31}	MG	20				80			1:4
P_{32}	MG	20				120			1:6
P_{33}	MG	20				160			1:8
P_{34}	MIF	20				80			1:4
P_{35}	MIF	20				120			1:6
P_{36}	MIF	20				160			1:8
P_{37}	S.E	20					80		1:4
P_{38}	S.E	20					120		1:6
P_{39}	S.E	20					160		1:8
P40	MG	20					80		1:4
P41	MG	20					120		1:6
P42	MG	20					160		1:8
P43	MIF	20					80		1:4
P44	MIF	20					120		1:6
P45	MIF	20					160		1:8
P46	P.M	20						84	1:1*
P47	P.M	20						168	1:2*
P48	P.M	20						252	1:3*
P49	CO.G	20						84	1:1*
P50	CO.G	20						168	1:2*
P51	CO.G	20						252	1:3*

S.E: solvent evaporation; MG: mixed grinding; P.M: physical mixture; CO.G: co-grinding; *: molar ratio

From this, cumulative % of dug released was calculated from the previously constructed standard calibration curve and plotted against function of time to study the pattern of drug release. Each test was performed in triplicate (n = 3) and calculated mean values of cumulative% drug release were used while plotting the release curves [8].

2.3.3. Statistical analysis of the obtained results

Statistical analysis was done for pure leflunomide and all formulae with respect to their percent released at 15 minutes using the two-way analysis of variance (ANOVA), followed by Tukey-Kramer multiple comparisons test.

2.3.4. Kinetic modelling of drug release

The release kinetics of leflunomide from different solid dispersions were evaluated by employing the Korsmeyer peppa's equation: $M_t/M_\infty = k\ t^n$, where M_t is the amount of the drug released at time t, M_∞ is the amount of the drug released after infinite time, k is the kinetic constant and n is the diffusional exponent indicative of the mechanism of drug release. When n is ≤ 0.5, the drug is released from the polymer with a fickian diffusion mechanism. If $0.5 < n < 1$ this indicates anomalous or non-fickian release, while if n= 1 this indicates Case II transport. Lastly, when n is > 1.0, Super Case II transport is apparent. Kinetic studies were performed by adjusting the release profiles to Higuchi, First and Zero order equations. The kinetic parameters and correlation coefficient were calculated for the in vitro release of all lefluonamide solid dispersions formulae[9].

2.3.5. *Fourier Transform Infrared Spectroscopy (FT-IR)*

Instrument used was Fourier transform infrared spectroscopy, Perkin-Elmer, FTS-1710, Beaconsfield, (UK). In this study, potassium bromide disc method was employed. Pure drug, pure carrier and solid dispersions and physical mixtures were studied by Fourier transform infrared spectroscopy. The provided samples were then compressed into transparent disc under high pressure using special disc. The disc was placed in IR spectroscopy using sample holder and spectrum was recorded [10].

2.3.6. Differential scanning calorimetry (DSC)

The thermal characteristics of pure drug, pure carrier and solid dispersions and physical mixtures were determined by Differential scanning calorimetry, Shimadzu, model DSC-50, (Japan). Samples were weighed and placed in sealed aluminum pan. An empty aluminum pan was used as a reference. The purity determination was performed using heating rate of 5°C/min in the temperature range from 30-300°C in nitrogen atmosphere with flow rate of 30 ml/min. The data were calculated in three replicates by Shimadzu TASYS software. DSC was preliminary calibrated with standard of indium [10].

2.4. Preparation of leflunomide tablets

Based on the results of the statistical analysis, eleven formulae were chosen and compressed into eleven formulae of leflunomide tablets as shown in Tables (2 and 3). Solid dispersions powder, avicel PH102 and cross carmellose sodium were weighted as per formula given in Table (3), these were then sifted through mesh size 40, transferred to a poly bag and blended for 5 minutes. To this homogeneous blend magnesium stearate pre-sifted through mesh size 60 was added and blended for 2 minutes. The resulted blend was compressed using Tablet compression machine with 10 mm, round, flat-faced single punch. A minimum of 50 tablets was prepared for each formula [11].

Table (2): The chosen formulae of leflunomide solid dispersions.

Powder formulae	Method of preparation	Ingredients (mg)							Drug: Carrier ratio
		Leflunomide	Poloxamer407	PVP K30	S.L.S	Urea	PEG 4000	β-CD	
P_4	S.E	20	80						1:4
P_{12}	S.E	20		160					1:8
P_{15}	MG	20		160					1:8
P_{16}	MIF	20		80					1:4
P_{21}	S.E	20			160				1:8
P_{24}	MG	20			160				1:8
P_{25}	MIF	20			80				1:4
P_{33}	MG	20				160			1:8
P_{40}	MG	20					80		1:4
P_{47}	PM	20						168	1:2
P_{49}	Co-G	20						84	1:1

Table (3): the suggested formulae of leflunomide tablets with different polymer ratios.

Tablet formulae	Ingredients (mg)				Total weight
	SD formulae	Crosscamelose Sodium	Avicel PH 102	Magnesium stearate	
C_4	P_4	11.5	117.4	1.15	230
C_{12}	P_{12}	11.5	37.4	1.15	230
C_{15}	P_{15}	11.5	37.4	1.15	230
C_{16}	P_{16}	11.5	117.4	1.15	230
C_{21}	P_{21}	11.5	37.4	1.15	230
C_{24}	P_{24}	11.5	37.4	1.15	230
C_{25}	P_{25}	11.5	117.4	1.15	230
C_{33}	P_{33}	11.5	37.4	1.15	230
C_{40}	P_{40}	11.5	77.4	1.15	230
C_{47}	P_{47}	11.5	29.4	1.15	230
C_{49}	P_{49}	11.5	113.4	1.15	230

2.5. Evaluation of leflunomide tablets

The prepared tablets from each formula were subjected to the following Quality control tests.

2.5.1. Content uniformity analysis:

Ten tablets from each formula were powdered and were mixed. An amount equivalent to 20 mg of leflunomide was taken and was dissolved in 50 ml methanol which added to 500 ml volumetric flask, then complete to the final volume with 0.1N HCl. The flask was shaken for 10 minutes. The obtained solution was filtered and 1ml of the filtrate were taken and diluted separately to 3 ml with 0.1N HCL. This diluted sample was measured using UV- Scanning spectrophotometer at 260 nm. Blank tablets without the drug were prepared and were subjected to the same analytical procedure to serve as the blank for spectrophotometric determination [(12)].

2.5.2. Disintegration time:

One tablet was placed in each of the six tubes of the basket and the apparatus was operated, using 0.1N HCl maintained at 37°C as the immersion fluid at the end of the time, the basket was lifted from the fluid, and the tablets were observed till disintegration of all tablets completely. The test was carried out according to USP and the disintegration time of each of six individual tablets was determined using tablet disintegration test apparatus [(13)].

2.5.3. *In-vitro* release study of leflunomide tablets

The *in-vitro* release study of leflunomide tablets and leflunomide commercial tablet were investigated adopting the USP rotating paddle apparatus II. The dissolution medium (900 ml) was 0.1N HCl. Each tablet was placed in a flask containing the used medium, the paddle was rotated at 75 r.p.m. at a constant temperature 37°C. Aliquots, each of 5 ml were withdrawn from the release medium at intervals 15, 30, 45, 60, 75, 90, 105 and 120 minutes. The same volume of the used medium replaced all samples. The samples were filtered, diluted and measured spectrophotometrically at 260 nm. The concentration of the drug was determined from the previously constructed standard calibration curve. The procedure was repeated three times and the mean reading was taken [(8)].

2.5.4.Statistical analysis of the obtained results

Statistical analysis was done for leflunomide tablets and leflunomide commercial tablet with respect to their percent released (greater than 85%) at 15 minutes using the two-way analysis of variance (ANOVA), followed by Tukey-Kramer multiple comparisons test.

2.5.5.Kinetic modelling of the drug release

The release kinetics of leflunomide from the prepared tablets and commercial tablet were evaluated by employing the Korsmeyer peppa's equation: $M_t/M_\infty = k\ t^n$, where M_t is the amount of the drug released at time t, M_∞ is the amount of the drug released after infinite time, k is the kinetic constant and n is the diffusional exponent indicative of the mechanism of drug release. When n is ≤ 0.5, the drug is released from the polymer with a fickian diffusion mechanism. If $0.5 < n < 1$ this indicates anomalous or non-fickian release, while if n= 1 this indicates Case II transport. Lastly, when n is > 1.0, Super Case II transport is apparent. Kinetic studies were performed by adjusting the release profiles to Higuchi, First and Zero order equations. The kinetic parameters and correlation coefficient were calculated for the *in-vitro* release of all lefluonamide tablets formulae and commercial tablet[(9)].

3. Results and Discussion

3.1. Solubility study of leflunomide in different ratios of carriers

The solubility of leflunomide in 0.1N HCl was studied alone and in the presence of different ratios (1:1, 1:2, 1:4, 1:6 and 1:8) of hydrophilic carriers, including poloxamer 407, PVP K30, S.L.S, urea, PEG 4000 and (1:1, 1:2 and 1:3 molar ratio) of β-CD. The results are shown in Table (4). The solubility of

leflunomide in 0.1 N HCl was found to be 0.036 mg/ml. Lefluonamide has a limited solubility in 0.1 N HCL as it is an organic compound [14].

The addition of poloxamer 407, PVP K30, urea and PEG 4000in the ratios of 1:1 and 1:2 drug to carrier had no effect on the solubility of leflunomide in 0.1 N HCl at 37°C. While the addition of these carriers in the ratios of 1:4, 1:6 and 1:8 drug to carrier was accompanied by gradual increases in the solubilized amount of leflunomide. The enhancement of the solubility of leflunomide with the carriers used may be attributed to the wetting effect of highly water soluble carrier in the intimate contact with it. They solubilized leflunomide by breaking up water clusters surrounding the non polar molecule, increasing the entropy of the system and producing a driving force for the solubilization[15].

Table (4): The effect of different carriers on the solubility of leflunomide in 0.1 N HCl at 37°C.

Carrier	Leflunomide : Carrier	Solubilized lefluonamide (mg/ml)
-	Pure leflunomide	0.036
Poloxamer 407	1:1	0.036
	1:2	0.036
	1:4	0.048
	1:6	0.052
	1:8	0.058
PVP K30	1:1	0.036
	1:2	0.037
	1:4	0.050
	1:6	0.063
	1:8	0.068
S.L.S	1:1	0.15
	1:2	0.23
	1:4	0.52
	1:6	0.68
	1:8	0.97
Urea	1:1	0.036
	1:2	0.037
	1:4	0.045
	1:6	0.051
	1:8	0.062
PEG 4000	1:1	0.036
	1:2	0.036
	1:4	0.041
	1:6	0.053
	1:8	0.060
β-CD	1:1	0.15
	1:2	0.22
	1:3	0.30

The solubility of leflunomide in 0.1N HCl solutions containing S.L.S in the ratios of 1:1, 1:2, 1:4, 1:6 and 1:8 drug to carrier was found to be 0.15, 0.23, 0.52, 0.68 and 0.97 mg/ml, respectively as shown in Table (4). It is evident that, the addition of S.L.S in any ratio was accompanied by gradual increase in the solubilized amount of leflunomide. This is due to increased wetting of the leflunomide by SLS and due to micellar solubilisation. Hence the presence of SLS in a formulation will lead to increased wetting, solubility and dissolution rate of leflunomide in 0.1 N HCl [16].The solubility of leflunomide in 0.1 N HCl solutions containing β-CD in the ratios of 1:1, 1:2, and 1:3 drug to carrier was found to be 0.15, 0.23 and 0.30 mg/ml, respectively as shown in Table (4). It is evident that, the addition of β-CD in any ratio was accompanied by gradual increase in the solubilized amount of leflunomide. It is assumed that the increase in solubility observed was due to the formation of an inclusion complex [17]. The β-CD molecules are cone-shaped with a somewhat hydrophobic central cavity and hydrophilic outer surface. They are capable of

forming inclusion complexes with many drugs by taking up a whole drug molecule, or more frequently, some hydrophobic part of it, into the cavity. So, β-CD was improving the solubility of the leflunomide [18].

3.2. Preparation of leflunomide solid dispersions

Based on solubility study, we prepared leflunomide formulae ($P_1 \rightarrow P_{45}$) containing the following carrier poloxamer 407, PVP K30, S.L.S, urea and PEG 4000in drug: carrier ratio (1:4, 1:6 and 1:8) by the solvent evaporation, mixed grinding and microwave induced fusion method. While leflunomide formulae ($P_{46} \rightarrow P_{51}$) containing β-CD in drug: carrier molar ratio (1:1, 1:2 and 1:3) were prepared by physical mixture and co-grinding method. leflunomide formulae were represented in Table (1).

3.3. Evaluation of leflunomide solid dispersions

3.3.1. Content uniformity analysis

The content of leflunomide in each formula was found to be between 95% and 105% which fulfils the USP specification [13]. This indicated that leflunomide was uniformly distributed in all these prepared solid dispersions.

3.3.2. *In-vitro* release study

Table (5) and Figures (1-6) show in-vitro release of leflunomide formulae in 0.1 N HCl at 37°C. After a careful observation in the table, all the prepared formulae showed an improved drug release compared to pure leflunomide sample. The trend observed was an increase in dissolution rate on increasing the amount of carriers. This enhancement can be attributed to the greater hydrophilic character of the systems due to the presence of the carrier, which can reduce interfacial tension between a poorly water-soluble drug and dissolution medium. The enhancement of the solubility of lefluonamide with carriers used may be attributed to the wetting effect of the highly water soluble carrier or polymer in the intimate contact with it. They solubilized leflunomide by breaking up water clusters surrounding the non polar molecule, increasing the entropy of the system and producing a driving force for the solubilization. Also, the improvement in the dissolution rate may be due to the enhancement of the physical amorphism of the drug, and this enhancement also might be attributed to the increase in the wettability and solubility of the drug [15].

The mixed-grinding method showed the maximum release at 15min with a % drug release greater than 80% with all carriers. This enhancement can be attributed to the phenomenon that a mechanical energy (compression, shear, friction) alters the physicochemical properties of a substance. It is considered that here various factors arising from mechanical manipulation, such as lattice defect or lattice modulation, increases in specific surface area and surface energy and so on, enhances the activity of the solid phase to encourage transition of the drug to an amorphous state and, hence, dispersion of the drug in this amorphous state into the carrier[19].

Co-grinding method of β-CD showed the maximum release at 15min. with a % drug release greater than 95% with all ratios compared with physical mixture method of β-CD. This enhancement can be attributed to the co-grinding method are capable of forming inclusion complexes with leflunomide by taking up a whole drug molecule, or more frequently, some hydrophobic part of it, into the cavity. Thus, the complex formed showed increase in drug dissolution. This was due to increased solubility and rapid wettability of the complexed drug [18].

Solvent evaporation method showed the minimum release with all carriers except P_{21} (1:8 drug to PVP K30 ratio). This can be attributed to that, the leflunomide has two polymorphs (form I and II). It was recrystallized from methanol (99.9%) and benzene (99%) to obtain forms I and II respectively. In methanolic system, conversion of form II to form I could be expected to happen at room temperature. Form I is more stable and less soluble than form II. So, the solvent evaporation method showed the minimum release when methanol used as a solvent [20]. While, P_{12} showed 100% release of leflunomide at 15 min.

This is due to the fact that, the glass transition temperature (T_g) of drugs increased upon increasing the fraction of PVP in the mixture due to high T_g of PVP. Mechanism of crystallization inhibition include anti plasticizing effect of PVP in which T_g of the system increased, as well as steric and specific interactions occurring between the drug and PVP [21].

Microwave induced fusion method showed % drug release higher than that of solvent evaporation method. This enhancement can be attributed to amorphization of drug by microwaves, improved surfactant and wetting characteristics of carrier with drug. The improved wetting of drug is due to better intimate contact between the leflunomide and carrier. Microwave equipment uses electromagnetic waves that pass through material and cause the molecules to oscillate, generating heat at each point of the material by the interaction of the electromagnetic field with its molecular and electronic structure. Thus microwaves, with their ability to penetrate any substance, allow the production of heat throughout the sample at the same rate resulting in rapid and uniform volumetric heating providing molecular dispersions with better intimate contact between drug and carriers [22 and 23].

Table (5): *In-vitro* release of leflunomide formulae and plain drug (20 mg) in 0.1 N HCl

Formulae	Percentage lefluonamide released after the following time intervals (minutes)							
	15	**30**	**45**	**60**	**75**	**90**	**105**	**120**
Plain drug	10.25	13.51	14.46	15.42	17.28	18.33	19.54	20.71
P_1	49.38	54.12	57.88	59.48	60.82	61.92	63.32	63.89
P_2	55.14	57.25	63.12	65.92	69.20	72.31	74.31	74.31
P_3	65.23	67.55	69.11	70.43	74.65	77.67	84.28	84.28
P_4	82.98	86.73	88.36	88.93	89.43	89.84	91.11	93.86
P_5	91.57	94.00	96.59	100	100	100	100	100
P_6	99.96	100	100	100	100	100	100	100
P_7	54.19	55.24	56.32	58.10	58.97	60.93	62.27	62.36
P_8	65.75	68.26	68.96	69.26	70.61	72.09	79.47	79.47
P_9	79.34	82.07	83.12	84.94	85.98	86.89	87.28	87.28
P_{10}	34.10	39.16	49.46	55.24	59.27	63.01	65.48	65.48
P_{11}	37.39	42.11	50.33	58.11	62.69	65.64	68.96	68.96
P_{12}	100	100	100	100	100	100	100	100
P_{13}	81.94	88.46	91.97	94.06	94.06	94.06	94.06	94.06
P_{14}	90.54	92.89	94.45	96.79	99.14	99.40	99.40	99.40
P_{15}	100	100	100	100	100	100	100	100
P_{16}	83.90	85.85	85.85	85.85	85.85	85.85	85.85	85.85
P_{17}	86.63	91.06	91.06	91.06	91.06	91.06	91.06	91.06
P_{18}	89.89	93.28	93.28	93.28	93.28	93.28	93.28	93.28
P_{19}	65.01	71.22	79.64	86.50	87.54	89.11	89.11	89.11
P_{20}	77.90	82.07	84.29	86.50	87.81	89.24	90.93	90.93
P_{21}	84.29	92.36	92.36	92.36	92.36	92.36	92.36	92.36
P_{22}	92.63	98.75	100	100	100	100	100	100
P_{23}	96.53	100	100	100	100	100	100	100
P_{24}	100	100	100	100	100	100	100	100
P_{25}	100	100	100	100	100	100	100	100
P_{26}	100	100	100	100	100	100	100	100
P_{27}	100	100	100	100	100	100	100	100
P_{28}	28.66	33.48	37.17	42.30	47.81	54.19	59.19	59.19
P_{29}	29.83	36.56	38.69	43.43	48.29	54.98	61.01	61.01
P_{30}	34.70	40.99	44.90	49.42	58.58	67.31	70.96	70.96
P_{31}	81.42	81.42	81.42	81.42	81.42	81.42	81.42	81.42
P_{32}	85.72	85.72	85.72	85.72	85.72	85.72	85.72	85.72
P_{33}	94.45	94.45	94.45	94.45	94.45	94.45	94.45	94.45
P_{34}	49.33	52.72	57.10	61.49	61.49	61.49	61.49	61.49
P_{35}	53.63	56.11	59.93	63.05	63.05	63.05	63.05	63.05
P_{36}	54.37	58.23	60.45	64.49	64.49	64.49	64.49	64.49
P_{37}	52.98	62.31	62.31	62.31	62.31	62.31	62.31	62.31
P_{38}	57.89	65.62	65.62	65.62	65.62	65.62	65.62	65.62
P_{39}	60.19	69.22	69.22	69.22	69.22	69.22	69.22	69.22
P_{40}	84.03	84.03	84.03	84.03	84.03	84.03	84.03	84.03
P_{41}	88.20	88.20	88.20	88.20	88.20	88.20	88.20	88.20
P_{42}	90.54	90.54	90.54	90.54	90.54	90.54	90.54	90.54
P_{43}	55.80	56.45	57.23	58.49	58.88	59.62	59.62	59.62
P_{44}	59.71	61.23	62.53	63.36	64.36	64.36	64.36	64.36
P_{45}	63.75	67.05	68.13	68.96	68.96	68.96	68.96	68.96
P_{46}	67.31	69.91	73.65	75.99	75.99	75.99	75.99	75.99
P_{47}	92.23	97.05	97.05	97.05	97.05	97.05	97.05	97.05
P_{48}	100	100	100	100	100	100	100	100
P_{49}	96.27	99.40	100	100	100	100	100	100
P_{50}	98.36	100	100	100	100	100	100	100
P_{51}	100	100	100	100	100	100	100	100

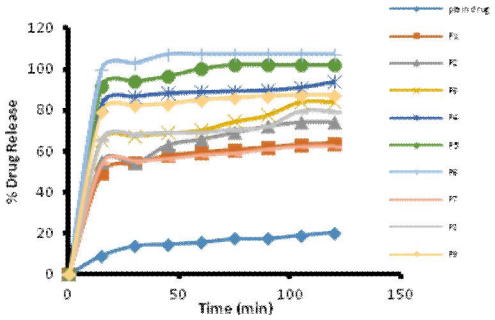

Fig.(1): *In-vitro* release of leflunomide from its solid dispersion (SE, MG and MIF) using poloxamer 407 as a carrier compared to plain drug in 0.1 N HCl

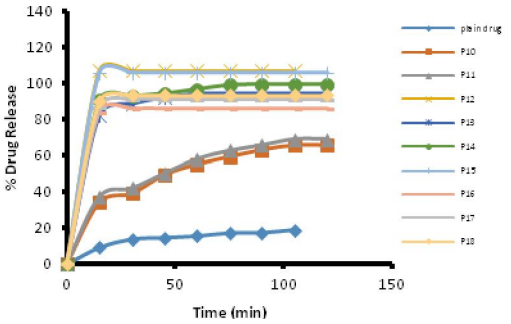

Fig.(2): *In-vitro* release of leflunomide from its solid dispersion (SE, MG and MIF) using PVP K30 as a carrier compared to plain drug in 0.1 N HCl

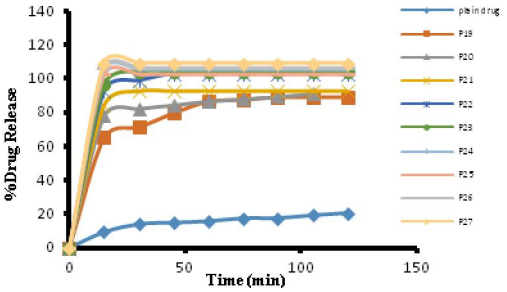

Fig.(3): *In-vitro* release of leflunomide from its solid dispersion (SE, MG and MIF) using SLS as a carrier compared to plain drug in 0.1 N HCl

3.3.3. Statistical analysis of the obtained results

Table (6) shows one way analysis of variance (ANOVA) of leflunomide formulae with respect to their % released (greater than 80%) at 15 minute followed by Tukey-Kramer multiple comparisons test. From this table, it was concluded that all formulae are non-significant with each others at $p<0.05$except: P_{13} vs $P_{15,}$ P_{31} vs $P_{33,}$ P_{32} vs P_{33}, so we were selected the formulae with lower carrier concentration, and all formulae vs pure leflunomide are significant at $p<0.05$, so we were selected the formulae with higher release than others. Therefore, The following formulae: $P_{4,}$ $P_{12,}$ $P_{15,}$ $P_{16,}$ $P_{21,}$ $P_{24,}$ $P_{25,}$ $P_{33,}$ $P_{40,}$ P_{47} andP_{49} were selected.

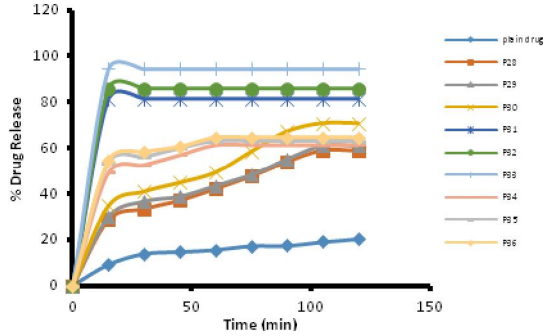

Fig.(4): *In-vitro* release of leflunomide from its solid dispersion (SE, MG and MIF) using Urea as a carrier compared to plain drug in 0.1 N HCl

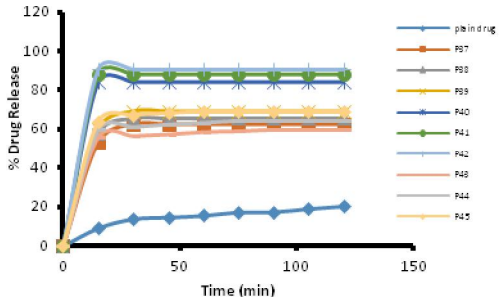

Fig.(5): *In-vitro* release of leflunomide from its solid dispersion (SE, MG and MIF) using PEG 4000 as a carrier compared to plain drug in 0.1 N HCl

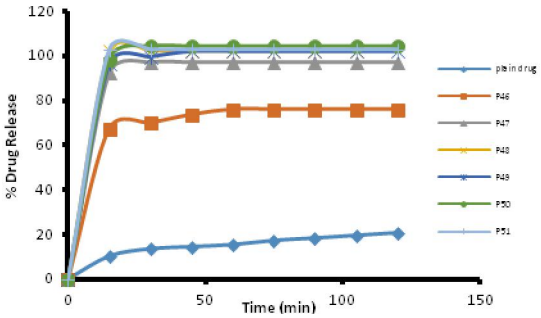

Fig.(6): *In-vitro* release of leflunomide from its complex (PM and CO.G) using β-CD as a carrier compared to plain drug in 0.1 N HCl

3.3.4. Kinetic modeling of drug release

Table (7) shows kinetic parameters for in-vitro release of leflunomide from SD according to zero order, first order, higuchi-diffusion model and Korsmeyer peppa's model. It can be concluded that the release exponent values of all the formulations

obtained and plain drug were from 0.0002 to 0.3768. Based on these values we can say that the formulations and plain drug exhibited Fickian release. The formulations P_2, P_{22}, P_{45}, P_{49} and P_{50} showed higher (r) values for first order plots indicating that drug release followed first order kinetics. While P_3, P_7, P_8, P_{28}, P_{29} and P_{30} showed higher (r) values for zero order plots indicating that drug release followed zero order kinetics. The rest of formulations and plain drug showed higher (r) values for diffusion order plots indicating that drug release followed diffusion order kinetics. Therefore, the kinetic data shows that the in-vitro release of leflunomide from solid dispersions in 0.1 N HCL follows different kinetic orders, and no definite kinetic order can express the drug release from different types of solid dispersions and complexes formulations [(1)].

Table (6): Tukey-Kramer multiple comparisons test of leflunomide formulae and plain drug (leflunomide 20 mg)

Comparison	Significance	Comparison	Significance	Comparison	Significance
P_4 vs P_5	NS	P_{13} vs P_{14}	NS	P_{16} vs P_{17}	NS
P_4 vs P_6	NS	P_{13} vs P_{15}	**	P_{16} vs P_{18}	NS
P_4 vs leflunomide	***	P_{13} vs leflunomide	***	P_{16} vs leflunomide	***
P_5 vs P_6	NS	P_{14} vs P_{15}	NS	P_{17} vs P_{18}	NS
P_5 vs leflunomide	***	P_{14} vs leflunomide	***	P_{17} vs leflunomide	***
P_6 vs leflunomide	***	P_{15} vs leflunomide	***	P_{18} vs leflunomide	***
P_{22} vs P_{23}	NS	P_{25} vs P_{26}	NS	P_{31} vs P_{32}	NS
P_{22} vs P_{24}	NS	P_{25} vs P_{27}	NS	P_{31} vs P_{33}	***
P_{22} vs leflunomide	***	P_{25} vs leflunomide	***	P_{31} vs leflunomide	***
P_{23} vs P_{24}	NS	P_{26} vs P_{27}	NS	P_{32} vs P_{33}	*
P_{23} vs leflunomide	***	P_{26} vs leflunomide	***	P_{32} vs leflunomide	***
P_{24} vs leflunomide	***	P_{27} vs leflunomide	***	P_{33}vs leflunomide	***
P_{40} vs P_{41}	NS	P_{47} vs P_{48}	NS	P_{49} vs P_{50}	NS
P_{40} vs P_{42}	NS	P_{47} vs leflunomid	***	P_{49} vs P_{51}	NS
P_{40} vs leflunomide	***	P_{48} vs leflunomide	***	P_{49} vs leflunomide	***
P_{41} vs P_{42}	NS			P_{50} vs P_{51}	NS
P_{41} vs leflunomide	***			P_{50} vs leflunomide	***
P_{42} vs leflunomide	***			P_{51} vs leflunomide	***

(***) = Significant at $p<0.001$; (**) = Significant at $p<0.01$; (*) = Significant at $p<0.05$; (NS) = Not significant

Table (7): The calculated correlation coefficient (r) and (n) value for leflunomide formulae and pure leflunomide based on in-vitro release study

Formula	Correlation coefficient (r)				(n) value	Comment
	Zero-order	First-order	Higuchi-diffusion model	Korsmeyer peppa's model		
Plain drug	0.9866	0.989	0.9941	0.9927	0.3240	Fickian diffusion mechanism
P_1	0.9470	0.9614	0.9815	0.9963	0.1243	Fickian diffusion mechanism
P_2	0.9624	0.9759	0.9708	0.9528	0.1707	Fickian diffusion mechanism
P_3	0.9768	0.9554	0.9490	0.9121	0.1274	Fickian diffusion mechanism
P_4	0.9451	0.9433	0.9598	0.9644	0.0495	Fickian diffusion mechanism
P_5	0.8618	0.8588	0.9167	0.9694	0.0608	Fickian diffusion mechanism
P_6	0.577	0.5773	0.6675	0.8985	0.0349	Fickian diffusion mechanism
P_7	0.9917	0.9914	0.9841	0.9573	0.0733	Fickian diffusion mechanism
P_8	0.9292	0.9089	0.8925	0.8654	0.0813	Fickian diffusion mechanism
P_9	0.9529	0.9677	0.9834	0.9941	0.0487	Fickian diffusion mechanism
P_{10}	0.9608	0.9772	0.9848	0.9880	0.1087	Fickian diffusion mechanism
P_{11}	0.9685	0.9824	0.9871	0.9695	0.2982	Fickian diffusion mechanism
P_{12}	0.5773	0.5773	0.6675	0.7615	0.0002	Fickian diffusion mechanism
P_{13}	0.7951	0.8357	0.8700	0.9304	0.0655	Fickian diffusion mechanism
P_{14}	0.9351	0.9511	0.9669	0.9774	0.0508	Fickian diffusion mechanism
P_{15}	0.5773	0.5773	0.6675	0.7615	0.0002	Fickian diffusion mechanism
P_{16}	0.5773	0.5773	0.6675	0.7615	0.0088	Fickian diffusion mechanism
P_{17}	0.5773	0.5773	0.6675	0.7615	0.0191	Fickian diffusion mechanism
P_{18}	0.5773	0.5773	0.6675	0.7615	0.0472	Fickian diffusion mechanism

Formula	Correlation coefficient (r)				(n) value	Comment
	Zero-order	First-order	Higuchi-diffusion model	Korsmeyer peppa's model		
P_{19}	0.8963	0.9286	0.9444	0.9714	0.0298	Fickian diffusion mechanism
P_{20}	0.9675	0.9892	0.9920	0.9979	0.0002	Fickian diffusion mechanism
P_{21}	0.5773	0.5773	0.6675	0.7615	0.0002	Fickian diffusion mechanism
P_{22}	0.6533	0.7633	0.7425	0.8846	0.0002	Fickian diffusion mechanism
P_{23}	0.5773	0.5773	0.6675	0.7615	0.0002	Fickian diffusion mechanism
P_{24}	0.5773	0.5773	0.6675	0.7615	0.3768	Fickian diffusion mechanism
P_{25}	0.5773	0.5773	0.6675	0.7615	0.3580	Fickian diffusion mechanism
P_{26}	0.5773	0.5773	0.6675	0.7615	0.3749	Fickian diffusion mechanism
P_{27}	0.5773	0.5773	0.6675	0.7615	0.0002	Fickian diffusion mechanism
P_{28}	0.9916	0.9893	0.9851	0.9777	0.0002	Fickian diffusion mechanism
P_{29}	0.9905	0.9861	0.9821	0.9762	0.0002	Fickian diffusion mechanism
P_{30}	0.9847	0.9804	0.9786	0.9718	0.1173	Fickian diffusion mechanism
P_{31}	0.5773	0.5773	0.6675	0.7615	0.0472	Fickian diffusion mechanism
P_{32}	0.5773	0.5773	0.6675	0.7615	0.0298	Fickian diffusion mechanism
P_{33}	0.5773	0.5773	0.6675	0.7615	0.0002	Fickian diffusion mechanism
P_{34}	0.8565	0.8609	0.9133	0.3018	0.1173	Fickian diffusion mechanism
P_{35}	0.8520	0.8559	0.9098	0.3555	0.0866	Fickian diffusion mechanism
P_{36}	0.8570	0.8619	0.9151	0.3609	0.0882	Fickian diffusion mechanism
P_{37}	0.5773	0.5773	0.6675	0.3960	0.0621	Fickian diffusion mechanism
P_{38}	0.5773	0.5773	0.6675	0.4435	0.0479	Fickian diffusion mechanism
P_{39}	0.5773	0.5773	0.6675	0.4567	0.0535	Fickian diffusion mechanism
P_{40}	0.5773	0.5773	0.6675	0.6932	0.0023	Fickian diffusion mechanism
P_{41}	0.5773	0.5773	0.6675	0.7342	0.0002	Fickian diffusion mechanism
P_{42}	0.5773	0.5773	0.6675	0.7475	0.0021	Fickian diffusion mechanism
P_{43}	0.9566	0.9582	0.9848	0.9752	0.0367	Fickian diffusion mechanism
P_{44}	0.9058	0.9096	0.9871	0.9802	0.0394	Fickian diffusion mechanism
P_{45}	0.7707	0.7782	0.6675	0.9162	0.0359	Fickian diffusion mechanism
P_{46}	0.8404	0.8468	0.8700	0.9467	0.0637	Fickian diffusion mechanism
P_{47}	0.5773	0.5773	0.9669	0.7615	0.0195	Fickian diffusion mechanism
P_{48}	0.5773	0.5773	0.6675	0.7615	0.0002	Fickian diffusion mechanism
P_{49}	0.6493	0.7621	0.6675	0.8910	0.0261	Fickian diffusion mechanism
P_{50}	0.5773	0.9582	0.6675	0.7615	0.0222	Fickian diffusion mechanism
P_{51}	0.5773	0.5773	0.6675	0.7615	0.0002	Fickian diffusion mechanism

3.3.5. Fourier transform infrared spectroscopy (FT-IR)

FT-IR drug studies were done for the selected formulae to detect the possible interactions between the leflunomide and carriers (poloxamer 407, PVP K30, S.L.S, urea, PEG 4000 and β-CD). It was clear that all characteristic bands of leflunomide and its solid dispersions with different carriers appeared nearly in the same regions and at the same ranges and there was no new bands appeared although the shape of the functional group regions in the spectra of the and the carrier used was not identical with that of pure drug alone (the results are not shown). This might be indicative of compatibility between leflunomide and the carrier used.

3.3.6. Differential scanning calorimetry (DSC)

DSC was done to confirm the result obtained from FT-IR. It was noticed that the characteristic peak of leflunomide in all systems was shifted to lower melting point and appears as very small peak. This may be due to decrease the crystallinity of the drug (the results are not shown). It is worthy to note that the heat of fusion decreased in all systems which might indicate that leflunomide has been transformed to an amorphous or less crystalline form. Moreover, the data also indicate there seems to be no interaction between the drug and polymer [24].

3.4. Preparation of leflunomide tablets

Based on the obtained previous results, the following solid dispersions and complexes (P_4, P_{12}, P_{15}, P_{16}, P_{21}, P_{24}, P_{25}, P_{33}, P_{40}, P_{47} and P49) were selected to be formulated in the form of leflunomide tablet as shown in Table 2 and 3. Depending on the fact that, tablet preparation containing diluents were found to release the drug in the order of avicel PH102 > Lactose, so we used avicel PH102 as a binder and diluents [25]. Magnesium stearate was selected also as it is a common lubricant may be used in tablet formulation. Crosecarmellose sodium was used as superdisintegrant.

3.5. Evaluation of leflunomide tablets

3.5.1. Content uniformity analysis:

The drug content of leflunomide tablets manufactured by direct compression technique was analysed. The average percentage drug content ranges from 96% to 105% and standard deviation ranges from 0.6 to 2.75. All the investigated tablets complied

with the pharmacopieal requirements for their content uniformity which was found to lie between ± 10% [12].

3.5.2. Disintegration time:

Figure (7) presents the different disintegration time of leflunomide tablets (20 mg) manufactured by direct compression technique. The value of disintegration time ranges from 11 seconds to 25.5 minutes and standard deviation ranges from 0.71 to 2.12. C40 showed the lowest disintegration time (11 seconds) and C_{21} showed the highest disintegration time (25.5 minutes).

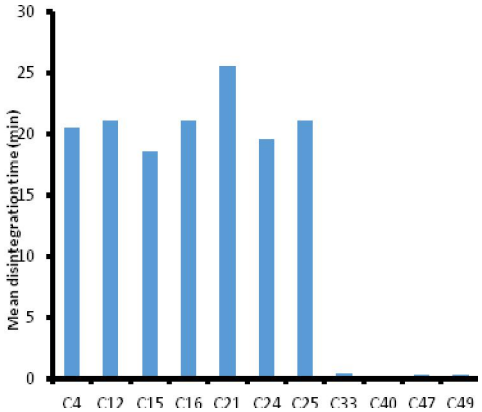

Fig.(7): Bar chart of leflunomide tablets showing the disintegration time

3.5.3. In-vitro release study of leflunomide tablets

Figure (8) shows the in-vitro release of leflunoamide from the prepared tablets compared with commercial tablet in 0.1 N HCl at 37°C. It was observed that all the prepared leflunomide tablets gave % release higher than the commercial tablet. The in-vitro release of leflunoamide from prepared tablets can be arranged, in descending order, regarding the release within 120 minutes dissolution as follows: C_{12} ,C_{15} , C_{24} ,C_{25} , C_{49} (100%) > C_{47} (99.01%) > C_{33} (94.58%) > C_4 (93.80%) > C_{21} (91.71%) > C_{16} (86.24%) > C_{40} (84.68%) > leflunomide commercial tablet(73.82%).

By comparing the time of the release of the selected SDs with that of the prepared leflunomide tablets, we can observed that, the following formulae (P_{12}, P_{15}, P_{16}, P_{21}, P_{24}, P_{25} and P_{33}) which complete their drug release within 15-30 minutes, when compressed into tablets, complete their drug release within 45-75 minutes. While, the following formulae (P_4, P_{47} and P_{49}) were taken the same time to complete their drug release as it is in the powder form and P_{40} which complete their drug release within 15 minutes, when compressed into tablets, complete their drug release within 120 minutes.

Surprisingly, as we shown, C_{40} showed release rate (within 2 hours) similar to those formulae which show disintegration time in the range of 20-25 minutes. Despite of, C_{40} showed the lowest disintegration time (11seconds). This phenomenon could be controlled by the binding effect of PEG 4000, which is more pronounced at high polymer ratio. So that, no correlation between disintegration time and dissolution of leflunomide tablets (C_{40}) containing PEG 4000 was observed, in contrast with several previous reports describing a direct correlation between these 2 parameters [26].

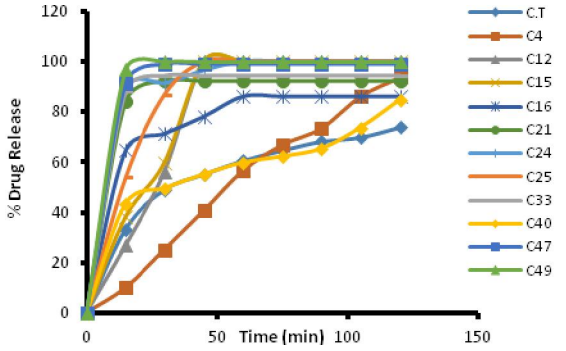

Fig.(8): *In-vitro* release of leflunomide from all prepared tablets and the commercial tablet

Table (9) showed rank order for in-vitro release of leflunomide from the prepared tablets in 0.1 N HCl at 15 minutes. Tablet formulae were ranked according to their percent mean released at 15 minutes. It was found that the release of leflunomide arranged descendingly as follows: C_{49} > C_{47} >C_{24} > C_{33} >C_{16} >C_{21} >C_{25} > C_{40} >C_{15} > C_{12}> C_4 .Therefore, the following formulae: $C_{49,}$ $C_{47,}$ C_{24} and C_{33} were selected as their % released (greater than 85%) at 15 minute.

Table (9): Rank order for in-vitro release of leflunomide tablets at 15 minutes

Formulae	Mean % released at 15 min.	*RO	Formula	Mean % released at 15 min.	*RO
C4	9.99	11	C33	88.33	4
C12	26.92	10	C40	43.43	8
C15	38.21	9	C47	91.45	2
C16	64.70	5	C49	96.92	1
C21	55.06	6			
C24	89.11	3			
C25	53.85	7			

***RO:** Rank order

3.5.4. Statistical analysis of the obtained results

Table (10) shows one way analysis of variance (ANOVA) of lefluonamide core tablets with respect to their % released (greater than 85%) at 15 minute followed by Tukey-Kramer multiple comparisons test. From this table it was concluded that all formulae are

non significant with C_{47} at $p<0.05$ so that this formula was cancelled, while C_{49}, C_{24} and C_{33} were selected.

Table (10): Tukey-kramer multiple comparisons test of selected leflunomide tablets (C_{49}, C_{47}, C_{24} and C_{33}).

Formulae	C_{24}	C_{33}	C_{47}	C_{49}
C_{24}		NS	NS	*
C_{33}	NS		NS	*
C_{47}	NS	NS		NS
C_{49}	*	*	NS	

(*) = Significant at $p<0.05$ (NS) = Not significant

3.5.5. Kinetic modelling of drug release

Table (11) showed kinetic parameters for in-vitro release of leflunomide from prepared tablets and commercial tablet according to Zero order, First order, Higuchi-diffusion model and Korsmeyer peppa's model. It can be concluded that the release exponent values of all the prepared tablets and commercial tablet except C_4 and C_{12} were from 0.0191 to 0.4859. Based on these values we can say that all the prepared tablets and commercial tablet except C_4 and C_{12} exhibited fickian release. While the release exponent value of the drug from C_4 was 1.0677. Based on this value we can say that the drug exhibited super case II transport. Also, the release exponent value of the drug from C_{12} was 0.6308. Based on this value we can say that the drug exhibited non-fickian release. The commercial tablet showed higher (r) values for first order plots indicating that drug release followed first order kinetics. While C_{40} showed higher (r) values for zero order plots indicating that drug release followed zero order kinetics. The rest of formulations showed higher (r) values for diffusion order plots indicating that drug release followed diffusion order kinetics. Therefore, the kinetic data shows that the in-vitro release of leflunomide from the prepared core tablets in 0.1 N HCl follows different kinetic orders and no definite kinetic order can express the drug release from different types of formulations [(1)].

Table (11): The calculated correlation coefficient (r) and (n) value for leflunomide tablets and commercial tablet based on in-vitro release study.

Formula	Correlation coefficient (r)				(n) value	Comment
	Zero-order	First-order	Higuchi-diffusion model	Korsmeyer peppa's model		
Commercial tablet	0.9487	0.9829	0.9817	0.8253	0.1687	Fickian diffusion mechanism
C_4	0.9912	0.9652	0.9981	0.9917	1.0676	Super case II transport
C_{12}	0.7564	0.7592	0.8331	0.8931	0.6308	Non-Fickian diffusion
C_{15}	0.7603	0.7587	0.8348	0.8983	0.4858	Fickian diffusion mechanism
C_{16}	0.8579	0.8696	0.9149	0.9539	0.1511	Fickian diffusion mechanism
C_{21}	0.8931	0.9352	0.9452	0.9729	0.2527	Fickian diffusion mechanism
C_{24}	0.8506	0.8605	0.9059	0.9417	0.0767	Fickian diffusion mechanism
C_{25}	0.6954	0.7627	0.7825	0.8541	0.2690	Fickian diffusion mechanism
C_{33}	0.5773	0.5773	0.6675	0.7614	0.0261	Fickian diffusion mechanism
C_{40}	0.9796	0.9270	0.9603	0.9584	0.2902	Fickian diffusion mechanism
C_{47}	0.5773	0.5773	0.6675	0.7614	0.0303	Fickian diffusion mechanism
C_{49}	0.5773	0.5773	0.6675	0.7614	0.0190	Fickian diffusion mechanism

4. Conclusion

All the studied carriers (poloxamer 407, PVP K30, S.L.S, urea, PEG 4000 and β-CD) increased the solubility and the dissolution rate of leflunomide. All the prepared leflunomide tablets gave % release higher than the commercial tablet. The maximum in-vitro release of leflunomide from the prepared tablets was observed after 15 minutes of dissolution to be 88.33% for leflunomide tablet containing Urea (MG) (1:8 drug: carrier), 89.11% for leflunomide tablet containing S.L.S (MG) (1:8drug:carrier), 91.45% for leflunomide tablet containing β-CD (PM)(1:2 drug: carrier) and 96.92% for leflunomide tablet containing β-CD (Co.G)(1:1 drug: carrier)while the leflunomide commercial tablet shows only (73.82%).

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