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# FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF LEFLUNOMIDE

**Naga Jyotsna Bandi*[1], Nakka Ravina*[2], Nallatheegala Ashwini[3], Dr. Tulja Rani[4]**

[1]Assistant Professor, Malla Reddy Pharmacy College.
[2]Student-Malla Reddy Pharmacy College.
[3]Student-Malla Reddy Pharmacy College.
[4]Principal-Malla Reddy Pharmacy College.

***Corresponding Author: Naga Jyotsna Bandi[1] & Nakka Ravina[2]**
Assistant Professor[1], Student[2], Malla Reddy Pharmacy College.
**Email id:** jyothsnapharmacy@gmail.com, nakkaravina2616@gmail.com,

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## ABSTRACT

Systems for pulsatile drug delivery are created to administer medication in accordance with the circadian behavior of illnesses. The product has a sigmoidal drug release profile, which is defined by a brief period of no release (lag time), then a quick and thorough release of the drug. By using such a method, the medicine can be supplied at the proper time, in the proper quantity, and at the proper location of action. Numerous disorders, including asthma, arthritis, cancer, diabetes, epilepsy, hypertension, ulcers, and hypercholesterolemia have been studied and their potential advantages proven. There are many capsular, osmotic, single- and multi-unit systems that can be regulated by rupturable membranes, soluble or erodible polymer coatings. These methods are helpful for diseases with chrono pharmacological behavior that call for nighttime dosage, for medications with a high first pass effect or site-specific GIT absorption, for medications with a high risk of toxicity or tolerance, and for other medications. Additionally, these methods increase patient compliance by reducing dose frequency.

## INTRODUCTION

### Classification of Pulsatile Drug Delivery Systems

The pulsatile administration of pharmaceuticals, for which conventional controlled drug-release systems with a continuous release are not optimal, has recently drawn more attention in the field of modern drug therapy. The development of "Pulsatile Drug Delivery Systems" is driven by the necessity for therapeutic concentration pulses in diseases where steady drug levels are not acceptable. In these systems, a predetermined off release period, or lag time, is immediately followed by a fast and temporary release of a specific number of drug molecules over a brief period of time. When a dosage form is introduced to an aqueous environment, the term "lag time" refers to the period of time that passes before the active component starts to leak out of the dosage form. The physiology of the disease and the characteristics of the drug molecule can be taken into consideration when designing different pulsatile delivery approaches, such as pH dependent systems, time dependent systems, microflora activated systems, etc. When treating illnesses that call for drug administration in a way to sustain therapeutic levels despite circadian rhythm pulsatile release of an active agent is preferred. Oral pulsatile drug delivery systems have been shown to be potentially helpful in the chronotherapy of some common diseases, including bronchial asthma, hypertension, angina pectoris, allergic rhinitis, and osteo-/rheumatoid arthritis with symptoms that tend to manifest primarily at night or in the early morning. The following factors contributed to the change from the traditional sustained release method to the modern pulsatile administration of medications.

### Methodologies for Pulsatile Drug Delivery

Methodologies for the pulsatile drug delivery system can be broadly classified into three classes;

1. Time controlled
2. Stimuli induced
3. Externally regulated Time controlled pulsatile release system
4. Pulsatile release is achieved using time-controlled drug delivery systems after a certain time period in order to simulate the circadian rhythm. Such a pulsatile drug delivery system consists of two parts: an instant release component and a pulsed release component. The following are different approaches that can be utilized for time-controlled pulsatile release systems

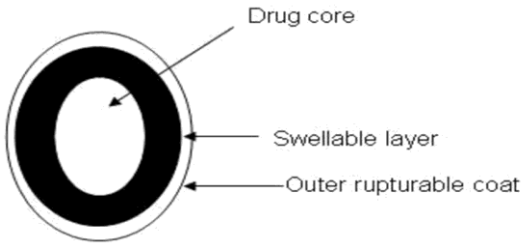


**Figure-1: Schematic diagram of deliver systems with rupturable coating layers.**

These systems have an exterior release mechanism that controls a water-impermeable but permeable coating that is vulnerable to mechanically induced coating rupture. Recently, many hard gelatin capsule and tablet systems were disclosed. These systems were all covered with inner swellable and exterior rutpurable layers. By adding swellable, osmotically effervescent additives to the reservoir, the film rupture can be achieved (Krogel & Bodmeier, 1999). Drug release can be achieved at a certain time interval by adjusting the mechanism.

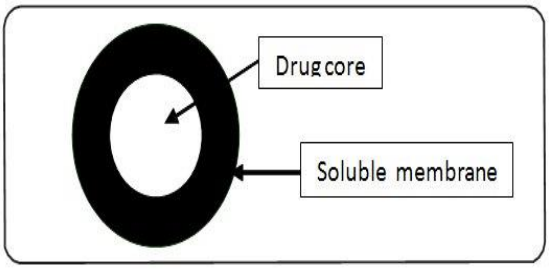


**Figure-2**: **Schematic diagram of Delivery system with erodible coating layer.**

In such systems, the outer layer that is put to the core carrying medicine dissolves or erodes, thereby controlling the drug release. By maximizing the thickness of the outer core, it is possible to achieve time-dependent release of the active ingredient.

**Capsule shaped system provided with release controlling plug**

These systems have a release-controlling plug that separates the compartments for immediate and pulsed releases. The cap quickly dissolves when it comes into contact with watery liquids, releasing both the immediate and pulsed release components. The plug that is put into the body provides the lag time.

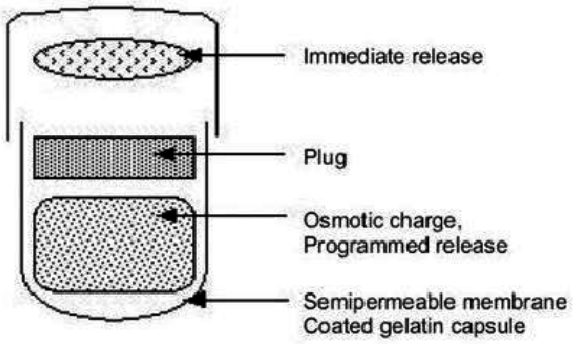


**Figure-3: Schematic diagram of capsule shaped system provided with release controlling plug.**

## MATERIALS

**Table-1: Materials used in the formulation.**

| S. No | Name of the ingredient | Uses |
|---|---|---|
| **1** | Cross povidone | Super Disintegrant |
| **2** | Cross Caramellose sodium | Super Disintegrant |
| **3** | Sodium starch glycolate | Super Disintegrant |
| **4** | Magnesium stearate | Lubricant |
| **5** | Polyvinyl pyyrolidone (K30) | Binding agent |
| **6** | Microcrystalline cellulose | Diluent |
| **7** | Hydroxy propyl methyl cellulose (K100) | Polymer |
| **8** | Ethylcellulose | Coating agent |
| **9** | Xanthum gum | Suspenting agent |
| **10** | Guar gum | Thickening agent |

## METHODOLOGY

**Formulation of Compressed Tablet of Leflunomide**

The methodology adopted includes

1) Preparation of core tablets of leflunomide
2) Coating of the core tablets.

**Formulation of core tablets of leflunomide**

**Table 2: Formulation of core tablets of leflunomide.**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| **Drug** | 10mg | 10mg | 10mg | 10mg | 10mg | 10mg |
| **Cross povidone** | 10mg | _ | _ | 20mg | _ | _ |
| **Cross camellose sodium** | _ | 10mg | _ | _ | 20mg | |
| **Magnesium stearate** | 5mg | 5mg | 5mg | 5mg | 5mg | 5mg |

| | | | | | | |
|---|---|---|---|---|---|---|
| **PVP** | 5mg | 5mg | 5mg | 5mg | 5mg | 5mg |
| **MCC** | 70mg | 70mg | 70mg | 60mg | 60mg | 60mg |
| **Total weight** | 100mg | 100mg | 100mg | 100mg | 100mg | 100mg |

The produced formulation table, which is displayed above, was used to direct compress the inner core tablet's preparation. Leflunomide, MCC, Crosscarmellose sodium, and crosspovidone were accurately weighed and then dry mixed for about 15 minutes before adding magnesium stearate. The mixture was then given one further 10 minutes mixing. The next step was to physically crush the resulting powder mixture using a punching machine to produce the core tablet.

**Formulation of compression coated tablets of leflunomide**

**Table 3: Composition of compression coated tablets.**

| PRESS COAT | P1(mg) | P2(mg) | P3(mg) | P4(mg) |
|---|---|---|---|---|
| HPMC | 150mg | 200mg | | |
| Ethyl cellulose | 150mg | 100mg | | |
| Xanthum gum | | | 150mg | 200mg |
| Guar gum | | | 150mg | 100mg |
| Total weight(mg) | 300mg | 300mg | 300mg | 300mg |

With coating components including HPMC, ethyl cellulose, xanthan gum, and guar gum, the optimized core tablets were covered. The core tablet was then physically positioned in the center of the correctly weighted half of the barrier layer material that had been deposited into a 16 mm die. The remaining barrier layer substance was poured into the die, then crushed. In a rotating compression tablet machine, tablets were compressed using a flat oval-shaped punch measuring 16.4 mm by 8 mm. The tablet qualities of each batch's manufactured tablets were assessed.

**Evaluation Parameters**

**1. Preformulation studies**

It is a crucial prerequisite for the creation of any drug delivery system. The medication underwent reformulation research, which included solubility, compatibility, and melting point analysis.

**2. Solubility**

Mebeverine's solubility in phosphate buffers at pH 1.2, pH 6.8, and pH 7.4 was assessed. By placing additional Mebeverine in various beakers with the solvents, solubility tests were carried out. The mixes were shaken continuously for 24 hours. Whattmann's filter paper Grade No. 41 was used to filter the solutions. At 211 nm, the filtered solutions underwent spectrophotometric analysis.

**3.Compatibility Studies**

**FTIR analysis**

A Shimadzu 8400 S FTIR spectrometer was used to research the interactions between drugs and polymers. Dry potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) was combined with 2% (w/w) of the sample. Using a mortar to grind the combination into a fine powder, the mixture was then 10000 PSI-pressurized into KBr discs in a hydraulic press. Using Happ-Genzelapodization, each KBr disc was scanned ten times at a resolution of 2 cm-1.The distinctive summits were noted.

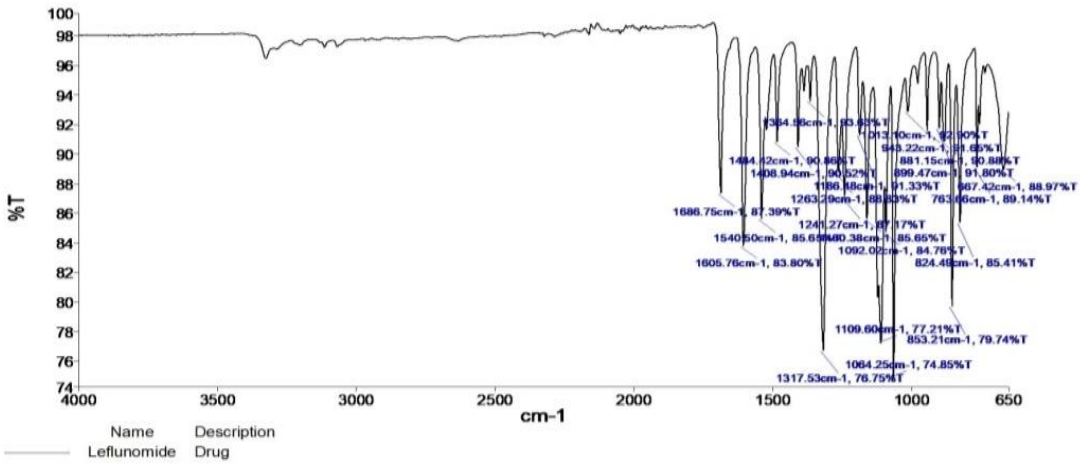


**Figure-3: FTIR studies of the leflunomide drug.**

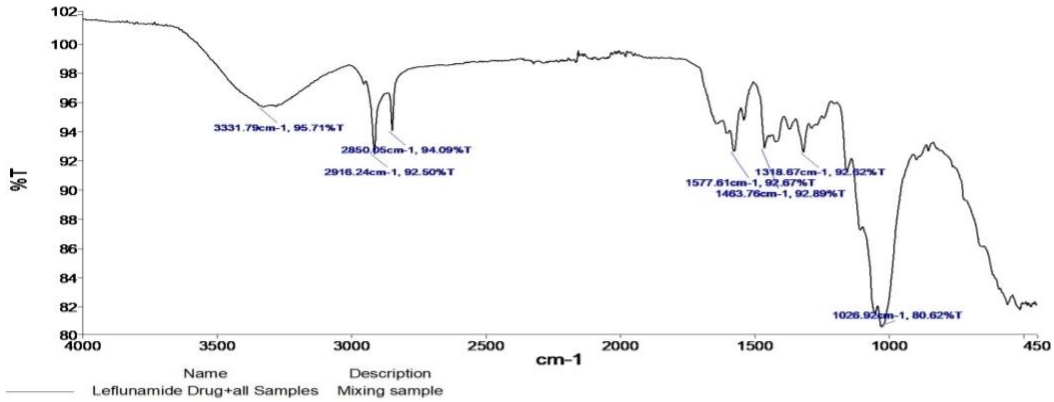


**Figure-4: FTIR studies of drug with all ingredients.**

**4. Flow properties**

**Angle of repose**

- The maximum angle that can be formed between the horizontal plane and the surface of the powder pile is known as the angle of repose.
- To calculate the powder or granules' angle of repose, the fixed funnel method was utilized.
- A measured amount of the powder mixture was taken and allowed to freely flow down the funnel onto the paper's surface to form a pile in the shape of a cone. The pile's height (h) and cone's diameter (d) were measured.
- From the diameter, radius (r) was calculated. The angle of repose (Θ) can determined by following equation.

$\Theta = \tan^{1} (h/r)$

Where, Θ = angle of repose,

h = height of pile,

r = radius of base of the pile

**Table-4: Angle of repose limits.**

| Angle of repose (Degree) | Flow property |
|---|---|
| Excellent | 25-30 |
| Good | 31-35 |
| Fair | 36-40 |
| Passable | 41-45 |
| Poor | 46-55 |
| Very poor | 56-65 |

**Bulk Density**

- The powder mixture was weighed out and then poured into a measuring cylinder.
- According to the reading on the measuring cylinder, the blend's bulk volume is documented.
- Bulk density is determined using the formula below.

Bulk density = Mass of the blend / Bulk volume of the blend.

**Tapped density**

- The weighed amount of powder mixture is poured into the graduated cylinder and tapped for 100 times to ascertain the density.
- The formula below is used to compute tapped density.

Tapped density = Mass of blend/ Tapped volume of the blend.

**Compressibility Index**

Mass of blend / Tapped volume of the blend equals tapped density. The compressibility index is crucial for determining how powder formulations tend to behave. It displays the blend's flow characteristics. Powder that flows freely has a low compressibility index %, whereas powder that flows poorly has a high compressibility index percentage. Bulk density and tapped density values were used to calculate compressibility index.

CI = (TD-BD) ×100/TD

Where, CI = Compressibility index, TD = Tapped density, BD = Bulk density

**Table-5: Compressibility index specifications.**

| S.no. | Carr's index | Type of flow |
|---|---|---|
| 1. | 5-15 | Excellent |
| 2. | 12-15 | Good |
| 3. | 18-21 | Fair |
| 4. | 23-30 | Poor |
| 5. | 33-38 | Very poor |
| 6. | >40 | Extremely poor |

**Hausners Ratio**

The Hausners ratio, which is determined by the ratio of tapped density to bulk density, describes the flow characteristics of the powder blend. Development of a UV approach for drug estimation:

Hausners ratio = Tapped density/Bulk density

Values of Hausner ratio; <1.25: good flow >1.25: poor flow

If Hausner ratio is between 1.25-1.5, flow can be improved by addition of glidants.

**UV method development for estimation of drug**

**Standard Stock**

To make a standard stock solution with a concentration of 1000 g/ml, 10 mg of the model drug was taken, added

to the appropriate media in a 10 ml volumetric flask, and the volume was increased to 10 ml.

**Working Stock**

To create a 100 g/ml solution, 1 ml of the aforementioned standard stock solution was obtained and added to the appropriate buffer medium in a 10 ml volumetric flask. Dilutions from the working stock were created using the appropriate media.

**Determination of absorption maxima**

To find the absorption maximum, 10 g/ml of solution was collected. A blank buffer solution was first preserved and scanned between 200 and 400 nm. After that, the sample was preserved for analysis and the same area was scanned.

**Calibration curves of Leflunomide**

UV visible spectrophotometer is used to determine leflunomide standard graphs. Leflunomide was measured by spectrophotometry in 0.1 N HCl, 7.4 pH buffer, and 6.8 pH phosphate buffer.

**Preparation of standard stock solution in 0.1 N HCl, 7.4pH buffer and pH 6.8 phosphate buffer**:

10 mg of mebeverine were accurately weighed and then dispersed in 10 ml of 0.1 N HCl, pH 7.4 and pH 6.8 phosphate buffer, respectively. To create the standard stock solution of mebeverine, 1 ml of this solution was taken out and diluted to 10 ml with 0.1N HCl, pH 7.4, and pH 6.8 phosphate buffer. (100µg/ml).

**Preparation of sample solution in 0.1 N HCl, pH 7.4 and pH 6.8 phosphate buffer**

0.5, 1, 1.5, 2.0, 2.5, and 3.0 ml of the stock solution were taken out and diluted to a final volume of 10 ml with 0.1 N HCl, pH 7.4, and phosphate buffer, yielding concentrations of 5, 10, 15, 20, 25, and 30 g/ml, respectively. Using a UV visible spectrophotometer, the absorbance was measured at 266 nm. The Mebeverine calibration curve was then plotted on a graph between the Concentration (g/ml) on the X-axis and the Absorbance values (nm) on the Y-axis.

**5.Post Compression Evaluations**

The following factors were assessed for the compressed micro tablets.

**Weight Variation Test**

- A digital weighing balance is used to conduct a weight fluctuation test.
- Twenty micro pills were chosen at random, and the average weight was determined after weighing each one separately. and contrasting the various weights with the mean weight.
- The formula used to compute the percentage of weight variation is as follows:

**Hardness Test**

- A Monsanto Hardness Tester was used to measure the hardness of each composition tester.
- The unit of measurement is kg/cm2.The amount of force needed to break a tablet is the definition of hardness.
- From each formulation, a random sample of mini pills was chosen, and the mean and standard deviation were computed.
- Tablets need to be strong or hard enough to withstand mechanical shocks from handling during production, packaging, and shipment.

**Thickness Test**

- Using a screw gauge and digital caliper, the thickness test of ten randomly chosen mini tablets from each formulation was recorded separately in mm.
- Values for the mean and standard deviation were computed. The regulation of tablet thickness makes packaging easier.

**Friability Test**

- Twenty miniature tablets, one of each formulation, are chosen at random, their initial weight (W0) measured, and they are put in a friabilitor.
- The small tablets were removed after 4 minutes of rotation at 25 rpm in the friabilitor. Weighing of little pills is repeated.
- The following formula was used to compute the percentage of friability.

$$\% F = W_0 - W_f / W_0 * 100$$

Whereas, % F = Percentage of friability

$W_0$ = Intial Weight

$W_f$ = Final weight

**Disintegration Test**

- Using the Disintegration Test, the disintegration test for small tablets was determined
- Apparatus that complies with Indian Pharmacopoeia requirements.
- Each of the six tubes in the basket contained a little tablet.
- As the immersion liquid, 900 ml of the dissolution media were used to operate the equipment.
- In a 37°C dissolving media, the assembly was elevated and lowered 30 times per minute.
- Next, make a note of how long micro pills take to dissolve.

**Drug Content**

- Five little tablets were weighed precisely and crushed in a mortar to ascertain their drug content.
- A weighed quantity of 5 mg of the medication was then transferred to a volumetric flask with a 100 ml phosphate buffer solution at pH 7.4 in a volumetric flask.

- The flasks were shaken to help the medication dissolve.
- A UV visible spectrophotometer was used to evaluate 1 ml of the aforementioned solution after diluting it by 10 ml and setting the appropriate nm. And use the following calculation to determine the medication content:

**Drug content = Sample absorbance/Standard absorbance*Standard Concentration*Dilution factor *Volume of dissolution medium /1000**

**Table-6: Post compression evaluation for core tablets.**

| F.C | Weight | Hardness (kg/cm$^3$) | Thickness (mm) | Disintegration(sec) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|---|
| F1 | 120 | 7 | 2.42 | 38 | 0.28 | 94.11 |
| F2 | 110 | 7.3 | 2.52 | 38 | 0.4 | 97.43 |
| F3 | 110 | 7.5 | 2.50 | 28 | 0.2 | 93.03 |
| F4 | 120 | 7.9 | 2.56 | 35 | 0.4 | 94.33 |
| F5 | 90 | 7.3 | 2.87 | 30 | 0.3 | 93.44 |
| F6 | 100 | 7.8 | 2.94 | 32 | 0.5 | 95.22 |

**Table-7: Post compression evaluation of coated tablet.**

| F.C | Weight | Hardness (kg/cm$^3$) | Thickness(mm) | Friability (%) |
|---|---|---|---|---|
| F1 | 410 | 3.3 | 3.96 | 0.5 |
| F2 | 390 | 4 | 3.87 | 0.5 |
| F3 | 390 | 4 | 3.20 | 0.6 |
| F4 | 380 | 4 | 4.75 | 0.5 |
| F5 | 400 | 5 | 4.44 | 0.5 |
| F6 | 410 | 3 | 6.75 | 0.7 |

**In Vitro Dissolution Studies**

- Utilizing USP dissolution type 1 (basket) equipment, in vitro dissolution investigations were performed. Placed in the basket and thoroughly submerged in the dissolution medium are miniature tablets containing capsules.
- Three distinct dissolving medium with pH buffers of 1.2, 6.8, and 7.4 were utilized to induce the pH alterations as well as the gastro intestinal tract.
- Throughout the experiment, the dissolution media were kept at a temperature of 37 0.5 0 C, and the basket's rotation speed was held constant at 50 rpm. Each time, 900 cc of the dissolving medium were employed.
- To prevent floating, mebeverine tiny pills in a capsule system were placed in a basket.
- Because the average gastric emptying time is two hours, the 0.1 N HCL was used for the first two hours of the experiment. Then, the dissolution medium was removed and fresh dissolution medium at pH 6.8 phosphate buffer was added for three hours. Finally, the pH 6.8 buffer was removed and fresh dissolution medium at pH 7.4 phosphate buffer was added for the remaining twelve hours of the experiment.
- At regular intervals, 5 ml of the dissolving media were removed and replaced with new media.
- UV visible spectrophotometer analysis was used to determine the cumulative amount of drug release over the sampling times for the withdrew samples.

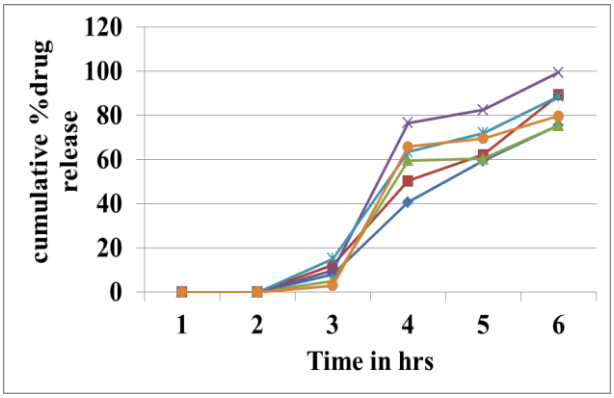


**Figure-5: Comparative Dissolution of all the formulation of core tablet.**

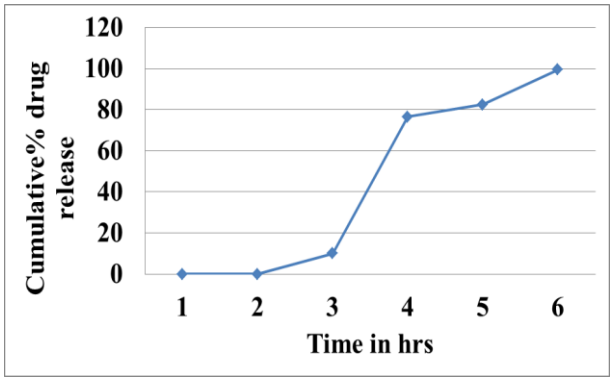


**Figure-6: Release of drug in optimized formulation P4F4.**

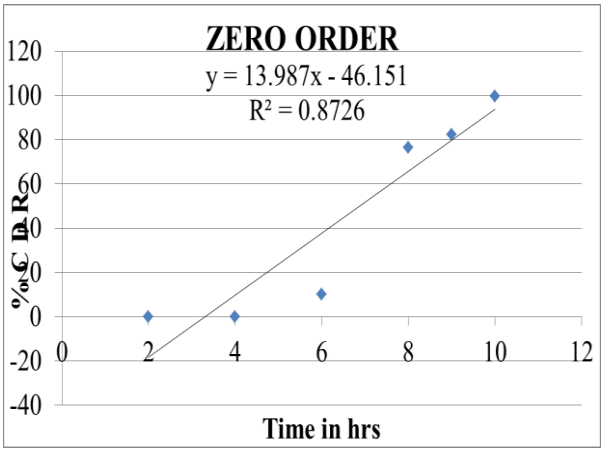


**Figure-7: Zero order kinetics**

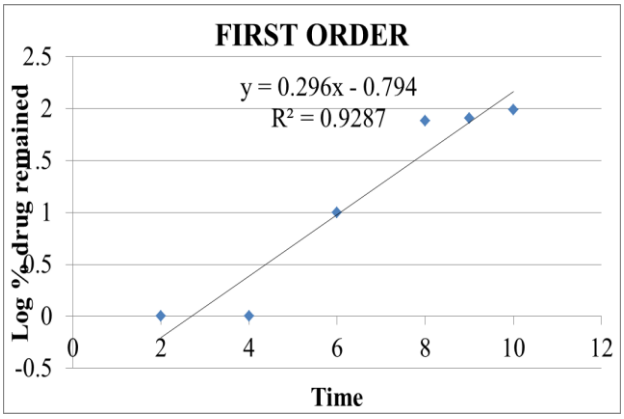


**Figure-8: First order kinetics.**

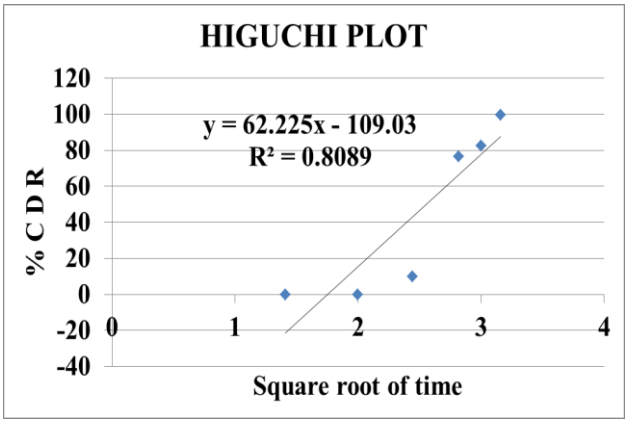


**Figure-9: Higuchi plot.**

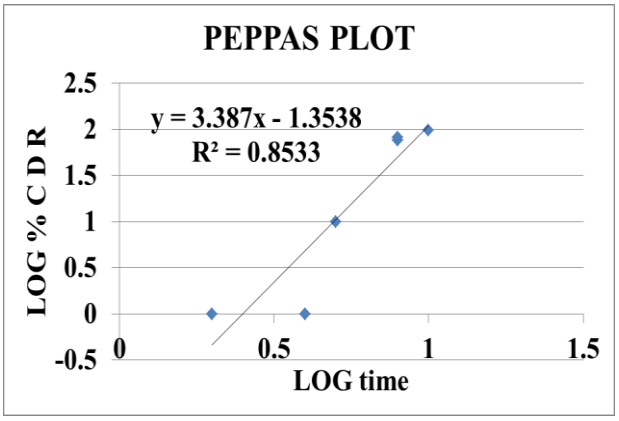


**Figure-10: Peppas plot.**

## RESULTS AND DISCUSSION

The core tablet in the coating layer for colon targeting was developed and assessed in the current investigation. The powder mixture was used in this work and subjected to several preformulation investigations, including Angle of repose, Tapped Density, Bulk Density, Compressibility Index, and Hausner's Ratio, before being crushed into the core tablets.

For post-compression evaluations such as weight fluctuation, thickness, hardness, friability, drug content, disintegration time, as well as dissolving investigations, the compressed core tablets were introduced.

### Preformulation Studies

**1. Solubility**

It was determined as per standard procedure.

Solubility studies of leflunomide in various solvents.

**Table-8: Solubility studies.**

| Solvents | Solubility (mg/mL) |
|---|---|
| 0.1 N HCL | 0.682 ± 0.035 |
| 6.8 pH Buffer | 1.150 ± 0.022 |
| 7.4 pH Buffer | 1.352 ± 0.015 |

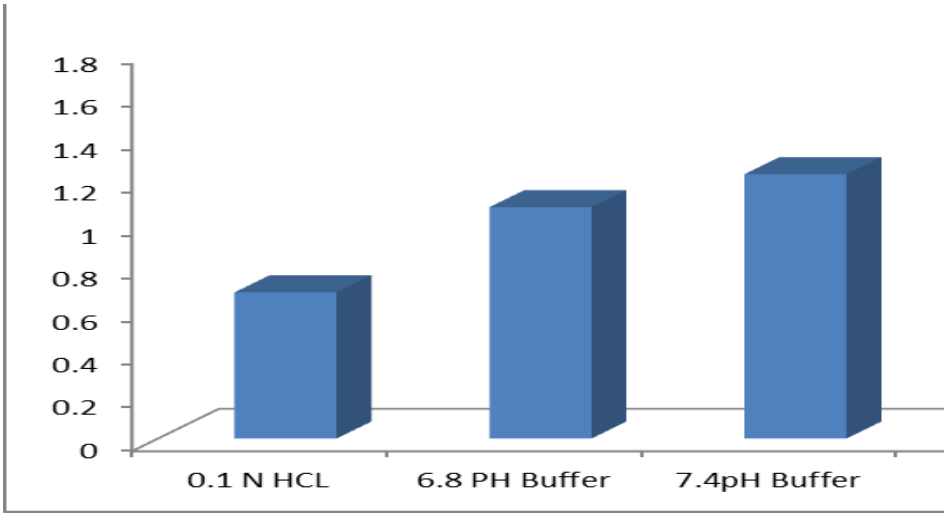


**Figure-11: Solubility studies of leflunomide in various solvents.**

Solubility studies of leflunomide in various solvents.

**Discussion:** Leflunomide was found to be soluble 7.4pH buffer.

### Drug-Excipient compatibility studies

It was discovered that the pure drug's IR spectra matched the leflunomide standard spectrum.

From the IR spectra of leflunomide, it was found that all were not affected for the leflunomide, and it is present in the combination spectrum without alteration, showing the compatibility of the formulation, as shown in the corresponding Figures.

Figure 6.2 FTIR spectrum of Leflunomide.

**Discussion:** FTIR was used to study the chemical interactions between the medication and the polymeric materials. Additionally, there was no distinction between the IR patterns of the leflunomide medication, its physical mixture, and its improved formulation.

**2. $\lambda_{max}$ Determination of Leflunomide**

**Standard Calibration curves of Leflunomide**

Leflunomide's calibration curve was assessed in a variety of pH mediums, including 0.1N HCl pH6.8 phosphate buffer and pH7.4 phosphate buffer.

**Calibration Curve of Leflunomide using 0.1NHCl(pH1.2)**

Leflunomide's calibration curve in 0.1 N HCl is linear at concentrations between 5 and 30 ng/mL, with a correlation coefficient of 0.9998.Leflunomide standard graph in 0.1NHCl at 211 nm.

**Table-9: Calibration curve of leflunomide of Hcl.**

| Concentration (µg/mL) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.113 |
| 4 | 0.221 |
| 6 | 0.328 |
| 8 | 0.435 |
| 10 | 0.541 |

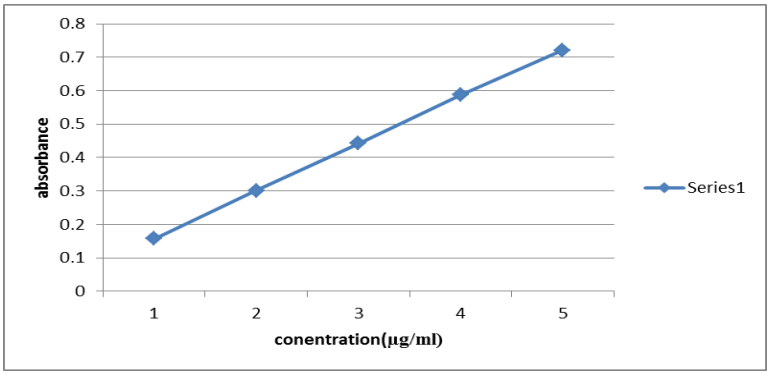


**Figure-12: Calibration curve of leflunomide of HCL.**

**Calibration curve of leflunomide using 6.8pHphosphatebuffer**

Leflunomide's calibration curve exhibits linearity in the concentration range of 5- 30 g/mL and has a correlation coefficient of 0. 9998. Leflunomide standard graph at 211 nm in pH 6.8 phosphate buffer

**Table-10: Calibration curve of leflunomide using PH 6.8 phosphate buffer.**

| Concentration (µg/mL) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.135 |
| 4 | 0.256 |
| 6 | 0.378 |
| 8 | 0.501 |
| 10 | 0.621 |

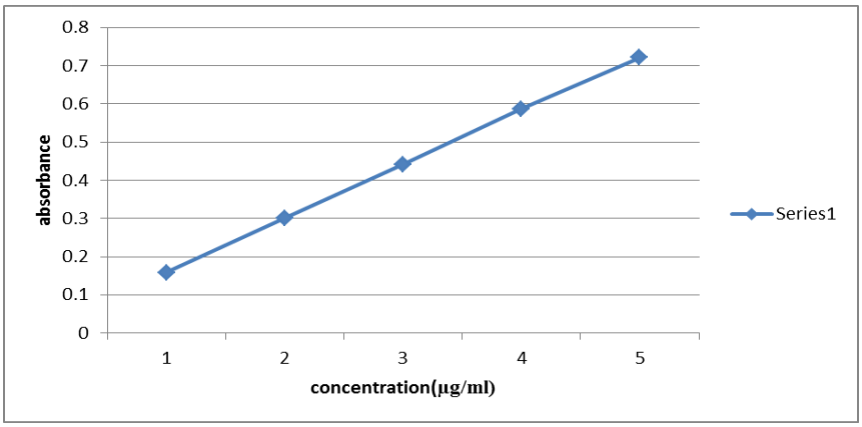


**Figure-13: Calibration curve of leflunomide using 6.8 PH phosphate buffer.**

**Calibration curve of Leflunomide using pH7.4phosphate buffer**

Leflunomide calibration curve in phosphate buffer pH 7.4 exhibit linearity in the concentration range of 5- 30 g with correlation coefficient of 0. 9998.Leflunomide standard graph in 7.4phosphate buffer at 211 nm.

**Table-11: Calibration curve of leflunomide using PH 7.4 phosphate buffer.**

| Concentration (µg/mL) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.152 |
| 4 | 0.387 |
| 6 | 0.440 |
| 8 | 0.573 |
| 10 | 0.722 |

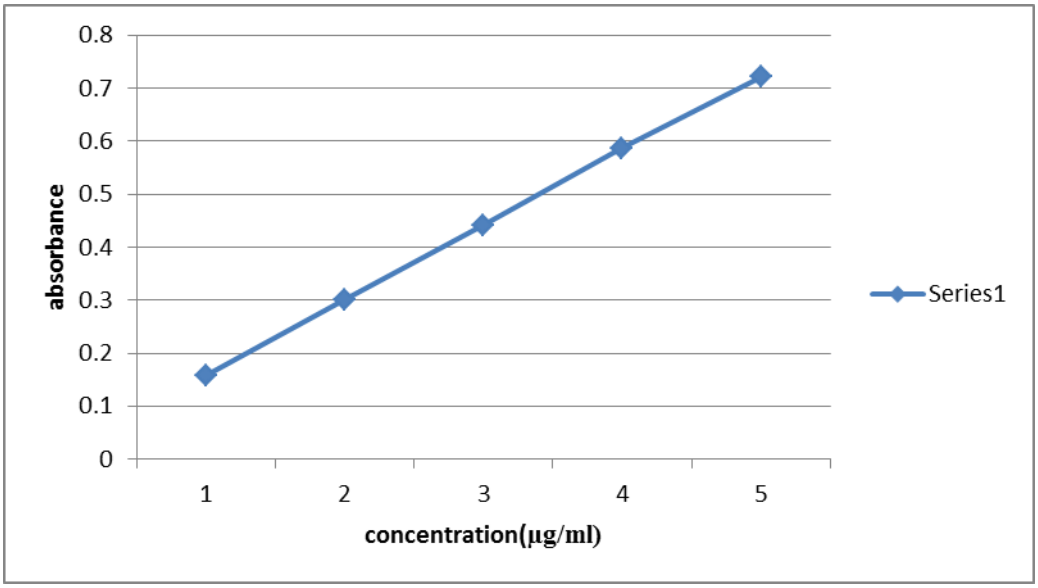


**Figure-14: Calibration curve of leflunomide using PH 7.4 phosphate buffer.**

## CONCLUSION

- The following conclusions can be taken from the current work in several ways. The medicine and the polymer and co-excipients are compatible, according to FTIR Spectroscopic investigations. All powder formulations' flow characteristics have been evaluated, and it has been found that they all exhibit good flow characteristics. Among them, F4 is regarded as an optimal formulation due to its outstanding bulk density of 0.53 grams per milliliter, tap density of 0.62 grams per milliliter, Carr's index of 13.38%, Hausner's ratio of 1.20, and Angle of repose of 26.42.
- The best formulation, according to the evaluation criteria that take into account dissolving, is F4, because the time it takes for the medicine to disintegrate into the core of the tablet is so short. F4 is chosen as the best formulation following all of these evaluation tests, and as a result, it is optimized as a pulsatile tablet.
- The quick release of the tablet may be ascribed to the optimum form of leflunomide with Polymers like Xanthum gum and Guar gum in concentration (0.3-0.1g). With an increase in the concentration of these polymers, it was found that tablet disintegration time decreased.
- The pressed coated tablet's hardness was measured at 4 kg/cm2, and its friability was less than 1%, indicating that it possessed a strong mechanical resistance. Drug release was found to be 96.5% after 10 hours, and drug content was determined to be high (>92.14%) and uniform in all tablet forms.
- Kinetics of drug release was performed and the result shows that release of drug follows zero order kinetics and drug is released by erosion that is it follows korsemeyer-peppas plot.
- Leflunomide pulsatile drug delivery system produced with press coatof gum and xanthum gum in a 2:1 ratio is the longest-acting formulation. according to the morning stiffness chronomodulated theorem. The 5 hour lag time requirement and sustained release over an extended period of time were met. The dose form can be taken at any time, and the early morning hours are when morning stiffness is most relevant are when the contents will be released.

**REFERENCE**


1. Lee JE, Kim IJ, Cho MS, Lee J. A Case of Rheumatoid Vasculitis Involving Hepatic Artery in Early Rheumatoid Arthritis. J Korean Med Sci., 2017 Jul; 32(7): 1207–10.
2. Fox CQ, Ahmed SS. Physician Assistant's Clinical Review Cards. Philadelphia: F. A. Davis Company, 2002; 138–9.
3. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med, 2011 Dec; 365(23): 2205–19.
4. Chaudhari K, Rizvi S, Syed BA. Rheumatoid arthritis: current and future trends. Nat Rev Drug Discov, 2016 May; 15(5): 305–6.
5. Picerno V, Ferro F, Adinolfi A, Valentini E, Tani C, Alunno A. One year in review: the pathogenesis of rheumatoid arthritis. Clin Exp Rheumatol, 2015 Jul-Aug; 33(4): 551–8.
6. Jha N., Bapat S., Chronobiology and chronotherapeutics, Kathmandu Uni. Med. J., 2004; 2(8): 384-388.
7. Arora S., Ali J., Ahuja A., Baboota S., Qureshi J., Pulsatile drug delivery systems: An approach for controlled drug delivery, Ind. J. Pharm. Sci., 2006, 68, 295-300. 3. http://www.uspharmacist.com/oldformat.asp?url =newlook/files/Feat/ACF2F15.cfm&pub_id. 4. Gothoskar A.V., Joshi A.M., Joshi N. H., Pulsatile Drug Delivery Systems: A Review, Drug Del. Tech., 2004, 4, 5. 5. Skloot G., Nocturnal Asthma: Mechanisms and Management, The Mount Sinai J. of Med., 2002, 69, 140-147. 6. Martin R. J., Schlegel S. B., Chronobiology of Asthma, Am. J. Respir. Crit. Care Med., 1998; 158: 1002–1007.