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Formulation and Evaluation of Osmotically Ontrolled Drug Delivery System of Lesinurad

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ABSTRACT
The immediate release conventional dosage forms are lack in the efficiency of controlling the proper plasma drug concentration. This results in the development of various controlled drug delivery system. Among the controlled drug delivery systems osmotic drug delivery system (ODDS) are gaining importance as these systems deliver the drug at specific time as per the path physiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. The present study is an attempt to develop an extended release formulation of Lesinurad based on osmotic technology. In this study, two-layer push-pull osmotic tablet system was developed and invitro evaluation was carried out for the release of model drug. Tablets was coated with a semipermeable membrane using 5% w/v cellulose acetate (CA) in acetone and castor oil (20% w/w of CA) as plasticizer. Drug release rate was increased as the increase of carbopol 934P with NaCl. Drug release rate was also increased significantly as the drug release was inversely proportional to weight gain but directly proportional to the orifice size. The drug release from developed formulations was independent of pH and agitation intensity of release media. DSC and FTIR studies demonstrated that there was no interaction between polymers and drug. The optimized formulation was stable after 3 months of accelerated stability studies.
Keywords: Lesinurad, Extended release, Osmotic technology.

I. INTRODUCTION

Osmotic devices are most promising strategy based system for controlled drug delivery. They are among the most reliable controlled drug delivery system and could be employed as oral drug delivery systems or implantable device. [1]

Osmotically controlled oral drug delivery systems (OCODDS) utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system.[2]

Osmosis is an aristocratic bio phenomenon, which is exploited for development of delivery systems with every desirable property of an ideal controlled drug delivery system. Osmotic system utilize the principles of osmotic pressure for delivery of drug.[3]

Lesinurad is an oral uric acid transporter 1 (URAT1) inhibitor indicated for the treatment of hyperuricemia associated with gout. It reduces serum uric acid concentration through the inhibition of URAT1, an enzyme responsible for reuptake of uric acid from the renal tubule, and OAT4, another uric acid transporter associated with diuretic-induced hyperuricemia.[4]

The present study is an attempt to develop an extended release formulation of Lesinurad based on osmotic technology. In this study, two-layer push-pull osmotic tablet system will be developed and invitro evaluation will be carried out for the release of model drug.

Osmotic pumps offer many advantages over other controlled drug delivery system.

- Easy to formulate and simple in operation
- Osmotic system is independent of pH and other physiological parameters to a large extent
- Decrease dosing frequency
- Reduce rate of rise of drug concentration in blood
- Sustained & consistent blood levels within the therapeutic window
- Reduce interpatient variability
- Reduce side effects.[5]

Limitations of osmotic drug delivery systems[6]

1. Special equipment is required for making an orifice in the system.
2. Residence time of the system in the body varies with the gastric motility and food intake.

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3. It may cause irritation or ulcer due to release of saturated solution of drug.

II. MATERIALS AND METHODS

MATERIALS

The Material used for preparingosmotically controlled drug delivery system of Lesinurad was obtained from Aurobindo Pharma Limited, Hyderabad, India. Carbopol 934P and Psyllium husk powder were obtained as gift samples from Noveon chemical limited, Mumbai, India and Atlas industries, Siddhpur, Gujarat respectively. All other ingredients used in present study were of AR grade.

METHOD

Push–Pull Osmotic Pump (PPOP). [7,8]

The two-layer push–pull osmotic tablet system appeared in 1980s. Push pull osmotic pump is a modified elementary osmotic pump through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. The push–pull osmotic tablet consists of two layers, one containing the drug and the other an osmotic agent and expandable agent. A semipermeable membrane that regulates water influx into both layers surrounds the system. While the push–pull osmotic tablet operates successfully in delivering water-insoluble drugs, it has a disadvantage that the complicated laser drilling technology should be employed to drill the orifice next to the drug compartment.[7]

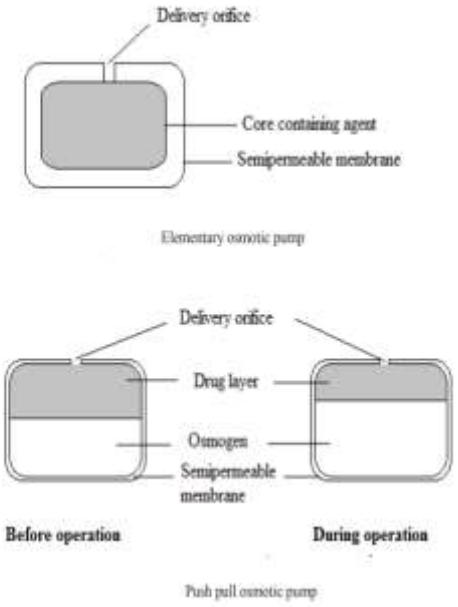

Fig 1: Push–Pull Osmotic Pump

PREFORMULATION TESTS

The evaluations for the following parameters

Identification test:

Identification of Lesinuradwas done by UV, DSC, and FTIR and confirmed as per monographs.

Solubility analysis:

Solubility analysis of Lesinuradwas carried out in various solvents like Methanol, DMSO and (DMF) dimethyl formamide.

Melting point determination:[9]

The determination of melting point was done by capillary method. A little amount of compound was placed in thin walled capillary tube of about 10-15cm long and 1mm inside diameter and closed at one end. The capillary tube containing sample and thermometer is then suspended in oil bath containing liquid paraffin.so, they can be heated slowly and evenly. The temperature range over which the sample is observed to melt is taken as the melting point.

FTIR Spectroscopy

This was established by using FTIR Spectroscopy method. The study was carried out for only the excipients of optimized formulation.
Binary physical mixtures of drug with individual excipients (1:1) was pressed into pallets and scanned using FT-IR Spectrophotometer (Shimadzu 8400S, JAPAN) the results are shown in figure.

DSC Studies[10]

DSC scans of about 5 mg, using automatic thermal analyser system performed accurately weighed and tablet containing same amount of drug (DSC 60, Shimadzu, Japan) sealed and perforated alluminium pans were used in the experiments ,for the samples temperature calibration were performed Using indium as standard. An empty pan sealed in the same way as a reference. The entire samples were run at 10oC/ min from 50-300˚ C the results are shown in figure.

Quantitative estimation of Lesinurad by UV-spectrophotometric method

Determination of λmax:

Lesinurad was dissolved in (DMF) dimethyl formamide, and further diluted with the same and scanned for determination of λ max in UV double beam spectrophotometer [Shimandzu-

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1700] in the range from 200 to 400 nm, using Distilled water as blank. The λ max of the drug was found to be 262.0 nm.

Standard curve of Lesinurad in Distilled water

100 mg of Lesinurad was accurately weighed and dissolved in 100 ml of DMF to prepare stock solution. The aliquot amount of stock solution was further diluted with DMF to get 5 µg, 10 µg, 15 µg, 25 µg, 30 µg and 35 µg of drug per ml of the final solution. Then the absorbance was measured in a UV spectrophotometer at 262.0 nm against DMF as blank. The absorbances so obtained were tabulated as in table and calibration curve was constructed

PREPARATION OF LESINURAD PUSH-PULL OSMOTIC TABLETS:

Bilayer osmotic tablets were prepared according to formulation given in table. The drug layer was comprised of Lesinurad (10mg), Carbopol 934 P, NaCl, MCC, and magnesium stearate. All the ingredients weighed accurately and shifted through 60# then mixed properly. The push layer comprise of Carbopol934P, MCC, NaCl, Magnesium stearate. All the ingredients weighed accurately and shifted through 60# then mixed properly. Bilayer standard convex tablets having 10 mm diameter and 6-7 kg/cm2 hardness were prepared. Prepared tablets were evaluated for various parameters.

COMPOSITIONOFOSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM OF LESINURAD

INGREDIENTS (mg\tab)	F1	F2	F3	F4	F5
Drug layer					
Lesinurad	10	10	10	10	10
Mannitol	30	50	70	90	110
MCC	130	110	90	70	50
Magnesium sterate	Trace	Trace	Trace	Trace	Trace
Push layer					
Carbopol 934 P	100	100	100	100	100
MCC	40	40	40	40	40
NaCl	10	10	10	10	10
Magnesium sterate	Trace	Trace	Trace	Trace	Trace

Table 1: Preparation of Lesinurad push pull osmotically controlled release tablets

PREPARATION OF LESINURAD PUSH-PULL OSMOTIC TABLETS:

Bilayer osmotic tablets were prepared according to formulation given in Table 2. The drug layer was comprised of Lesinurad (10mg), Psyllium husk powder, NaCl, Mannitol, PVP and magnesium stearate. All the ingredients weighed accurately and shifted through 60# then mixed properly. Then mix powder was blended and granulated with IPA in a mortal pastle. The wet mass was forced through 16 # and the granules so obtained were dried at 40 °C for 2 hr in the oven. Dried granules were passed through 20 # and the fines were separated using 40 # to obtain 20-40 # granules. These granules were lubricated with mixture of talc and magnesium stearate. The push layer comprise of Psyllium husk powder, MCC, NaCl, Magnesium stearate. All the ingredients weighed accurately and shifted through 60# then mixed properly. Bilayer standard convex tablets having 10 mm diameter and 6-7 kg/cm2 hardness were prepared. Prepared tablets were evaluated for various parameters.

INGREDIENTS (mg\tab)	F6	F7	F8	F9	F10
Drug layer:					
Lesinurad	10	10	10	10	10
P.husk	30	50	70	90	110

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Mannitol	30	30	30	30	30
MCC	100	80	60	40	20
Pvp k30	30	30	30	30	30
Magnesium sterate	Trace	Trace	Trace	Trace	Trace
Push layer:					
P.husk	70	70	70	70	70
MCC	80	80	80	80	80
NaCl	10	10	10	10	10
Magnesium sterate	Trace	Trace	Trace	Trace	Trace

Table 2: Preparation of Lesinurad push pull osmotically controlled release tablets

COATING OF TABLETS:

A 5% w/v solution of cellulose acetate in acetone was used as a semipermeable membrane provider. Castor oil was used as a plasticizer. The tablets were warmed to 40 ^{o}C before applying coating solution.

All weighed tablets put in coating pan. Spray the coating solution by spray gun on tablet and also supply hot air to dry tablets. During this procedure coating pan rotated continuously. After coating dry tablets were weighed for percentage weigh gain up to 12 %.

EVALUATION

Loose bulk Density: An accurately weighed quantity of powder was transferred to a 10ml measuring cylinder and the volume occupied by the powder in terms of ml was recorded.

Tapped bulk Density: The loosely packed powder in the measuring cylinder was to tapping 100 times on a plane hard wooden surface and volume occupied in mL was noted.

Weight of powder in gm .[11]

Hausner's factor:

Haunser found that the ratio D F / D O was related to interparticle friction and, as such, could be used to predsict powder flow properties.

Carr's Compressibility Index: [12]

A volume of fine particles is filled into a graduated glass cylinder and repeatedly tapped for a known duration. The volume of powder after tapping is measure.

Angle of Repose:

It is measured to find frictional forces in loose powder or granules.

It is the maximum angle possible between the surface of a pile of powder or granules and horizontal plane.

Weight variation test (IP 1996 method): 6 Tablets were randomly selected from each batch and weighed on an electronic balance. Average weight was calculated from each batch and shown in table.

Hardness test:6 Tablets were randomly selected from each batch and hardness of each tablet was determined by using a Rollex hardness tester .Values were calculated for each batch and shown in table.

Friability test: It is the ability of tablets to withstand mechanical shocks during handling and transportations. The % of friability of prepared tablet were shown in table 13. 6 Tablets were randomly picked from each batch and weighed and placed in the Riche-rich friability test apparatus and operated at rate of 25 RPM for 4 minutes (or up to 100 revolutions), tablets were de-dusted and weighed again. The loss of tablet weight due to abrasion and fracture was measured in terms of % friability.[13]

Drug content estimation

The Lesinurad tablets were tested for their drug content. Five tablets were finely powdered; quantities of the powder equivalent to 10 mg of Lesinurad were accurately weighed and transferred to a 100-ml of volumetric flask. The flask was filled with Phosphate buffer (pH 7.4) solution and mixed thoroughly. The solution was made up to volume and filtered. Dilute 10 ml of the resulting solution to 200 ml with Phosphate buffer (pH 7.4) and measure the absorbance of the resulting solution at the maximum at 276 nm using a Shimadzu UV/Vis double beam spectrophotometer. The linearity equation obtained from calibration curve as described previously was use for estimation of Lesinurad in the tablet formulations. Values are shown in table.

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In-vitro Dissolution studies

In vitro drug release studies of the prepared matrix tablets were conducted for a period of 12 hours using an eight station USP XXII type 2 apparatus at 37±0.50C the paddle speed was 100 ± 1 rpm. The dissolution medium used in each flask was 900 ml of buffer media pH – 7.4 at different intervals, 10 ml of samples were withdrawn and filter through a whatman filter paper. The equivalent volume of the medium was added to the dissolution vessel. After filtration and appropriate dilution, the sample solutions were analysed at 276 nm by using double beam U.V spectrophotometer (SHIMADZU-1700) and dissolution medium as blank. Experiments were performed in triplicates. The amount of drug present in the samples was calculated with the help of calibration curve constructed from reference standard. Dissolution data of prepared tablets are reported in following table.

Acelerated stability studies

Stability studies for orally disintegrating mini-tablet of salbutamol sulphate was carried out as per ICH guidelines. Stability studies are conducted for optimized formulations was kept at 40 ± 2^0C with 75 ± 5% RH for a period of 3 months. The physical condition and drug content was measured.[14]

III. RESULTS

Solubility: soluble in Methanol, DMSO and (DMF) dimethyl formamide.

Melting point: It was found to be in the range of 365°C to 367°C.

U.V. Spectroscopy. The standard solutions and pharmaceutical sample were prepared in DMF. Absorbance of Lesinurad was measured at 290.0 nm.

STANDARD CURVE FOR LESINURAD

The solubility of drug was found to be in Methanol and Phosphate buffer solution pH 7.4 absorbance was measured in a UV spectrophotometer at 290.0 nm Methanol. The absorbances so obtained were tabulated as in Table 8. Calibration curve was plotted and shown in Figure

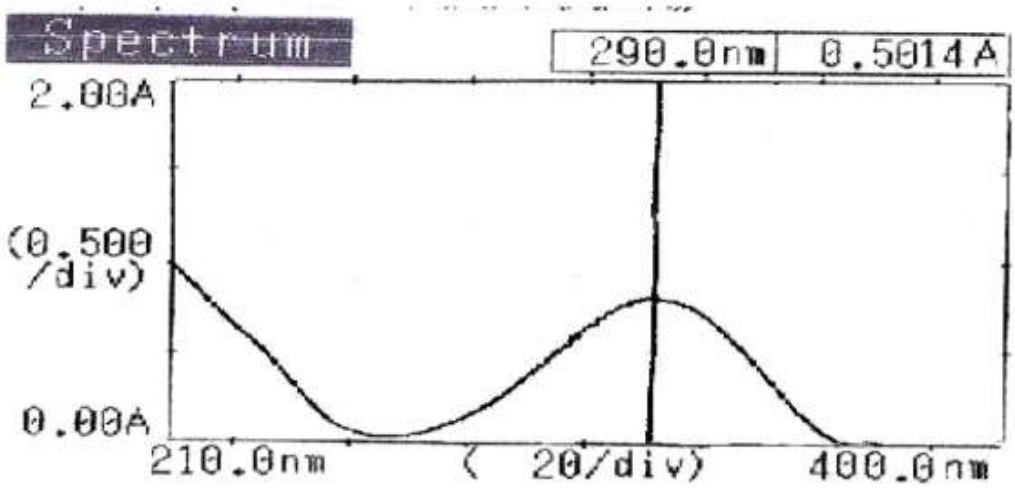

Fig 2: Absorbance maxima of Lesinurad in Methanol µgm/ml

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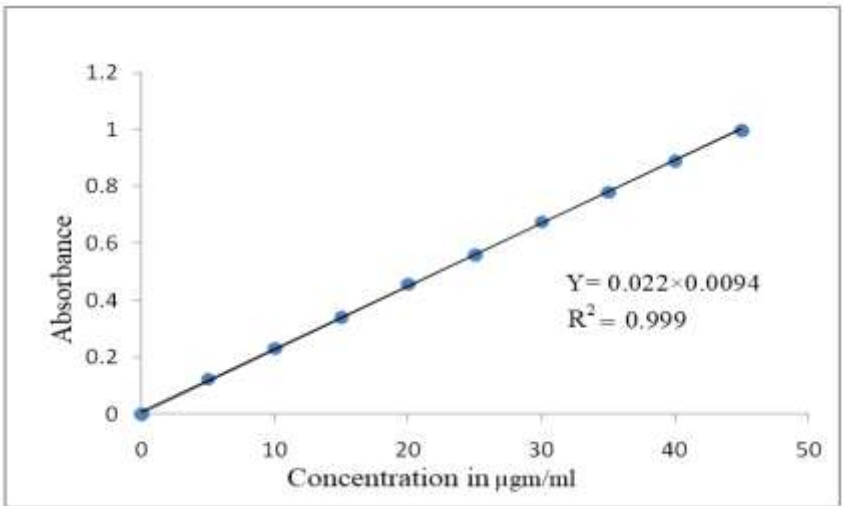

Fig 3: Standard Curve of Lesinurad in Methanol

Sl. No	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.113
3	10	0.241
4	15	0.362
5	20	0.448
6	25	0.569
7	30	0.665
8	35	0.749
9	40	0.877
10	45	0.998
Equation of line		Y= 0.022 X 0.0094
R^2		0.999
Beer's law limit		5-45 mcg/ml
Λmax		290.0nm

mean±SD (n=3)

.**Table 2: Spectrophotometric Data for the Estimation of Lesinurad**

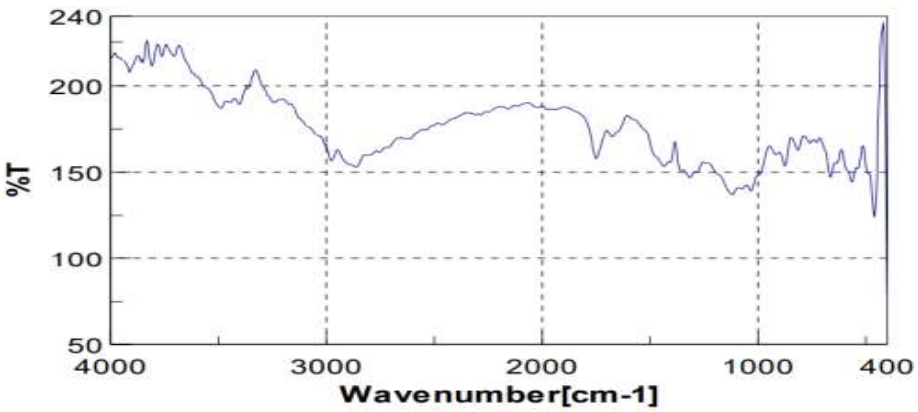

Fig 4: FTIR spectra of Lesinurad.

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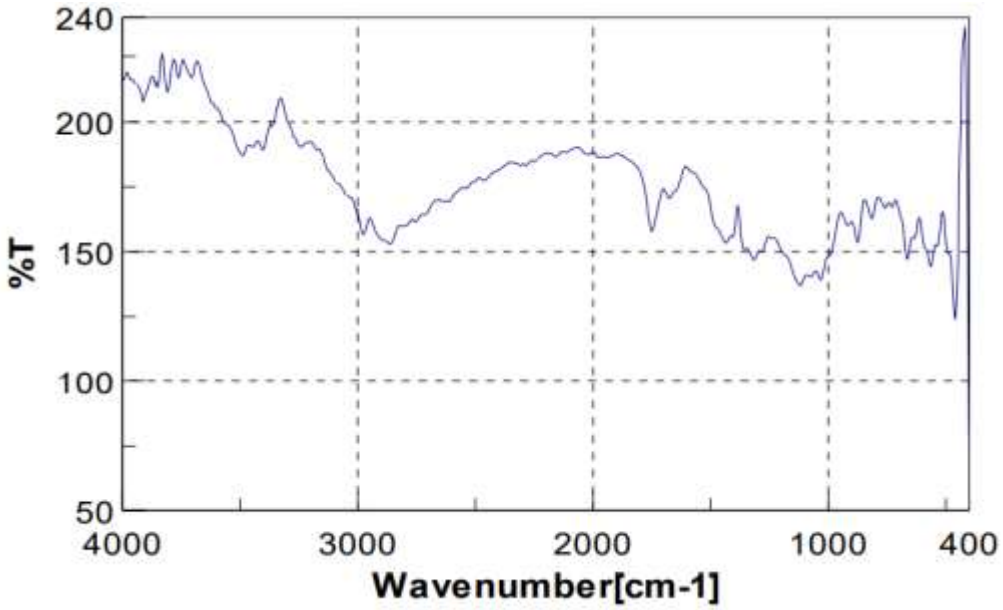

Fig 5: FTIR spectra of Lesinurad with carbopol 934P

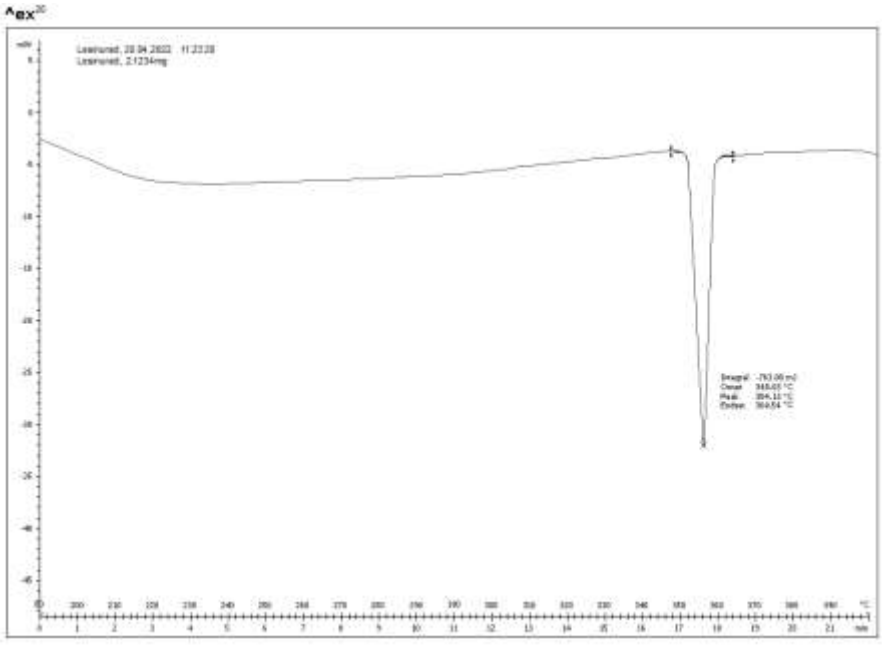

Fig 6: DSC thermogram of Lesinurad pure drug.

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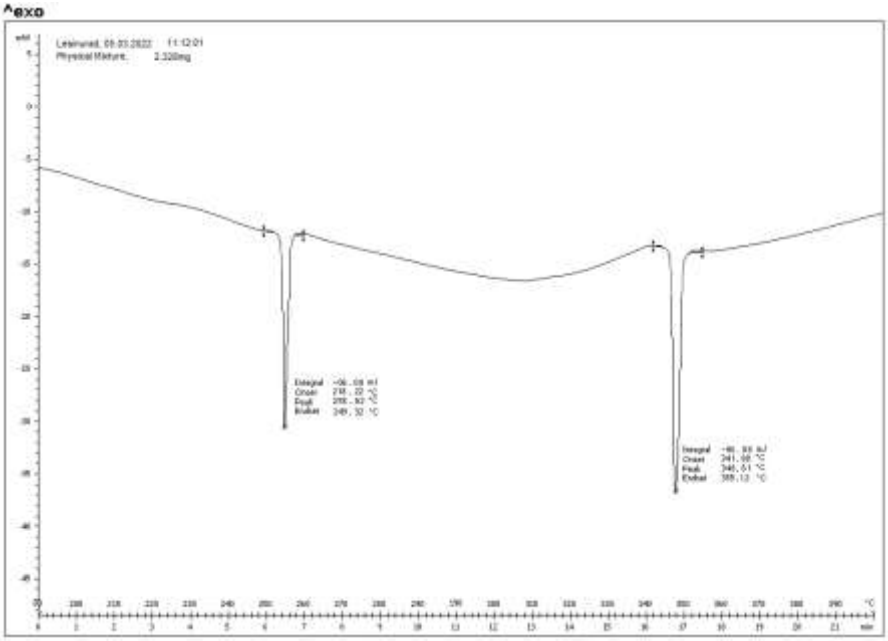

Fig 7: DSC thermogram of Physical mixture

Formulation Code	Angle of repose	Loose Bulk density (g/ml)	Tapped Density (g/ml)	Hausner factor	Carr's Index (%)
F1	25.74	0.37	0.49	0.91	9.22
F2	24.23	0.46	0.49	0.89	9.90
F3	26.98	0.52	0.50	0.90	9.08
F4	29.11	0.51	0.50	0.90	7.41
F5	27.68	0.50	0.50	0.94	5.64
F6	29.11	0.46	0.53	0.90	9.42
F7	25.96	0.51	0.55	0.95	5.43
F8	24.64	0.52	0.53	0.92	7.17
F9	29.38	0.50	0.55	0.94	7.03
F10	25.15	0.51	0.57	0.89	9.51

Table 4: Values of pre- compressive parameters of drug layer (n=3)

Formulation Code	Angle of repose	Loose Bulk density (g/ml)	Tapped Density (g/ml)	Hausner factor	Carr's Index (%)
F1	26.18	0.51	0.56	0.91	9.23
F2	28.55	0.52	0.54	0.90	5.64
F3	29.13	0.49	0.53	0.88	9.43
F4	25.22	0.48	0.52	0.91	9.23
F5	30.27	0.51	0.51	0.91	5.63
F6	26.75	0.50	0.55	0.93	5.34
F7	28.54	0.51	0.56	0.90	9.62
F8	29.35	0.52	0.55	0.93	9.63
F9	23.43	0.50	0.52	0.93	5.65
F10	30.38	0.53	0.56	0.91	7.52

Table 5: Values of pre- compressive parameters of push layer (n=3)

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All these results obtained indicate that the granules possessed satisfactory flow

Formulation Code	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content uniformity (%)
F1	6.2	0.88	352.42	97.66
F2	6.4	0.81	351.24	98.42
F3	6.2	0.74	350.31	96.95
F4	6.3	0.63	349.53	93.94
F5	6.0	0.74	349.72	97.42
F6	6.2	0.51	350.72	91.36
F7	6.3	0.31	350.91	94.31
F8	6.2	0.91	349.43	95.63
F9	6.3	0.84	350.64	93.20
F10	6.1	0.88	351.11	94.06

Table 6: Physical characteristics of prepared push pull tablets (n=3)

In vitro drug release study

In vitro drug release studies of the prepared matrix tablets were conducted for a period of 10 hours using an eight station USP XXII type 2 apparatus at 37±0.50C the paddle speed was 100 ± 1 rpm. The dissolution medium used in each flask was 900 ml of buffer media pH 7.4

At every 1 hour interval samples of 10 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant and maintain sink conditions. After filtration and appropriate dilution, the sample solutions were analysed at 290nm by using double beam U.V spectrophotometer and dissolution medium as blank. Experiments were performed in triplicates. The amount of drug present in the samples was calculated with the help of calibration curve constructed from reference standard. Dissolution data of tablets are reported in following table.

Dissolution data treatment:

The dissolution of drug from tablets at different time periods was plotted as cumulative % drug release v/s time curve for prepared tablets as shown figure 10 & 11. The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, korsmeyer-peppas models**.** Results were shown in table and figure.

Time (hour)	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	41.04443	32.88376	27.12365	21.12287	15.48176
2	46.32965	40.32448	34.56676	24.60598	17.52354
3	51.37554	45.96566	39.6117	27.96886	23.09475
4	55.94176	51.12554	43.81654	32.41197	31.20989
5	63.3885	58.92665	49.70176	36.61586	34.09399
6	71.31698	63.24776	57.38876	41.30086	35.17754
7	77.20509	70.44754	59.07487	43.82509	40.10143
8	82.85465	76.56855	60.40176	47.55076	43.22676
9	86.10345	82.44945	65.08843	51.75655	46.71787
10	90.4334	86.88945	67.01543	54.64440	49.59111
11	91.28476	90.37008	70.14367	60.76987	53.32329
12	92.49445	94.33087	71.11165	63.17698	57.28967

Table 7: Drug release profile F1-F5

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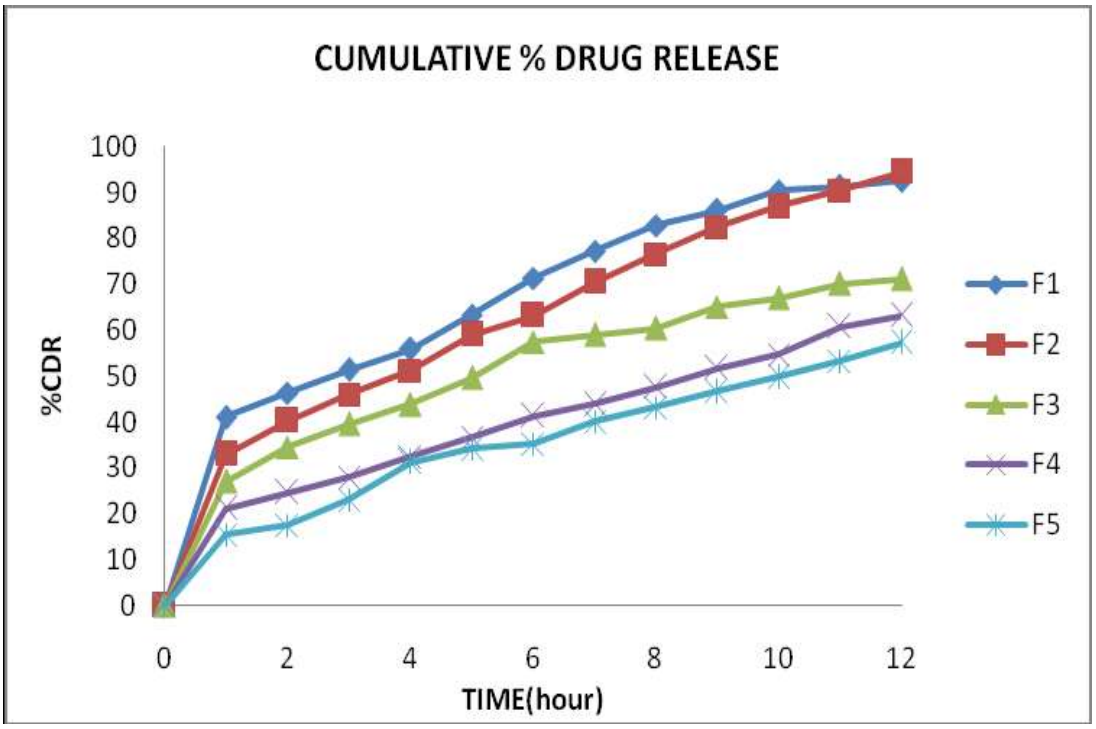

Fig: 8 Cumulative % drug release from formulation F1- F5

Time (hour)	F6	**F7**	**F8**	**F9**	**F10**
0	0	0	0	0	0
1	33.96007	30.65337	28.08367	22.68276	18.84989
2	38.88876	33.22712	33.48678	24.48574	22.08765
3	44.65365	37.43131	39.13176	27.00876	23.43445
4	47.89855	44.23621	43.93698	30.25150	29.2909
5	52.58454	48.43165	51.90756	35.17532	33.2546
6	58.35057	53.48759	53.90756	39.13932	35.41807
7	63.27743	58.54408	57.27454	42.62576	39.02254
8	67.12516	62.46105	60.88098	47.42843	42.26765
9	70.49389	67.76849	65.44876	51.03554	46.59243
10	75.42154	69.72623	68.81587	54.76890	49.23736
+11	78.79016	72.65429	69.90357	57.76076	52.12398
12	83.23938	78.98304	71.47146	60.77764	56.32972

Table 8: Cumulative % drug release from formulation F6- F10

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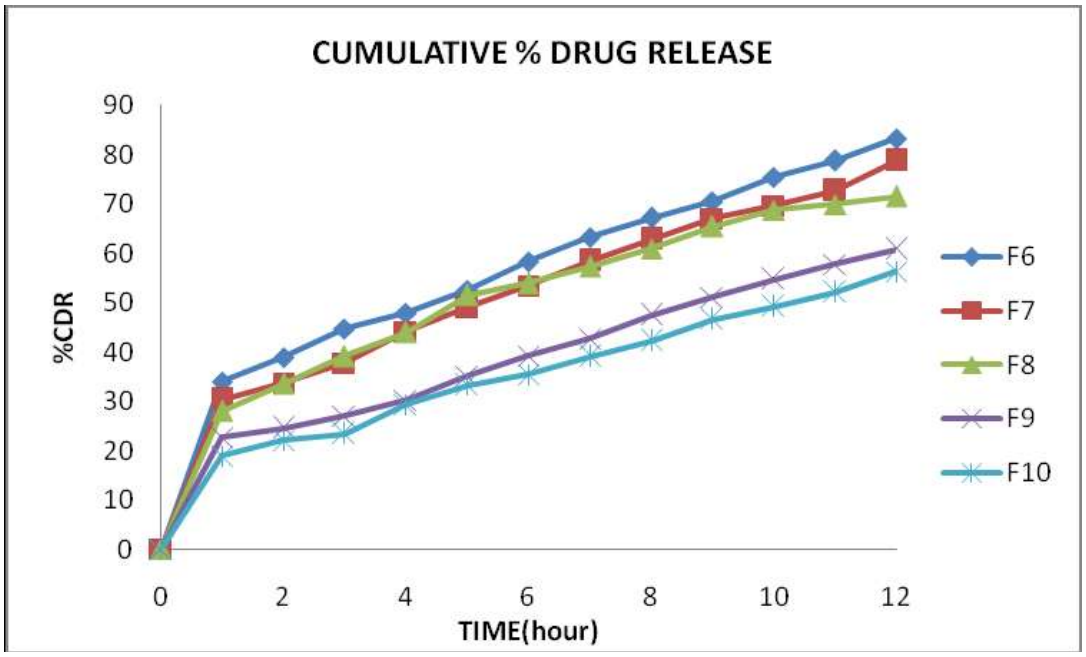

Fig 9: Cumulative % drug release from formulation F6- F10

FORMULATION CODE	Coefficient of Determination (R^2)			
	Zero Order	First Order	Koresmeyer	Higuchi Square
F1	0.864	0.976	0.880	0.977
F2	0.925	0.944	0.926	0.984
F3	0.867	0.983	0.905	0.992
F4	0.942	0.985	0.924	0.974
F5	0.954	0.996	0.926	0.985
F6	0.887	0.995	0.939	0.984
F7	0.905	0.984	0.926	0.983
F8	0.879	0.992	0.905	0.996
F9	0.934	0.988	0.893	0.962
F10	0.943	0.993	0.922	0.971

Table 9: Coefficient of determinations for prepared bilayer push pull tablets of Lesinurad.

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Fig10: Zero order treatment for F1-F5

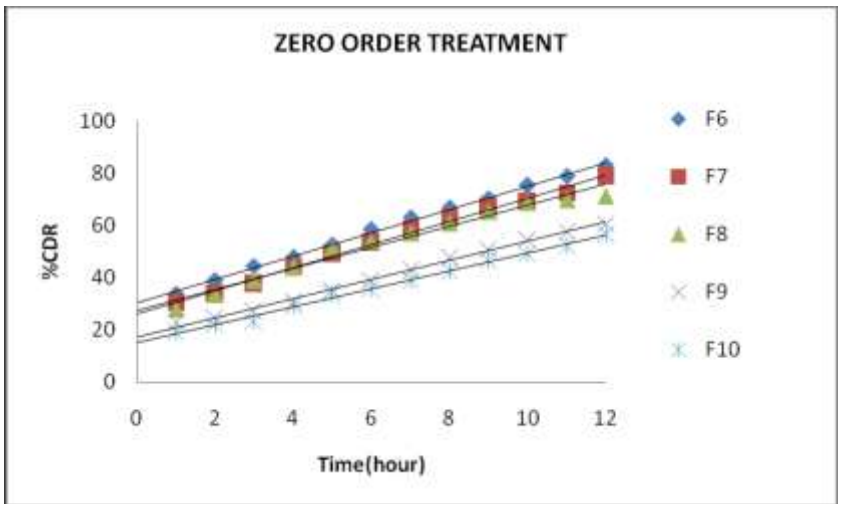

Fig 11: Zero order treatment for F6-F10

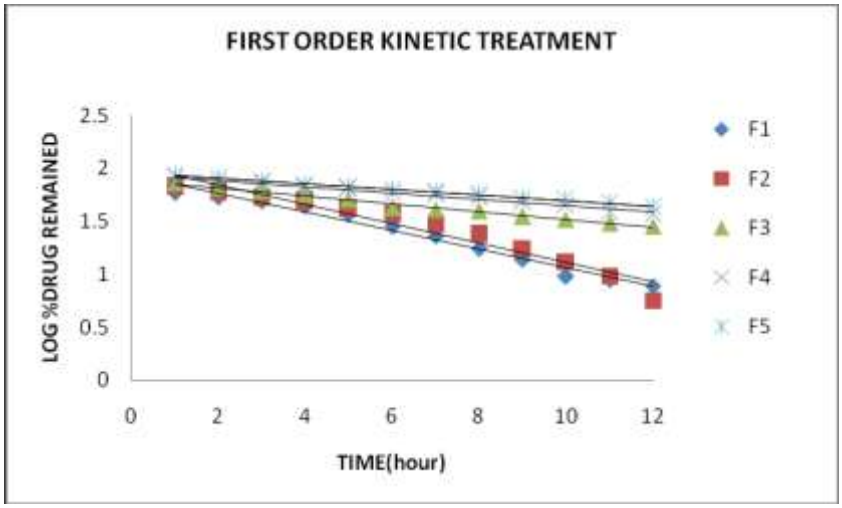

Fig 12: First order kinetic treatment for F1 – F5

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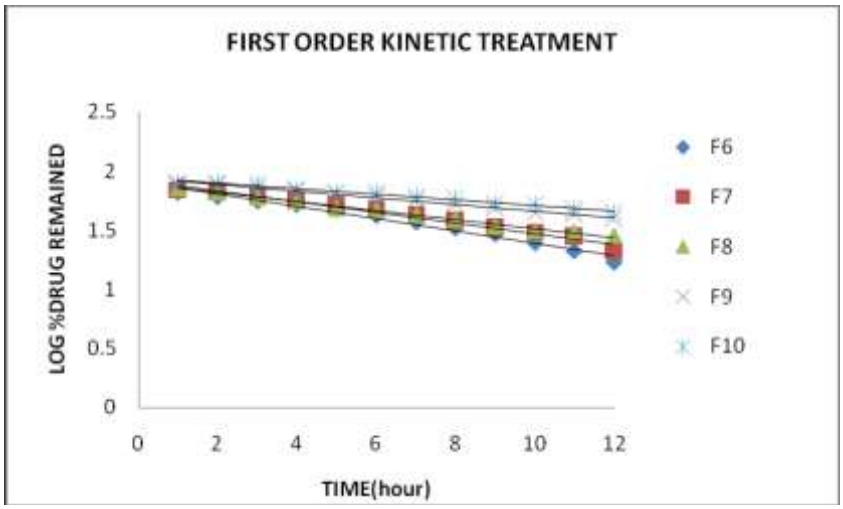

Fig 13: First order kinetic treatment for F1 – F5

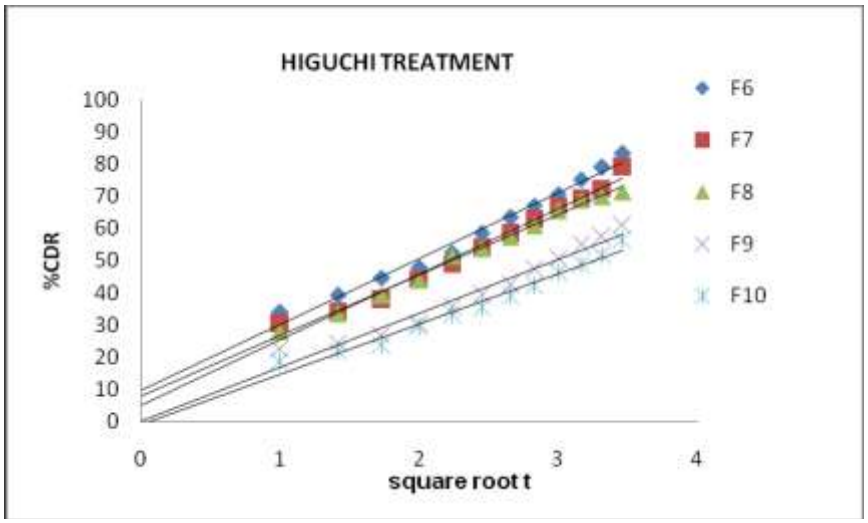

Fig14: Higuchi treatment for F1 –F5

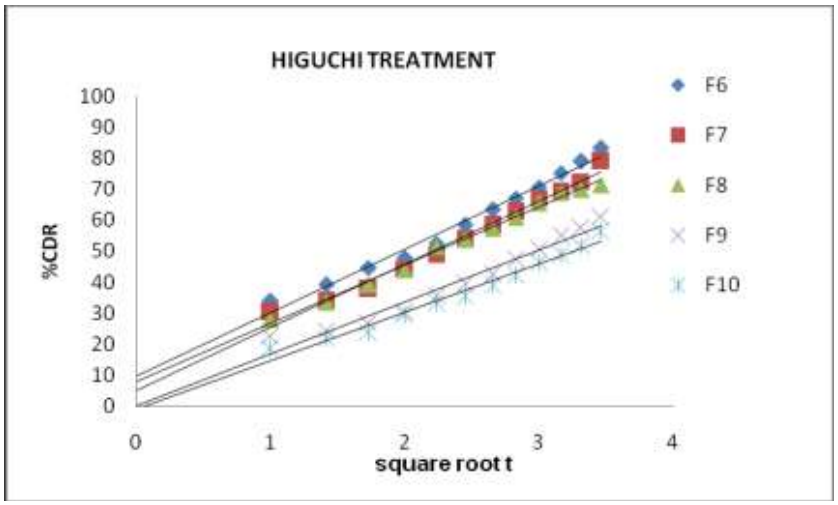

Fig 15: Higuchi treatment for F6 – F10

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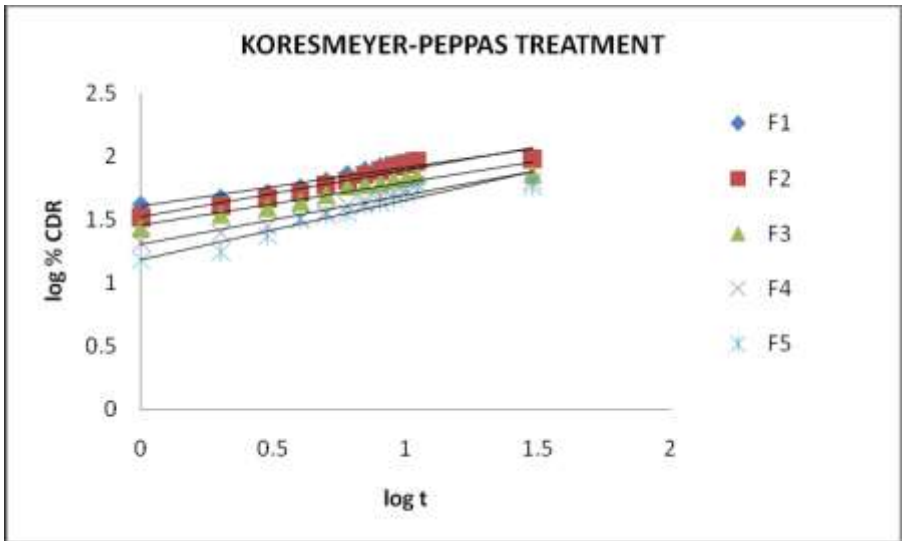

Fig 16: Koresmeyer-peppas treatment for F1-F5

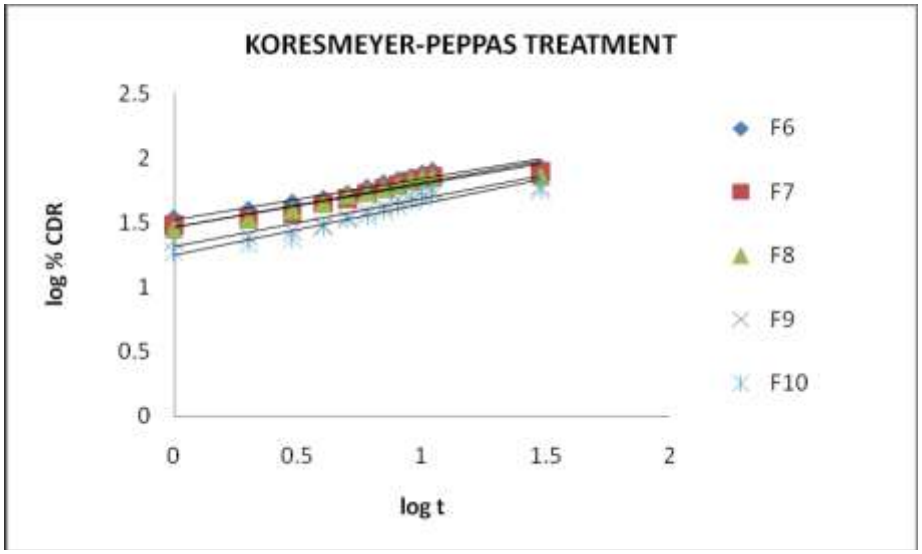

Fig 17: Koresmeyer-peppas treatment for F6-F10

RESULTS OF STABILITY STUDIES

Optimized formulations of Lesinurad were packed, maintained at 40 ˚C and 75% RH for 3 months. The samples were withdrawn periodically and evaluated for drug content, hardness, and release studies. The results of the accelerated stability studies are given in the following tables. It shows that a slight reduction in %drug content at the end of 2 months.

Initial			**3 month**		
Hardness (Kg/cm2)	Weight variation (mg)	Uniformity of content (%)	Hardness (Kg/cm2)	Weight variation (mg)	Uniformity of content (%)
6.3	351.26	98.42	6.2	351.3	97.38

Table 17: Characteristic of Lesinurad osmotic push pull tablet

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IV. CONCLUSION

Extended release formulations of Lesinurad were developed based on push-pull osmotic technology. Formulation **F2** was selected as optimized formulation. The effect of different formulation variable was studied to optimize release profile. The release rate increased significantly as the increase of carbopol 934P amount from 30mg to 110mg in push layer. When we increase amount of carbopol 934P more than 100 coating of tablet was ruptured. Drug release was inversely proportional to the coating thickness, but directly proportional to the orifice size. When we increase the coating thickness from 10 to 12 and then 14% w/w it was decrease in drug release rate. The release from developed formulations was independent of pH and agitation intensity of release media, assuring the release to be fairly independent of pH and hydrodynamic condition of body. The manufacturing procedure was standardized and found to be reproducible. Developed formulations were found to be stable after 3 month of storage.

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