**International Journal of Farmacia (IJF)**

***IJF |Vol.10 | Issue 4 | Oct - Dec -2024***

**www.ijfjournal.com**

DOI : https://doi.org/10.61096/ijf.v10.iss4.2024.101-112

**ISSN: 2231-3656**

**Research**

# Effect of rate retarding polymers in the formulation of extended release tablets of lovastatin

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Published on: 27 Sept 2024

Published by:
DrSriram Publications



## Abstract

The present study was aimed to developed formulation of extended release (ER) tablets of Carbamazepine using HPMC K100M, Carbopol 71 G, and HPMC (K4M) polymer. Carbamazepine extended release tablets were prepared by direct compression method by employing polymer (HPMC K100M, Carbopol 71 G, HPMC (K4M) and Eudragit RSPO). The matrix granules were prepared by mixing drug along with polymer and diluents in different polymer ratio. The prepared granules were evaluated for various physicochemical parameters by official procedure and compressed in tablets. *In-vitro* release profiles of Carbamazepine from extended release tablets were determined using USP apparatus type II (Paddle), 50rpm and bath temperature 37ºC. Tablets dissolution was carried out in 900 ml of media (0.1N HCL and 6.8 phosphate buffer). Samples were withdrawn at predetermined time intervals up to 24 Hrs and analyzed using UV at a wavelength of 225 nm. It followed First order release kinetics mechanism.

**Keywords:** Carbamazepine, HPMC K100M, Carbopol 71 G, HPMC (K4M), Eudragit RSPO and extended release tablets.

## INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. [1,2]

There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drugdelivery system, two pre-requisites would be required: Firstly single

dose for the duration of treatment whether for days or weeks as with infection, diabetes orhypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.

It is desirable to maintain a therapeutic blood concentration in order to achieve the desirable pharmacological effects. To maintain a narrow range of therapeutic blood concentration it is desirable to have a dosage form that can deliver the drug in a more sustainable or controlled way to achieve the desired results. Extended release tablets and capsules are commonly taken once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drugs that promptly produces the desired therapeutic effect, followed by gradual release of additional amount of drugs to maintain this effect over a predetermined period. The sustained plasma drug levels provided by extended release products often eliminate the need for night dosing, which benefits not only the patient but the patient but the caregiver as well.[4]

**Drawbacks of Conventional Dosage Form**

- ✓ Poor patient compliance, increased chances of missing the dose of a drug with short halflife for which frequent administration is necessary.
- ✓ The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- ✓ A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- ✓ The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) whenever over medication occur.

**Advantages of Extended Release Delivery System.**

- ✓ Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- ✓ Improvement in treatment efficacy.
- ✓ Minimize drug accumulation with chronic dosing.
- ✓ Improve the bioavailability of some drugs.
- ✓ Usage of less total drug.
- ✓ Improve the ability to provide special effects. For example, Morning relief of arthritis through bed time dosing.

**Disadvantages of Extended Release Delivery System.**

- ✓ Some differences in the release rate from one dose to another dose but these have been minimized by modern formulations.
- ✓ High cost of preparation.
- ✓ Sometimes the target tissue will be exposed to constant amount of drug over extended period results in drug tolerance.

**Factors Affecting Extended Release Formulation9-10**

**Physicochemical Properties of Drug**

**Aqueous Solubility**

Generally drugs are weak acids or weak bases, since the unchanged form of a drug preferentially permeates across lipid membranes, drugs aqueous solubility will be decreased by conversion to an unchanged form. Drugs with low water solubility will be difficult to incorporate into extended release mechanism. The lower limit on solubility for such product has been reported 0.1 gm/ml. Drugs with extreme water solubility are equally difficult to incorporate in extended release system because it is difficult to control release of drug from dosage form. pH dependent solubility, particularly in the physiological pH range, would be another problem because of the varied pH of gastro intestinal tract, which ultimately gives variation in dissolution profile. e.g.: Aspirin, which is less soluble in stomach, but more soluble in intestine.

**Partition coefficient**

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. As biological membrane is lipophilic in nature through which the drug has to pass though, so partition co-efficient of drug influence the bioavailability of drug very much. Drug having lower partition coefficient values less than the optimum activity are undesirable for oral ER drug delivery system, as it will have very less lipid solubility and the drug will be localized at the first aqueous phase it come in contact e.g. Barbituric acid. Drug having higher partition co-efficient value greater than the optimum activity are undesirable for oral ER drug delivery system because more lipid soluble drug will not partition out of the lipid membrane once it gets in the membrane. The value of partition co-efficient at which optimum activity is observed is approximately 1000:1 in 1-octanol/water system.

**Drug pKa and Ionization at Physiological pH**

As we know only unionized drugs are well absorbed and permeation of ionized drug is negligible, since its rate of absorption of ionized drug is 3 to 4 times less than that of the unionized drug. pKa range for acidic drug where ionization is pH sensitive is around 3.0 to 7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0 to 11.0 are ideal for optimum positive absorption. Drug shall be non-ionized at the site to an extent 0.1 – 5.0%. Drugs existing largely in ionized form are poor candidates for oral ER drug delivery system. e.g.:- Hexamethonium.

**Drug stability**

Drugs when administered orally can undergo both acid/base hydrolysis and enzymatic degradation. The degradation will proceed at the reduced rate for drugs in the solid state. For the drugs that are unstable in stomach, formulation systemsthat prolong delivery to the entire GI tract are beneficial. Compounds that areunstable in the small intestine may demonstrate decreased bioavailability when administered in extended release dosage form. This is happening due to the fact that a greater quantity of drug is delivered in small intestine and is being subjected to more degradation.

**Molecular size and diffusivity**

With large molecular size are poor candidate for oral extended release (ER) where it is 1st time drug delivery system because the ability of the drug to diffuse polymeric membrane is a function of its diffusivity (or diffusion co-efficient). Diffusivity depends on size shape of the cavities of the membrane. The diffusion co-efficient of intermediate molecular weight drug is 100 to 400 Daltons; through flexible polymer range is 10-6 to 10-9 cm2 /sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10-12 cm2 /sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.

**Protein binding**

The Pharmacological response of drug depends on unbound drug concentration rather than total concentration and almost all drugs bind to some extent to plasma and or tissue proteins. Protein binding plays a significant role in its therapeutic effect regardless the type of dosage form as extensive binding to plasma increase biological half life and thus sometimes ER drug delivery system is not required for this type of drug.

**Biological Properties of Drug**

**Absorption**

The absorption behavior of a drug can affect its suitability as an extended release product. The aim of formulating an extended release product is to place a control on the delivery system. It is essential that the rate of release is much slower than the rate of absorption. If we assume the transit time of most drugs and devices in the absorptive areas of GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours. Otherwise the device will pass out of absorptive regions before drug release is complete. Therefore the compounds with lower absorption rate constants are poor candidates for extended release systems. Some possible reasons for a low extent of absorption are poor water solubility, small partition co-efficient, acid hydrolysis, and metabolism or its site of absorption.

**Distribution**

The distribution of drugs in tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug, are poor candidate for oral ER drug delivery system e.g. Chloroquine. For design of extended release products, one must have information on disposition of the drug.

**Metabolism**

Drug, which extensively metabolized is not suitable for ER drug delivery system. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption or first-pass effect is poor candidate for ER delivery, since it could be difficult to maintain constant blood level e.g. Levodopa, Nitroglycerine. Drugs that are metabolized before absorption, either in lumen or the tissues of the intestine, can show decreased bioavailability from the extended releasing systems. Most intestinal walls are saturated with enzymes. As drug is released at a slow rate to these regions, lesser drug is available in the enzymesystem. Hence the systems should be devised so that the drug remains in that environment to allow more complete conversion of the drug to its metabolite.

**Biological half-life**

The main target of an oral extended release product is to maintain therapeuticblood levels over an extended period. To implement this, drug must enter in the circulation approximately with the same rate at which it is eliminated. The elimination rate is quantitatively described by half-life (t1/2). Therapeutic compounds with short half-lives are excellent candidates for extended release preparations because this can reduce dosing frequency. A drug having biological half-life between 2 to 8 hours is best suited for oral ER drug delivery system. As if biological half-life < 2hours the system will require unacceptably large rate and large dose and biological half-life > 8hours formulation of such drug into oral ER drug delivery system is unnecessary.

**Margin of safety**

Larger the value of therapeutic index, safer is the drug. Drugs with less therapeutic index are usually poor candidates for formulation of oral ER drug delivery system due to technological limitation of control over release rates.

**Plasma Concentration**

Response Relationship Generally pharmacological response of drug depends on plasma drug concentration rather than dose. But pharmacological activity of some drugs is independent of plasma concentrations, which are poor candidate for oral ER drug delivery system e.g. Reserpine.

**Concentration Dependency on Transfer of Drug**

Transfer of drug from one compartment to other if follows zero kinetic process then such drugs are poor candidate for oral ER delivery system, it should be first order kinetics.

**Dissolution Profile**

This test is to check the amount of drug available, which can be estimated based on the amount of drug dissolved in the dissolution medium. The drug concentration in plasma can be exemplified via dissolution rate, extent and time. The method involves placing the tablet in a hemispherical cylinder vessel filled with the dissolution medium and a mechanical stirrer attached with a rotator to move the stirrer at variable speeds, which can be set at a fixed speed. The samples are withdrawn at specific time intervals and the drug content is calculated. The amount of the drug available in the body is estimated by in-vitro in-vivo correlation. Severalreviews have been published reporting the research that has gone into the development of extended release tablets. This review is aimed at understanding novelty and feasibility of design approach in the development of extended release formulation by matrix technology. [17,18]

**Approaches to Achieve Extended Release Drug Delivery**

The purpose of designing ER dosage form is to develop a reliable formulation that has all the advantages of immediate release dosage form and yet devoid of the dose dumping. Various techniques have been used in the formulation of ER products. In general, extended formulations can be divided into different categories based on the mechanism of drug release. [19,20]

1) Dissolution Controlled Release
2) Diffusion Controlled Release
3) Ion Exchange Resins Controlled Release
4) Swelling Controlled Release.

## MATERIALS AND METHODS

Lovastatin-Procured From Natco Pharma ltd, Hyderabad, India, Gum Acacia-Signet chemical, corporation Pvt ltd, Mumbai, India, Almond gum-Merck Specialities Pvt Ltd, Mumbai, India, Grewia gum-Signet chemical corporation Pvt ltd, Mumbai, India, Lactose-Strides arcolab, Bangalore, India, Magnesium stearate-Hetero labs,Hyderabad, Talc-Merck Specialities Pvt Ltd, Mumbai, India.

**Methodology**

**Analytical method development**

**Determination of Wavelength**

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

**Determination of Calibration Curve**

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

**Preformulation parameters**

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

**Angle of repose**

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$  $\tan \theta$ = Angle of repose

h = Height of the cone , r = Radius of the cone base

**Table 1: Angle of Repose values (as per USP)**

| Angle of Repose | Nature of Flow |
|---|---|
| <25 | Excellent |
| 25-30 | Good |
| 30-40 | Passable |
| >40 | Very poor |

**Bulk density**

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm$^3$. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.
The bulk density was calculated using the formula:

$\text{Bulk Density} = M / V_o$

Where, M = weight of sample

$V_o$ = apparent volume of powder

**Tapped density**

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$\text{Tap} = M / V$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

**Measures of powder compressibility**

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference

between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

**Table 2: Carr's index value (as per USP)**

| Carr's index | Properties |
|---|---|
| 5 – 15 | Excellent |
| 12 – 16 | Good |
| 18 – 21 | Fair to Passable |
| 2 – 35 | Poor |
| 33 – 38 | Very Poor |
| >40 | Very Very Poor |

**Formulation development of Tablets**

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Lovastatin. Total weight of the tablet was considered as 100mg.

**Procedure**

1) Lovastatin and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

**Table 3: Formulation composition for tablets**

| INGREDIENTS | FORMULATION CHART | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
| Lovastatin | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Gum Acacia | 5 | 10 | 15 | 20 | - | - | - | - | - | - | - | - |
| Almond gum | - | - | - | - | 5 | 10 | 15 | 20 | - | - | - | - |
| Grewia gum | - | - | - | - | - | - | - | - | 5 | 10 | 15 | 20 |
| Lactose | 74 | 69 | 64 | 59 | 74 | 69 | 64 | 59 | 74 | 69 | 64 | 59 |
| Magnesium stearate | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Total Weight | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

*All the quantities were in mg*

## RESULT AND DISCUSSION

The present study was aimed to Develop Extended tablets of Lovastatin using various polymers. All the formulations were evaluated for physicochemical properties and *in-vitro* drug release studies.

**Analytical Method**

Graphs of Lovastatin were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 238 nm and 242 nm respectively.

**Table 4: Observations for graph of Lovastatin in 0.1N HCl (238 nm)**

| Conc [µg/ml] | Absorbance |
|---|---|
| 0 | 0 |
| 5 | 0.148 |
| 10 | 0.274 |
| 15 | 0.386 |
| 20 | 0.511 |
| 25 | 0.647 |

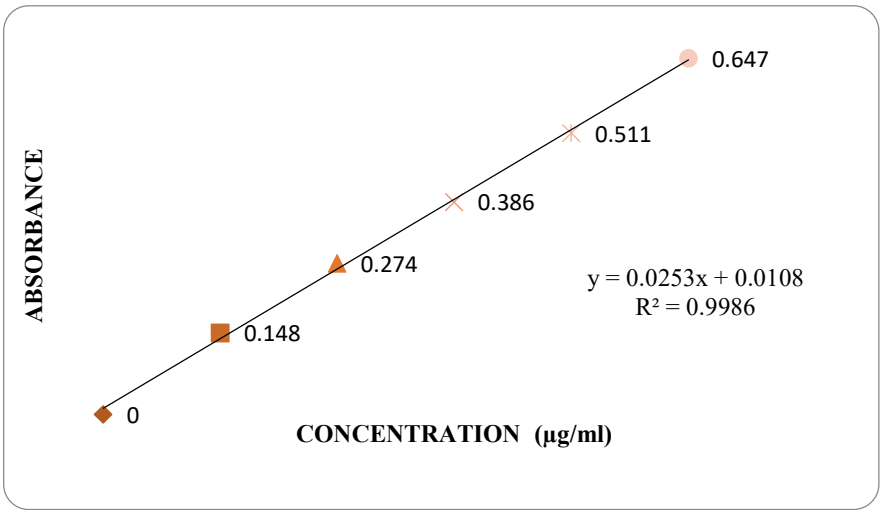


**Fig 1: Standard graph of Lovastatin in 0.1N HCl**

**Table 5: Observations for graph of Lovastatin in pH 6.8 phosphate buffer (242 nm)**

| Concentration [µg/ml] | Absorbance |
|---|---|
| 0 | 0 |
| 5 | 0.128 |
| 10 | 0.254 |
| 15 | 0.372 |
| 20 | 0.482 |
| 25 | 0.597 |

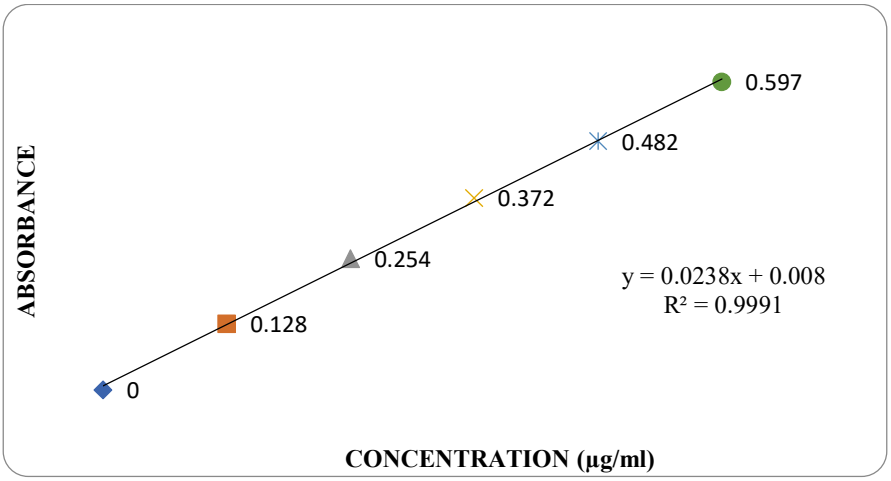


**Fig 2: Standard graph of Lovastatin pH 6.8 phosphate buffer (242 nm)**

**Preformulation parameters of powder blend**

**Table 6: Pre-formulation parameters of Core blend**

| Formulation Code | Angle of Repose | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index (%) | Hausner's Ratio |
|---|---|---|---|---|---|
| **F1** | 35.24±0.07 | 0.525±0.11 | 0.619±0.02 | 15.32±0.09 | 1.197±0.07 |
| **F2** | 36.27±0.06 | 0.522±0.34 | 0.621±0.04 | 14.87±0.35 | 1.185±0.06 |
| **F3** | 34.65±0.08 | 0.526±0.65 | 0.614±0.01 | 15.62±0.72 | 1.187±0.13 |
| **F4** | 33.54±0.04 | 0.522±0.25 | 0.615±0.04 | 15.64±0.26 | 1.175±0.02 |

| | | | | | |
|---|---|---|---|---|---|
| **F5** | 32.21±0.01 | 0.516±0.24 | 0.622±0.05 | 14.96±0.15 | 1.186±0.03 |
| **F6** | 39.23±0.01 | 0.527±0.45 | 0.618±0.01 | 16.53±1.6 | 1.198±0.21 |
| **F7** | 31.10±0.02 | 0.522±0.36 | 0.623±0.02 | 14.56±0.20 | 1.170±0.01 |
| **F8** | 32.19±0.02 | 0.525±0.99 | 0.611±0.01 | 14.91±0.33 | 1.175±0.03 |
| **F9** | 33.28±0.01 | 0.517±1.05 | 0.617±0.03 | 15.66±0.10 | 1.185±0.15 |
| **F10** | 30.86±0.03 | 0.518±0.25 | 0.613±0.02 | 15.35±0.3 | 1.18±0.01 |
| **F11** | 31.24±0.04 | 0.523±0.45 | 0.612±0.01 | 14.95±0.66 | 1.17±0.02 |
| **F12** | 30.48±0.02 | 0.515±1.47 | 0.610±0.01 | 15.57±1.4 | 1.18±0.01 |

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.515±1.47 to 0.527±0.45 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.610±0.01 to 0.623±0.02 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 16.53 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.198 indicating the powder has good flow properties.

**Quality Control Parameters For tablets**

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

**Table 7: *In-vitro* quality control parameters for tablets**

| Formulation codes | Average Weight(mg) | Hardness(kg/cm2) | Friability (%loss) | Thickness (mm) | Drug content (%) |
|---|---|---|---|---|---|
| **F1** | 98.12 | 4.2 | 0.19 | 2.36 | 98.15 |
| **F2** | 97.64 | 4.9 | 0.24 | 2.64 | 97.36 |
| **F3** | 100.0 | 4.6 | 0.72 | 2.19 | 99.12 |
| **F4** | 99.86 | 4.3 | 0.48 | 2.85 | 96.49 |
| **F5** | 95.69 | 4.8 | 0.34 | 2.41 | 99.86 |
| **F6** | 98.34 | 4.1 | 0.52 | 2.75 | 99.0 |
| **F7** | 99.28 | 4.6 | 0.64 | 2.39 | 95.98 |
| **F8** | 97.99 | 4.9 | 0.38 | 2.54 | 98.34 |
| **F9** | 98.67 | 4.2 | 0.28 | 2.84 | 97.22 |
| **F10** | 99.33 | 4.7 | 0.35 | 2.16 | 99.64 |
| **F11** | 97.21 | 4.6 | 0.46 | 2.57 | 97.85 |
| **F12** | 99.36 | 4.8 | 0.61 | 2.79 | 98.14 |

**Weight variation test**

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 8.4. The average weight of the tablet is approximately in range of 95.69 to 100.0 mg, so the permissible limit is ±7.5% (>100 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

**Hardness test**

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 4.1 to 4.9 kg/cm$^2$, which was within IP limits.

**Thickness**

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 2.16 to 2.85 mm.

**Friability**

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

**Drug content**

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 95.98 – 99.86 %.
All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies**

**Table 8: Dissolution Data of Lovastatin Tablets F1-F12**

| Time | CUMULATIVE PERCENT DRUG RELEASE | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (hr) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
| **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **0.5** | 7.23 | 8.13 | 9.65 | 8.98 | 9.21 | 9.28 | 9.22 | 9.54 | 22.82 | 12.66 | 10.30 | 15.54 |
| **1** | 15.61 | 15.81 | 19.76 | 13.57 | 15.98 | 13.40 | 17.97 | 13.28 | 33.69 | 17.28 | 18.93 | 24.28 |
| **2** | 19.59 | 21.32 | 26.32 | 19.58 | 18.98 | 19.75 | 28.22 | 24.26 | 37.36 | 25.15 | 22.66 | 32.47 |
| **3** | 28.12 | 25.61 | 38.76 | 26.57 | 29.85 | 26.05 | 37.35 | 36.62 | 42.74 | 30.55 | 38.31 | 38.59 |
| **4** | 38.45 | 34.15 | 46.83 | 38.69 | 40.51 | 30.58 | 44.10 | 42.72 | 48.55 | 39.47 | 42.69 | 47.26 |
| **5** | 50.61 | 39.29 | 57.24 | 45.97 | 52.28 | 36.57 | 53.34 | 50.73 | 56.78 | 52.82 | 55.74 | 54.12 |
| **6** | 56.18 | 52.84 | 68.12 | 57.62 | 59.84 | 40.04 | 62.23 | 62.48 | 63.12 | 58.83 | 59.98 | 59.63 |
| **7** | 68.92 | 63.26 | 71.25 | 65.48 | 68.87 | 47.96 | 68.76 | 68.29 | 67.81 | 66.02 | 65.82 | 66.81 |
| **8** | 73.29 | 74.82 | 75.91 | 68.74 | 73.11 | 58.45 | 73.38 | 73.68 | 72.68 | 72.52 | 74.21 | 72.27 |
| **9** | 82.72 | 79.81 | 81.96 | 71.38 | 81.29 | 66.11 | 79.45 | 82.30 | 78.35 | 76.91 | 78.84 | 78.44 |
| **10** | 86.24 | 84.96 | 83.29 | 75.35 | 87.74 | 72.74 | 84.56 | 87.74 | 81.43 | 83.11 | 81.23 | 83.11 |
| **11** | 90.17 | 88.21 | 97.13 | 79.42 | 91.66 | 80.04 | 88.15 | 90.19 | 88.97 | 89.24 | 86.52 | 88.75 |
| **12** | 95.54 | 91.55 | | 85.75 | 94.56 | 84.74 | 90.12 | 97.56 | 98.82 | 94.23 | 91.76 | 90.81 |

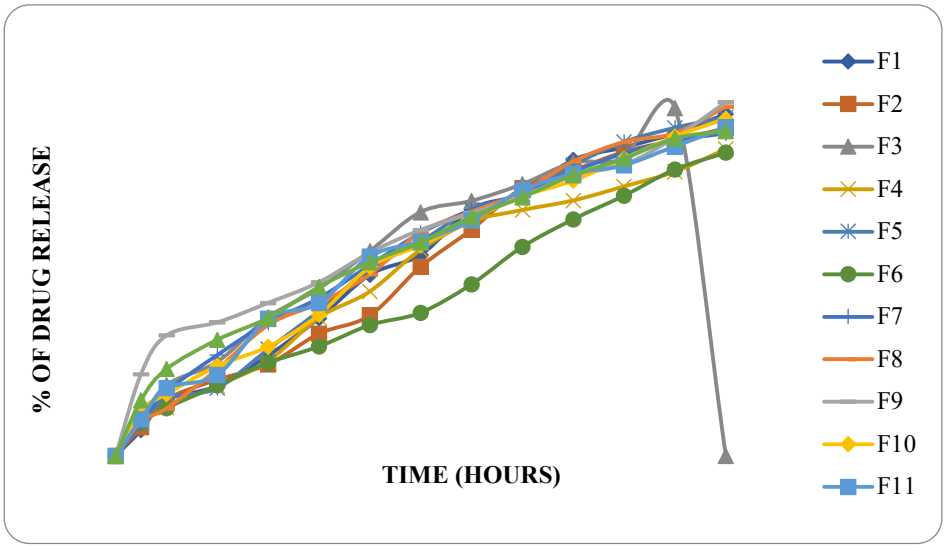


**Fig 3: Dissolution profile of Lovastatin (F1-F12 formulations)**

From the dissolution data it was evident that the formulations prepared with Gum Acacia as polymer were able to retard the drug release up to desired time period i.e., 12 hours. Formulations prepared with Almond gum retarded the drug release in the concentration of 20 mg (F8 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 97.56 % in 12 hours with good retardation. The Formulations prepared with Grewia gum were 5 mg (F9 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.82 % in 12 hours with good retardation. Finally concluded that F9 formulation contains Grewia gum was optimized formulation.

**Application of Release Rate Kinetics to Dissolution Data**

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

**Table 9: Release kinetics data for optimised formulation**

| Cumulative (%) Release Q | Time ( T ) | Root (T) | Log( %) Release | Log ( T ) | Log (%) Remain | Release Rate (Cumulative % Release / T) | 1/Cum% Release | Peppas Log Q/100 | % Drug Remaining | Q01/3 | Qt1/3 | Q01/3-Qt1/3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | | | 2.000 | | | | 100 | 4.642 | 4.642 | 0.000 |
| 22.82 | 0.5 | 0.707 | 1.358 | -0.301 | 1.888 | 45.640 | 0.0438 | -0.642 | 77.18 | 4.642 | 4.258 | 0.384 |
| 33.69 | 1 | 1.000 | 1.528 | 0.000 | 1.822 | 33.690 | 0.0297 | -0.472 | 66.31 | 4.642 | 4.048 | 0.594 |
| 37.36 | 2 | 1.414 | 1.572 | 0.301 | 1.797 | 18.680 | 0.0268 | -0.428 | 62.64 | 4.642 | 3.971 | 0.670 |
| 42.74 | 3 | 1.732 | 1.631 | 0.477 | 1.758 | 14.247 | 0.0234 | -0.369 | 57.26 | 4.642 | 3.854 | 0.787 |
| 48.55 | 4 | 2.000 | 1.686 | 0.602 | 1.711 | 12.138 | 0.0206 | -0.314 | 51.45 | 4.642 | 3.719 | 0.922 |
| 56.78 | 5 | 2.236 | 1.754 | 0.699 | 1.636 | 11.356 | 0.0176 | -0.246 | 43.22 | 4.642 | 3.509 | 1.132 |
| 63.12 | 6 | 2.449 | 1.800 | 0.778 | 1.567 | 10.520 | 0.0158 | -0.200 | 36.88 | 4.642 | 3.329 | 1.313 |
| 67.81 | 7 | 2.646 | 1.831 | 0.845 | 1.508 | 9.687 | 0.0147 | -0.169 | 32.19 | 4.642 | 3.181 | 1.461 |
| 72.68 | 8 | 2.828 | 1.861 | 0.903 | 1.436 | 9.085 | 0.0138 | -0.139 | 27.32 | 4.642 | 3.012 | 1.630 |
| 78.35 | 9 | 3.000 | 1.894 | 0.954 | 1.335 | 8.706 | 0.0128 | -0.106 | 21.65 | 4.642 | 2.787 | 1.854 |
| 81.43 | 10 | 3.162 | 1.911 | 1.000 | 1.269 | 8.143 | 0.0123 | -0.089 | 18.57 | 4.642 | 2.648 | 1.993 |
| 88.97 | 11 | 3.317 | 1.949 | 1.041 | 1.043 | 8.088 | FALSE | -0.051 | 11.03 | 4.642 | 2.226 | 2.416 |
| 98.82 | 12 | 3.464 | 1.995 | 1.079 | 0.072 | 8.235 | FALSE | -0.005 | 1.18 | 4.642 | 1.057 | 3.585 |

**Table: kinetics Correlation coefficient values**

| Release Kinetics | Correlation coefficient values |
|---|---|
| Zero order release kinetics | $R^2 = 0.931$ |
| Higuchi release kinetics | $R^2 = 0.988$ |
| Peppas release kinetics | $R^2 = 0.973$ |
| First order release kinetics | $R^2 = 0.961$ |

The *in-vitro* release data was treated according to zero order, first order, Higuchi's and Korsmeyer. The release rate kinetic data for all the models can be seen in Table 8.6. In the present study, the *in vitro* release profiles of drug from F9 formulation could be best expressed by Higuchi's equation,as correlation coefficient value ($r^2$): 0.988 shows high linearity respectively. Thus, as the data fitted the Higuchi release kinetics model.

**Drug – Excipient compatability studies**
**Fourier Transform-Infrared Spectroscopy**

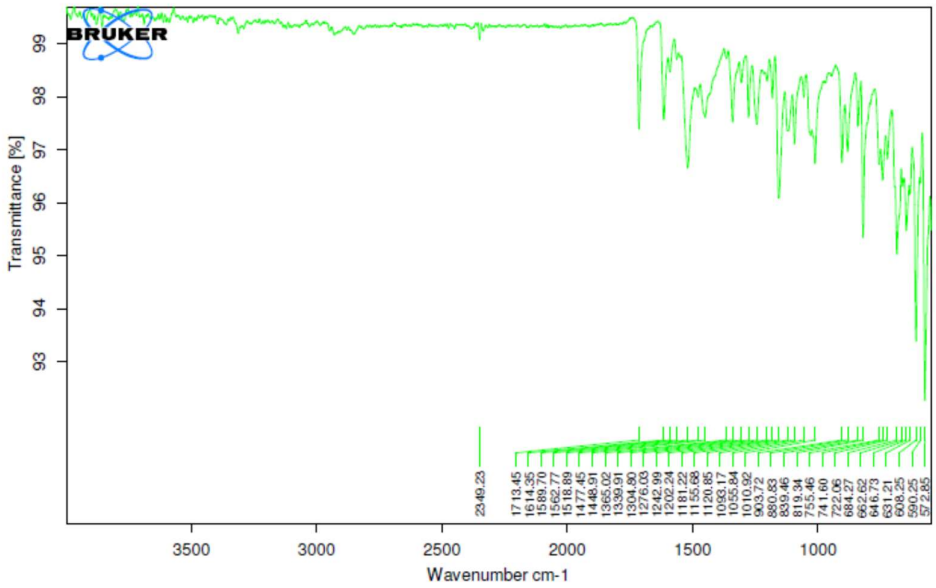


**Fig 4: FT-TR Spectrum of Lovastatin pure drug**

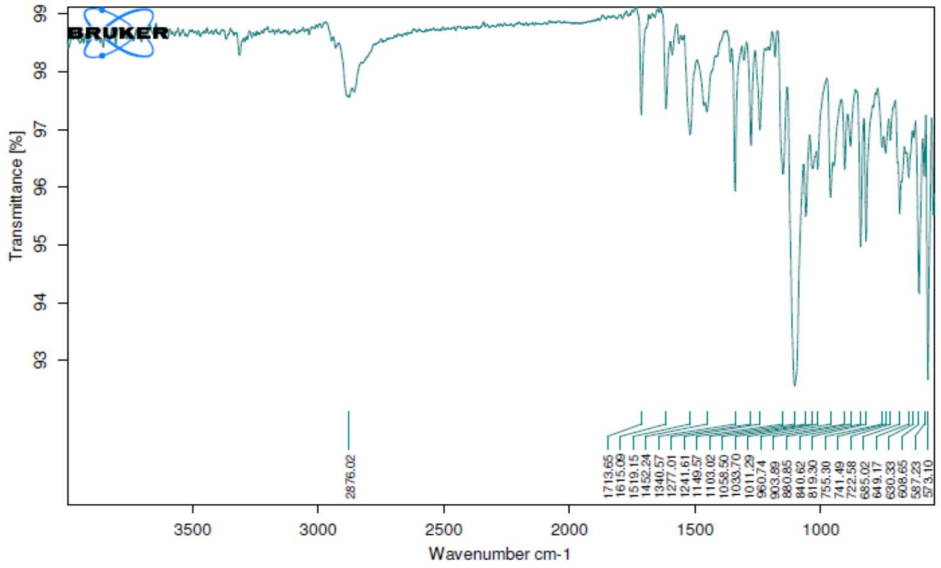


**Fig 5: FT-IR Spectrum of Optimised Formulation**

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Lovastatin and excipients used in the preparation of different Lovastatin extended release formulations. Therefore the drug and excipients are compatible to form stable. Formulations under study, The FTIR spectra of Lovastatin and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

## SUMMARY AND CONCLUSION

The present study was carried out on Lovastatin. It has half life about 5.3 hrs. The main aim of this study is to extend the drug release up to 12 hrs. Drug wavelength and calibration curve was developed in 0.1N HCl and pH 6.8 Phosphate buffer.

The drug and excipient compatibility studies were shown good compatibility between drug and excipients. Tablet powder blend was subjected to various pre-formulation parameters indicating the powder has good flow properties.

Post compression studies like Weight variation, Hardness, thickness, friability, drug content was determined. The average weight of the tablet is approximately in range of 95.69 to 100.0 mg, so the permissible limit is ± 5.0%. The results showed that the hardness of the tablets is in range of 4.1 to 4.9 kg/cm$^2$, which was within IP limits. The result showed that thickness of the tablet is raging from 2.16 to 2.85 mm. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 95.98 -99.0 %.

From the dissolution data it was evident that the formulations prepared with Gum Acacia as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Formulations prepared with Almond gum retarded the drug release in the concentration of 20 mg (F8 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 97.56 % in 12 hours with good retardation. Grewia gum were 5 mg (F9 Formulation ) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.82 % in 12 hours with good retardation. Finally concluded that F9 formulation contains Grewia gum was optimized formulation.

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