

**DEVELOPMENT AND EVALUATION OF A LAMOTRIGINE EXTENDED-RELEASE
MINI-TABLET DOSAGE FORM**

**A Dissertation submitted to
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY,
Chennai-600 032**

In partial fulfilment for the requirements for the award of the Degree of

MASTER IN PHARMACY

IN

BRANCH - I - PHARMACEUTICS

Submitted by

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DECLARATION

I hereby declare that the dissertation work entitled “**DEVELOPMENT AND EVALUATION OF A LAMOTRIGINE EXTENDED-RELEASE MINI-TABLET DOSAGE FORM**” has been originally carried out by me under the guidance and supervision of **Dr. R. KUMARAVEL RAJAN, M. Pharm., Ph.D., Professor, Department of Pharmaceutics, C.L. Baid Metha College of Pharmacy,** and **Mr. M. Ramalingam, M. Pharm., Associate Vice-President & Plant Head, FOURRTS (INDIA) LABORATORIES PVT. LTD,** Kandigai, Chennai -600127 during the academic year 2019-2021. This work has not been submitted in any other degree at any other university and that all the sources we have used or quoted have been indicated and acknowledged by complete reference.

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LIST OF ABBREVIATION

Abbreviation	Expansion
%	Percentage
µg	Microgram
µm	Micrometer
AED	Anti Epileptic drugs
LTG	lamotrigine
ER	Extended release
IR	Immediate release
GABA	Gamma amino butyric acid
SUDF	Single unit dosage form
MUDF	Multiple unit dosage form
HPMC	Hydroxy propyl methyl cellulose
CRDDS	Controlled Release Drug Delivery System
MT	minitabiet
ODT	Oral dispersible tablets
NSAID	Non steroidal anti inflammatory drugs
DOE	Design of Experiment
HPLC	High Performance Liquid Chromatography
hr	Hrs
IP	Pharmacopoeia of India
mg	Milligram
Min	Minutes
ml	Millilitres
mm	Millimeter
UV	Ultra violet

w/v	Weight/Volume
w/w	Weight/Weight
AIC	Akaike Information Criterion
API	Active Pharmaceutical Ingredients
AUC	Area Under Curve
AUMC	Area Under First Moment Curve
Avg.Wt	Average Weight
BIC	Bayesian Information Criterion
Conc	Concentration
HCl	Hydrochloride
HBr	Hydrobromide
IAEC	Institutional Animal Ethical Committee
MCC	Microcrystalline cellulose
MDT	Mean Dissolution Time
MRT	Mean Resident Time
MSC	Model Selection Criterion
MSE	Mean Square Error
rpm	Revolution Per Min
SD	Standard Deviation
SM	Surface Morphology
WSS	Weighed Sum of Squar
SSR	Sum of Squared Residual
VDT	Variance of Dissolution Time

1. 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]

Oral administration is the mainstay of Antiepileptic drugs (AED) delivery for patients with chronic epilepsy and consists essentially of Immediate-Release (IR) and modified-release (delayed-release and Extended-Release [ER]) dosage formulations.^[2] In order to improve the patient compliance and decrease the toxicity of antiepileptic drugs, the recent strategy management has been to expand the use of Extended-release (ER) formulations. Lamotrigine (LTG) is a phenyltriazine class anticonvulsant that shows efficacy against partial and generalized epilepsies. It exerts its antiepileptic effects by blocking voltage-sensitive sodium channels and inhibiting the release of excitatory neurotransmitters, particularly glutamate and aspartate.^[3]

Mini-tablets represent a new trend in solid dosage form design, with the main goal of overcoming some therapeutic obstacles. Mini tablets are multiple unit dosage forms and are advantageous than pellets or any other oral dosage forms as they are easy to manufacture and stability problems are less. The objective of controlled drug delivery systems is to reduce the frequency of the dosing and to increase the effectiveness of the drug by localization.^[4]

1.1 Modified release drug delivery system:

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits like multiple dosing and single doses of sustained and controlled delivery formulations.^[5]

Modified-release dosage formulations have been developed to achieve this goal by delaying or extending the rate of drug absorption, or by altering its site of release. [6]

1.1.1 The drug delivery systems can be divided into the following categories:

- i) Delayed release
- ii) Controlled release
- iii) Sustained release
- iv) Extended release
- v) Site specific targeting
- vi) Receptor targeting

i)Delayed Released Drug Delivery system: This is a specific type of modified release dosage form that releases the drug at a particular time. E.g. Enteric coated tablet.

ii)Controlled release (time delivery release) system: The dosage form in which the drug is released in a planned, predictable and slower than conventional dosage form.

iii)Sustained released: This is a specific type of modified release dosage form that allows at least a two-fold reduction in the dosage frequency compared to conventional drug delivery system.

iv)Extended released: Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate and necessarily reduce the dosage frequency by two folds.

v)Site specific targeting: These systems refer to targeting of a drug directly to an certain biological system. In this case the target is adjacent to or in the diseased organ or tissue.

vi)Receptor targeting: Site specific targeting and receptor targeting systems satisfy the aspect of drug delivery and are also considered to be controlled drug delivery systems. [6]

1.1.2 Extended-release drug delivery system:

Extended-release drug delivery system is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration single dose and important role in epilepsy treatment. ER formulations may be helpful in improving efficacy and tolerability and also adherence to the therapeutic regimen.^[7]

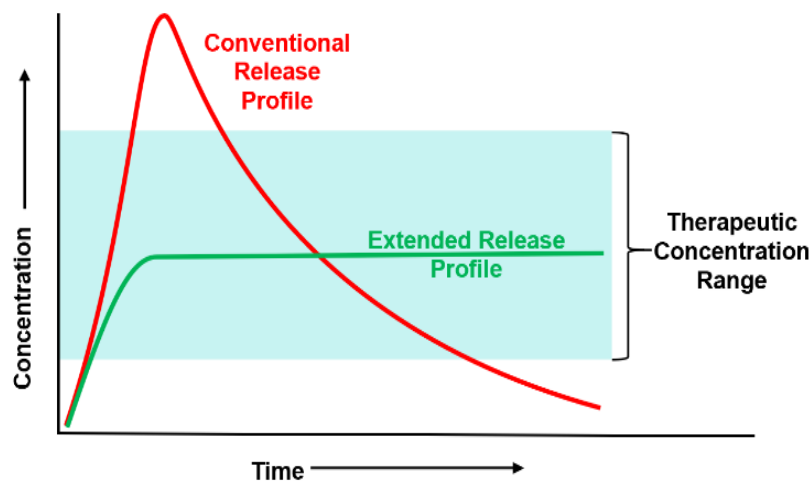


Fig. 1: Conventional release vs Extended release

1.1.3 Advantages of Extended-release drug delivery system:

- The frequency of drug administration is reduced.
- Patient compliance can be improved and drug administration can be more convenient as well.
- Improve the treatment efficacy.
- The blood level oscillation occurs by multiple dosing of conventional dosage form is reduced.
- The total amount of drug administered can be reduced, thus

Maximizing availability with minimum dose

Minimize drug accumulation with chronic dosing.

Minimize the local and systemic side effect.

- Safety margins of high potency drug can be increased.^[8]

Disadvantages of Extended-release drug delivery system:

- Economical factors must be assessed, since more costly preparation.
- Relatively poor *In vitro/In vivo* correlation.
- Reduced potential for dose adjustment.^[9]

1.1.4 Approaches to Achieve Extended-Release Drug Delivery:

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.^[10]

- i) Dissolution Controlled Release
- ii) Diffusion Controlled Release
- iii) Ion Exchange Resins Controlled Release
- iv) Swelling Controlled Release
- v) Erosion controlled Release

i) Dissolution controlled release:

This type of controlled release involves two processes, the detachment of drug molecules from the surface of their solid structure to the adjacent liquid interface, followed by their diffusion from the interface into the bulk liquid medium. The rate of dissolution and the amount dissolved per unit of time from this system can be calculated using Noyes-Whitney equation which relates the rate of dissolution of solids to the properties of the solid and the dissolution medium, and the relation is given by:

$$\frac{dW}{dt.L} = DA(C_s - C)$$

dW/dt is the rate of dissolution

A is the surface area of the solidification

C is the concentration of the solid in the bulk dissolution medium

C_s is the concentration of solid in the diffusion layer surrounding the solid

D is the diffusion coefficient and

L is the diffusion layer thickness.

ii) *Diffusion Controlled Release:* ^[11]

In this type of controlled release system, the active ingredient diffuses through the polymeric material. These are mainly classified as

- Reservoir system
- Matrix system

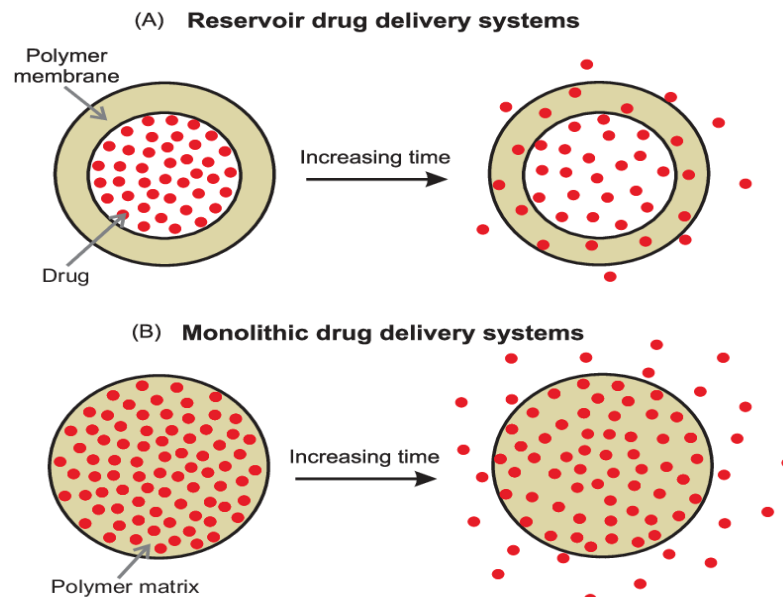


Fig. 2: Reservoir and monolithic (matrix) delivery system

- **Reservoir system:** Cellulose derivatives are commonly used in the reservoir systems. It consists of a core (the reservoir) and coating membrane (the diffusion barrier). The active ingredient diffuses from the reservoir through the coating membrane.
- **Matrix system:** Matrix controlled release for design of extended-release tablets. A matrix system consists of active and inactive ingredients that are homogeneously dispersed and mixed in the dosage form. It is by far the most commonly used oral extended-release technology and the popularity of the matrix systems can be attributed to several factors. The release from matrix type formulations is governed by Fick's first law of diffusion.^[12]

Polymers used in matrix tablet:

- **Hydrogels:** Poly Hydroxy Ethyl Methyl Acrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO) and Polyacrylamide (PA).
- **Soluble polymers:** Polyethylene glycol (PEG), polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP) and Hydroxypropyl methyl cellulose (HPMC)
- **Biodegradable polymers:** Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyamides, Poly ortho esters.
- **Non-biodegradable polymers:** Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA) and Ethyl cellulose (EC).

Types of Matrix System

The matrix system can be divided into two categories depending on the types of retarding agents or polymeric materials.

- Hydrophobic matrix system
- Hydrophilic matrix system
- ***Hydrophobic Matrix System:*** This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used.
- ***Hydrophilic matrix system:*** The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell when in contact with aqueous solution and form a gel layer on the surface of the system. When the release medium (i.e. water) is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. ^[13]

iii) Ion Exchange Resins Controlled Release

Ion exchange resins are cross-linked water-insoluble polymers carrying ionizable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrant because of their swelling ability. It forms irreversible complex

with ionizable drugs upon prolonged exposure of the drug to the resin. A resin bound-drug is removed when appropriate ions are in contact with ion-exchanged groups. The area and length of diffusion pathway, and the amount of cross-linked polymer in the resin moiety governs the rate of drug release.

iv) *Swelling Controlled Release:*

Swelling controlled release systems are initially dry, and when placed in the body will absorb water or other body fluids and swell. Swelling controlled systems are based upon swelling of ER polymer. Due to the viscoelastic properties of the polymers, which are enhanced by the presence of cross-linked network, anomalous penetrate transport can be observed. This behavior is bound by pure Fickian diffusion and case II transport. Therefore transport can be reduced to three driving forces. The penetrate concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery, and possibly zero-order release.^[14]

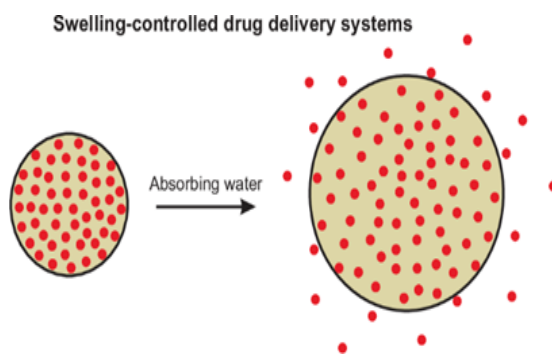


Fig. 3: Swelling Controlled Release

v) *Erosion controlled release systems:*

In erosion controlled extended-release systems that rate of drug release is controlled by the erosion of a matrix in which drug is dispersed. The matrix is normally a tablet, i.e. the matrix is formed by a tableting operation and the system can be described as a continuous liberation of matrix material (both drug and excipients) from the surface of the tablet, i.e. surface erosion. The consequence will be a continuous reduction in tablet weight during the course of the release process.^[15]

1.2 Oral controlled release drug delivery systems can be classified in two broad groups:

- i) Single unit dosage forms (SUDF's)
- ii) Multiple unit dosage forms (MUDF's)

i) Single unit dosage forms (SUDF's) such as tablets or capsules. In a single unit dose e.g. Matrix or tablet is bounded in diffusion membrane, is a depot which release drug during the passage of entire GI tract without disintegrating. The empty core or shell is discharged. To retain a depot, effect the dose unit to be administered should be intact as dividing dosage form before administration would result in unintended rapid release.

ii) Multiple unit dosage forms (MUDF's), such as granules, pellets or mini-tablets. A multiple units dose consists of many mini-units, e.g. Pellets or mini tablets contained in a capsule or a tablet. These mini-depots are dispersed and distributed throughout the gastro intestinal tract when the capsule or tablet disintegrates. The dose in (MUDF's) is divided into number of subunits, each one containing the drug. The dose is then the sum of the quantity of the drug in each subunit and the functionality of the entire dose is directly correlated to the functionality of the individual subunits.^[16]

1.3 Minitablets:

Mini-tablets are suitable for paediatric as well as geriatric use since they may provide flexible and accurate dosing and administration. Mini tablet is with diameter of 3-6mm. Majority of the drugs absorption is more in upper part of small intestine (duodenum), for a drug to reach the small intestine it had to pass through stomach. So, drug absorption depends on gastric emptying time.^[17] If the gastric emptying is too fast drug may not absorb to required level or if it too slows it may get mix-up with gastric contents and may adsorb to food which gives unintended effects. These effects are more in case of single unit dosage forms because of their size but in case of mini tablets will not depend on gastric emptying and easily get passed through pylorus.^[30]



Fig. 4: Minitablets

Direct compression is the preferred manufacturing technique for mini-tablets, provided that the powder mixture has sufficient flow properties. Multiple-tip tools are generally used since this increases the output. Mini-tablets could be either filled into hard capsules or compacted into bigger tablets.

1.3.1 Constituents of Mini-Tablets:

Different mini-tablets can be formulated and designed individually, incorporated into a capsule to release the drug at different sites and at different rates. Different combinations of mini-tablets include immediate release, delayed release, and/or controlled release formulations. Also, combining different mini-tablets together, incompatible drugs can be administered. This as a result, improves overall therapeutic outcome and also concurrent diseases can be treated effectively.^[19]

1.3.2 Release profile:

Due to increased surface in relation to volume, the drug can be released more efficiently in case of mini-tablets. By applying uniform layer of a retarding film coat, the release rate of the drug can be controlled with greater certainty. Also, mini-tablets that are formulated using different concentrations of HPMC K100M, provides a prolonged drug release rate. The drug contained in the mini-tablets gets released at different rates, depending upon composition of mini tablets. Based on the release kinetic parameters calculated, it can be concluded that minitables containing HPMC K100M are particularly suitable to release the drug over hours of time periods. By combining different doses of mini tablets, it is possible to achieve various releases with one formulation. Due to significant smaller dimensions of the mini

tablets, when compared to normal tablets, they pass through the stomach at more even rate. As a result, the concentration of the drug in the blood can be easily reproduced.^[20]

1.3.3 Advantages of Mini Tablets:

- Mini Tablets can be manufactured relatively easily.
- They offer high drug loading, a wide range of release rate designs, and fine tuning of these release rates.
- They have excellent size uniformity, regular shape and smooth surface.
- They combine the advantages of multiple unit dosage forms with the well-known manufacturing techniques in tableting and have fewer constrictions compared to extrusion or Spheronization.
- They offer high degree of dispersion in the GI tract, thus minimizing the risks of high local drug concentrations.
- They have less risk of dose dumping.
- Mini-tablets also offer an alternative for pellets because of their relative ease of manufacturing and because dosage forms of equal dimensions and weight with smooth regular surface are produced in a reproducible and continuous way.
- They offer a substrate which is easy to coat with polymeric membranes for modified release purposes.
- Mini tablets have less inter and intra- subject variability.
- Mini tablets are good coating substrates as they have excellent size uniformity, regular shape and a smooth surface.
- Improve efficiency in treatment and minimize drug accumulation with chronic dosing.^[21]

Advantages of mini tablets over pellets:

- Pellets are small bead like structures, usually with medium to high uniformity and are usually filled into capsules or compressed into tablets.

- Technically demanding process like fluid bed granulation, extrusion or spheronization are required for the production of pellets. Whereas, mini tablets can be manufactured via simple tableting procedures.
- Unlike pellets, mini tablets does not require any solvents for its production, as a result problems with stability can be avoided.^[22]

1.4 Types of minitables:

Mini tablets can be classified based on the target site, method of manufacturing, patient needs as follows:^[23]

- a) Pediatric mini tablets
- b) Extended-release mini tablets
- c) Oral disintegrating mini tablets
- d) Gastro retentive min tablets
- e) PH responsive mini tablets
- f) Bio-adhesive mini tablets
- g) Biphasic mini tablets

a) Pediatric mini tablets:

Syrups, tablets and capsules are commonly used dosage forms for children. Syrups are liquid dosage forms which are simple to administer and dose can be easily altered to the patient needs on the other side disadvantages with these liquids dosage forms are chemical, physical, and microbial instability, taste issues, lack of controlled release and formulation problems. In case of tablets as they are big in size difficulty in swallowing and dose adjustment is difficult. Some time we have to break the tablets and administer which causes loss of activity of the tablets. Patient compliance is another issue with the conventional dosage forms. To overcome all the above issues formulating mini tablets can result in good patient acceptance. Mini tablets are easily accepted by children than other dosage forms like tablets, syrups, and capsules.^[24]

b) Extended-release (ER) mini tablets:

In this system, the active substance is gradually released for a long time. This can be achieved via extending transition time over the gastrointestinal tract or by modifying the drug diffusion from dosage form. The slow release in extended-release tablets can be obtained via changing the dissolution and diffusion of the drug over barrier coating, or matrix system.

Extended drug release could be achieved by incorporating the compound into a matrix system (membrane system or osmotic system). So far, mini-tablets have mainly been explored in the domain of sustained drug release through matrix system technology. The release of extended-release mini tablets will be slow, increasing system hydrophobicity will slow down the drug release, Hydroxypropyl methyl cellulose (HPMC) is a hydrophilic polymer, which performs an important role in forming a resistant or less permeable hydrogel layer.^[25]

c) Oral disintegrating Mini Tablets:

Oral Dispersible Tablets (ODTs) are the unique dosage form which promptly disintegrates in the mouth i.e., 1-3 minutes without the required of water, chewing upon oral administration and dissimilar other conventional oral solid dosage form. ODTs are also known as bite-dispersible, mouth-dissolve, rapidly disintegrating, fast dissolve, crunch-melt, quick-dissolve, and oral dispersible tablets. ODTs are additional proper for pediatric patients since pleasant mouth feel, fast disintegration in mouth and their lesser size.

The ODTs must have the following characters they must disintegrate in the mouth without additional water. The disintegrated tablet ought to turn into a fluid suspension or soft paste which can give smooth swallowing and great mouth feel. Because ODTs break down or deteriorate in the patient's mouth, the drug will be mostly dissolved in nearness to the taste buds. A pleasant taste inside the mouth ends up basic for patient acceptance. Unless the drug is tasteless or does not have an unwanted taste, taste-masking methods ought to be utilized. The taste-masking innovation should likewise be perfect with ODTs formulations.^[26]

d) Gastro retentive mini tablets

Gastro retentive tablets are intended to release the drug in stomach for long time. Generally, for tablets to float on the Gastro intestinal fluids, we had to formulate tablets by using gas generating agents in them. These tablets when meets food generate CO₂ and the generated gas is trapped in swellable hydrocolloid, it makes the tablet to float and retain in stomach. Drug loading is low as the polymer used for floating is high in normal single unit tablets. In mini tablets, Eudragit coating in place of swellable polymers is used in formulation to increase the drug loading and it can be coated with sodium bicarbonate or calcium carbonate as gas generating agents, Fluid bed processor can be used for coating of mini tablets.^[27]

e) pH responsive mini tablets:

The pH of human Gastro Intestinal Tract varies greatly (Stomach 1.5-3.0 upper part of small intestine Duodenum 4.0-5.0, lower parts of SI jejunum and ileum 6.5-7.5 and colon 5.6-6.9). The pH responsive drug release is required when absorption of drug is more at a site this can be achieved by coating with pH responsive release polymers like Eudragit. Generally coating is done to granules and then they are filled into capsules to achieve the required release at required pH. In case of pellets control of size and size distribution is important before coating. To get reproducible results, desirable pellet size and a narrow particle size distribution are required in pellets which are difficult to achieve. To overcome this problem in place of pellets Mini tablets can be used. Mini tablets are easy to manufacture and coating them is easy when compared to pellets as they have smooth surfaces. Uniform size can be obtained so less variation with in unit to unit. Reproducible results can be achieved by uniform coating. So, mini tablets can be used as an alternative to pellets.^[28]

f) Biphasic Mini tablets:

A biphasic mini tablet contains two parts a fast-releasing part and a slow releasing part. First part releases drug immediately after administration and the second part releases drug slowly in a controlled manner. This type can be advantageous for drugs used for hypertension where repetitive dosing can be reduced. Different drugs can be compressed in to mini tablets and can be filled in same capsules to treat different diseases.^[29]

g) Bio Adhesive Mini Tablets:

The dosage forms which are meant for vaginal drug delivery should be easy to administer without irritation or discomfort and should have uniform distribution and long maintenance time there by increasing patient compliance. The various available dosage forms for vaginal drug delivery are creams, gels, ointments and tablets. The problems with these are leakage, untidy, less patient compliance and less retention time. Nano pharmaceuticals can be used but the problem related with them is low residence time as they are liquid in nature. To overcome the above problems, we can use bio adhesive Vaginal Mini Tablets.

Bio adhesive mini tablets prepared with hydroxypropyl cellulose and HPMC have reported adequate mechanical and bio adhesive properties. The pH of vaginal varies from women to women of different ages. To withhold those pH conditions, bio adhesive vaginal mini tablets are to be designed using non-ionic cellulose ethers with bio adhesive property.

1.6.1 Steps involve in manufacturing of tablets:

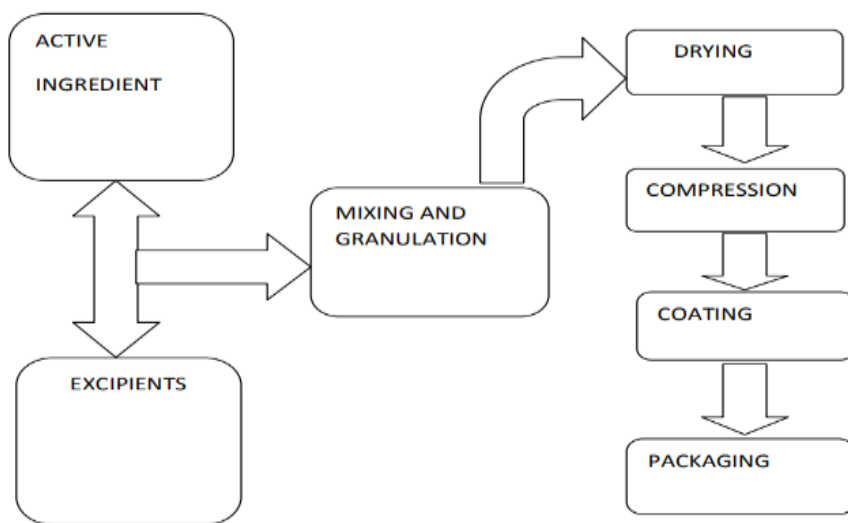


Fig.5: Manufacturing of tablets

1.7 Methods of manufacturing mini tablets:

Some of the methods that can be used for the manufacturing of mini tablets are

- i) Direct compression
- ii) Dry granulation
- iii) Wet granulation
- iv) Melt- extrusion

i) Direct compression technique: Direct compression is the process by which tablets are compressed directly from powder blends containing API and excipients directly compressed the powder blend into biconvex mini tablet. Excipients of direct compression grade are used here to get the required hardness. Stability problems are less compared to that of tablets prepared by wet granulation.^[30]

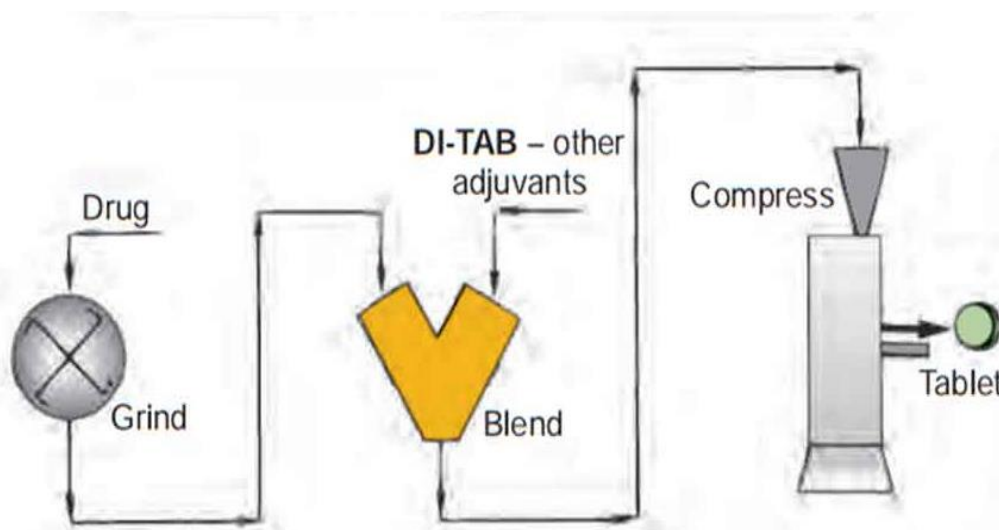


Fig. 6: Direct compression of tablets

ii) Dry granulation technique: Dry granulation is rational technique of choice for the manufacture of tablets containing thermo labile and moisture-sensitive drugs. This technique employs processing equipment known as roller compactor. This machine compresses pre-mixed powders between two counter rotating rollers under extreme pressure. The resultant material is in the form of a brittle ribbon, sheet, or piece depending

on the configuration of the roller. The compressed material is reduced to the proper size to form granules that are mixed with other in-active excipients and finally compressed on a rotary compression machine. There is another method instead of making brittle ribbon sheets, the slugs can be formed by forcing the initial blend of powders into the dies of a large capacity tablet press and is compacted by means of flat faced punches. The formed compacted masses are called 'slugs' and the process is referred as 'slugging'. The slugs are then screened or milled to produce granules. These granules are mixed with other excipients and finally subjected to compression.

iii) Wet granulation: Wet granulation involves the use of binder solution to form granules which then compressed in compression machine to get mini tablets. Polyvinyl pyrrolidone of different grades is generally used as a binding agent.^[31]

iv) Melt-Extrusion technique: In melt-extrusion technique, the powder (API + excipients) were premixed this premixed powder is then transferred to melt-extruder. In melt-extruder parameters like screw speed, feed rate and temperature are set in the range of melting point range of material. After the process the extrudates are then milled and sieved. The obtained granules are then compressed to mini tablets using compression machine.^[32]

1.7.1 Possibilities for formulating the mini-tablets dosage forms:^[17]

- a) Tablet in tablet systems
- b) Compressed mini-tablets systems are presented as a biphasic delivery system
- c) Tablet-in-capsule systems

a) Tablet in tablet systems:

There has been an increasing interest in the development of MUDFs incorporated into tablets instead of hard gelatin capsules, in order to overcome the higher production costs of capsules. Because of their size uniformity, regular shape, smooth surface, low porosity and high attainable strength, mini-tablets can maintain their structure and shape in a more reproducible way than usual pellets or granules, once they have been compressed into a tablet system. It can be hypothesized that when shape irregularity and surface roughness of the mini-particles (pellets and granules) increases, the compression behavior changes towards a more complex process that, besides deformation and densification, includes also

fragmentation and attrition of the subunits. Although less popular, tablet-in-a-tablet technology gained increased interest in the recent years for creating modified released products. This type of tablet has two parts, internal core and surrounding coat.

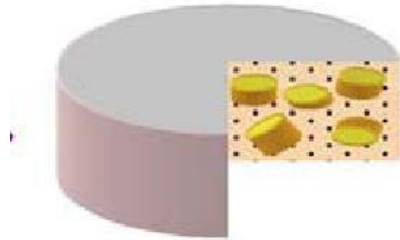


Fig.7: Compressed minitablet

The core is small porous tablet and prepared on one turret. After tablet core manufacture it is transferred (centrally positioned) to another slightly larger die that is partially filled with coating powder. More coating powder is filled on the top of the core and compressed again resulting in tablet with in tablet. Mechanically, it is a complex process, as the tablet may be tilted when transferred to the second die cavity. Mostly, the coat is water soluble and disintegrates easily after swallowing, in order to achieve immediate release product. This tablet readily lend itself in to a repeat action tablet as the outer layer provides the initial dose while the inner core-release the drug later on. But, when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose toxicity. To avoid immediate release of both the layers, the core tablet is coated with enteric polymer so that it will not release the drug in stomach while, the first dose is added in outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, inner core may be of liquid formulation to provide immediate release of core after the coat gets dissolved.^[33]

b) Compressed mini-tablets systems are presented as a biphasic delivery system:

Biphasic delivery systems are designed to release a drug at two different rates or in two different periods of time: they are either quick/slow or slow/quick. A quick/ slow-release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time and in slow/quick release system provides release vice versa. Biphasic release system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration.

Suitable candidate drugs for this type of administration include non-steroidal anti-inflammatory drugs (NSAIDs) antihypertensive, antihistaminic, and anti-allergic agents.



Fig. 8: Biphase minitables

c) Formulation of mini-tablet-in-capsule systems:

The formulation process of mini-tablet-in-capsule systems can be divided into three important steps:

- i) The formulation/production of mini-tablets,
- ii) Coating of these mini-tablets with appropriate coating polymer
- iii) Filling of coated mini-tablets into hard gelatin or HPMC capsules (Mini-tablets-in-capsule systems).

i) Formulation/production of mini tablets: ^[34]

▪ **Preparation of mini-tablets-in capsule system and granules-mini-tablets-in-capsule systems:** Formula used for the calculation of immediate-release dose. The pharmacokinetic parameters of drug were utilized for the calculation of theoretical drug release profile for coated mini-tablet-in-capsule system. The immediate-release part of drug was calculated using the following equation.

$$DL = C_{max} V_d$$

Where

C_{max} is maximum plasma concentration,

V_d is volume of distribution.

▪ **Preparation of immediate release component:** (Granules) Calculated amount of immediate-release dose drug and other suitable excipients [Microcrystalline cellulose

(Avicel PH 102)] were used because of its good compaction and disintegration properties. Any suitable super disintegrants was used to obtain an immediate release of the drug. The granules were prepared by wet granulation method.

- **Preparation of Immediate-release coated mini-tablet (IRCMT):** The IRCMT was prepared using the wet granulation method.
- **Preparation of Sustained-release coated mini-tablet (SRCMT):** The SRCMT was prepared using the same method as used for preparing the IRCMT. However, the SRCMT did not contain the any super disintegrants. A coating suspension was prepared from HPMC (5cps/15cps), ethyl cellulose, magnesium stearates, ethyl alcohol and water. Magnesium stearate was used in the coating preparation to minimize friction between the surfaces of mini- tablets, the minitables-filling system and the HPMC capsules.^[35]
- **Preparation of Coated mini-tablet-in-capsule system (CMTICS):** To prepare the CMTICS, two IRCMT and three SRCMT were placed in each HPMC capsule (size1). Both similar/different ratios of SRCMT were placed in each HPMC capsule to achieve various sustained release profiles of the CMTICS.

ii) Coating of these mini-tablets with appropriate coating polymer

Tablet coating processes in most cases, the coating process is the last critical step in the tablet manufacturing process. Successful application of the coating solution to a tablet improves the visual characteristics of the product, based on which the quality of the product can be judged. The type of coating process chosen usually depends on the type of coating material that has to be applied, whereas the durability of the tablet core depends both on the coating material and application process.



Fig.9: Coated minitables in capsule

Generally, four main types of coating procedures are used in the pharmaceutical industry:

- Sugar coating,
- Film coating,
- Compression coating,
- Enteric coating.

Encapsulated mini-tablets system usually comprises immediate-release mini-tablets (IRMT) and sustained release mini-tablets (SRMT) in a capsule made from HPMC, a water-soluble polymer. HPMC capsule which contains the mini-tablets later disintegrates and releases these subunits into the system. As several mini-tablets can be placed in each capsule, tablets with different dose, content and release characteristics can be included. Inclusion of IRMT permits the development of rapid acting dosage forms for fast action.^[36]

Encapsulated minitabiet systems can be designed to yield various sustained release drug profiles by combining different types, quantities and combinations of mini-tablets, thereby improving patient compliance. Mini-tablets are usually coated with enteric coating polymers in fluid bed coater or in modified coating pans. Enteric coating is a polymer barrier, which when applied to a drug protects it from the acidic pH of the stomach, and releases the drug in the alkaline environment of the small intestine. That is, they will not get dissolved in the acidic juices of the stomach, but breaks down in the alkaline environment of the small intestine. Materials used for enteric coatings mostly include fatty acids, waxes, phthalates, shellac, plastics, and plant fibres. Drugs that cause irritation to gastric mucosa or inactivated in the stomach, can be coated with a substance that will dissolve only in the small intestine.

Polymers used for enteric coating of mini tablets:

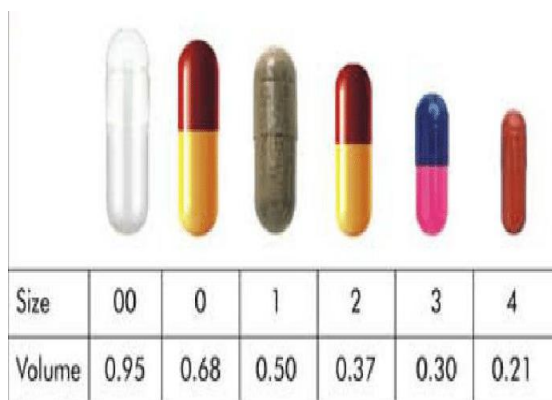
- Methacrylic acid/ethyl acrylate
- Cellulose acetate succinate
- Cellulose acetate trimellitate
- Cellulose acetate phthalate (CAP)

iii) Mini tablets can be administered by following methods:

- Directly administered as single units.
- Filled in hard gelatine capsules.
- Use of automatic Dose dispensing device.

Directly administered as single units: Mini tablets can be directly administered as such. Required dose can be easily taken and these are packed in bottles. Sometime compressed mini tablets are again compressed to get tablets of normal size.

Filled in hard gelatin capsules: As it is difficult to handle the mini tablets these are usually filled in hard gelatin capsules and then administered.



Size	00	0	1	2	3	4
Volume	0.95	0.68	0.50	0.37	0.30	0.21

Fig. 10: capsule size



Fig.11: Tablet in capsule

Automatic dose dispensing device: Dose is decided on the basis of patient population average dose individualization is important as administration of right drug in wrong dose will result in adverse effects of decreased efficiency. Generally tablets are most commonly used but limited strengths available for administration. Dividing tablets for getting required dose or combining different strengths will not give the desired therapeutic effect so an automatic dose dispensing device can used to dispense tablets of required dose.



Fig.12: Dose dispensing device

It consist of

- (A) - Cassette filled with micro tablets,
- (B) - Plastic components,
- (C) - Electronic motor,
- (D) - Photocell which monitors the number of micro tablets transported from the Mcassette to the receiving compartment
- (E) - Actuator
- (F) - Releases the micro tablets into a collecting vessel or a glass of water.
- (G) - The digital display
- (H) - The buttons used to adjust the dose.

The dose dispensing device comprises a cassette filled with micro tablets, buttons operated by the patient (with an associated digital display) for dose adjustment, a battery-driven electronic motor, a photocell monitoring the number of micro tablets dispensed from the cassette to a receiving compartment, and an actuator, by which the micro tablets are emptied from the receiving compartment into a collector or a glass of water. The usefulness of the automatic dose dispenser and patient acceptance of the device were evaluated in patients with Parkinson's disease.^[37]

1.7.2 Tooling used in compression of mini tablets:

Compression of mini tablets can be done by using different tooling when compared to tooling's that used for compression of conventional tablets. Compression of normal tablets is normally done by using single tip tooling which are interchangeable according to the requirement. Compression of mini tablets involves the use of multi tip tooling i.e., several number of tips to the same punch which allows us to compress more number of tablets at a time. The use of multi tip tooling also reduces the time required for production. The usage of multiple punches is advantageous as it shortens the filling time and thus reducing the possibility of powder segregation.^[38]



Fig.13: Various punches used for compression of minitables



Fig.14: Multi Tip punches

The benefits of using multiple punches are

- Increase productivity, shorten the working time, low cost
- Does not require a different production, only mold cost

➤ No separate equipment is required to collect the products obtained.

1.7.3 Patent in minitablets:^[39]

Patent is a property right granted to an inventor for his/her novel contribution in the scientific community and it is approved by respective sovereign authority. Various scientists have worked in the field of minitablet and their work is comprised in the below Table in form of patents.

Table 1: List of patents representing distinct minitablets

S.No	Patent No.	Patent Title	Approval Date
1	USOO6110494A	Cisapride Mini-Tablet formulations	Aug. 29, 2000
2	US8,093,261	Rapid Release Mini-tablet	Jan. 10, 2012
3	US2012/0141584A1	Multi-layer Mini-tablet	Jun. 7, 2012
4	US8,945,616B2	Controlled Release Budesonide Mini tablets	Feb. 3, 2015
5	US2015/0238425A1	Mini-Tablets	Aug. 27, 2015
6	EP3187176A1	Paliperidone mini tablets	Jul. 05, 2017
7	US2020/0054530	Dosing Device for Measuring and Dispensing Mini-Tablet	Feb. 20, 2020
8	US10,722,494B2	Melatonin Mini-Tablet and Method of Manufacturing	Jul. 28, 2020

1.8 Epilepsy:

Epilepsy is a chronic medical disorder or condition, usually resulting in unpredictable, unprovoked recurrent seizures that affect a variety of mental and physical functions. It is one of the most common neurological diseases. A “seizure” is a paroxysmal alteration of neurologic function caused by the excessive, hyper synchronous discharge of neurons in the brain. “Epileptic seizure” is used to distinguish a seizure caused by abnormal neuronal firing from a nonepileptic event, such as a psychogenic seizure. “Epilepsy” is the condition of recurrent, unprovoked seizures. Epilepsy has numerous causes, each reflecting underlying brain dysfunction.^[40]

1.8.1 Classification of Seizures:

Seizures are a symptom of epilepsy. Epilepsy types are generally into two categories, which are based on the specific biologic mechanisms involved in the seizure and the anatomical location of the seizure.^[41] The two types are:

- Partial (focal) seizures
- Generalized seizures

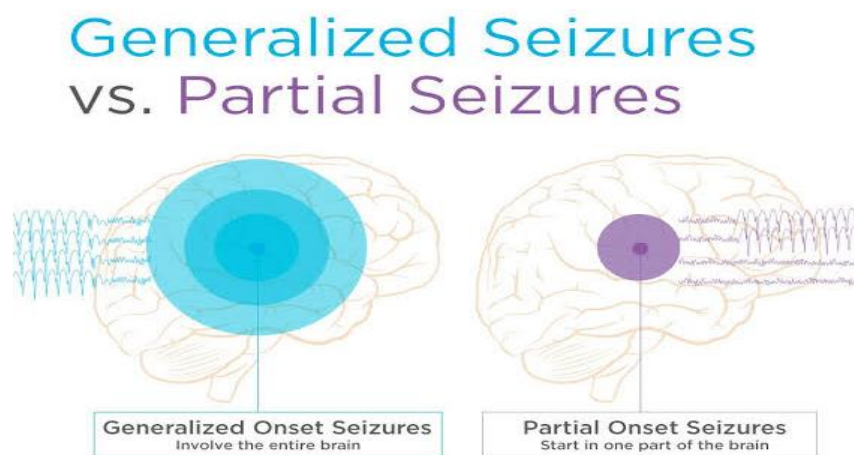


Fig. 15: Generalized and partial seizures.

- **Partial (also called focal or localized) seizures:** These seizures are more common than generalized seizures and occur in one or more specific locations in the brain. In some cases, partial seizures can spread to wide regions of the brain. They are likely to develop from specific injuries, but in most cases the exact origins are unknown. These seizures are subcategorized as "simple" or "complex partial."

• **Simple Partial Seizures:** A person with a simple partial seizure (sometimes known as Jacksonian epilepsy) does not lose consciousness, but may experience confusion, jerking movements, tingling, or odd mental and emotional events. Such events may include déjà vu, mild hallucinations, or extreme responses to smell and taste. After the seizure, the patient usually has temporary weakness in certain muscles.^[42]

• **Complex Partial Seizures:** Slightly over half of seizures in adults are complex partial type. About 80% of these seizures originate in the temporal lobe, the part of the brain located close to the ear. Disturbances there can result in loss of judgment, involuntary or uncontrolled behavior, or even loss of consciousness. They may lose consciousness briefly and appear to others as motionless with a vacant stare. Emotions can be exaggerated; some sufferers even appear to be drunk. After a few seconds, a patient may begin to perform repetitive movements, such as chewing or smacking of lips. Episodes usually last no more than 2 minutes. They may occur infrequently, or as often as every day. A throbbing headache may follow a complex partial seizure.^[43]

➤ **Generalized seizures:** These seizures typically occur in both sides of the brain. Many forms of these seizures are genetically based. There is usually normal neurologic function. Generalized seizures are caused by nerve cell disturbances that occur in more widespread areas of the brain than do partial seizures. Therefore, they have a more serious effect on the patient.

They are further subcategorized as

- Tonic-clonic (or grand mal)
- Absence (petit mal) seizures.

• **Tonic-Clonic (Grand Mal) Seizures:** The first stage of a grand mal seizure is called the tonic phase, in which the muscles suddenly contract, causing the patient to fall and lie stiffly for about 10 - 30 seconds. Some people experience a premonition or aura before a grand mal seizure. Most, however, lose consciousness without warning. If the throat or larynx is affected, there may be a high-pitched musical sound (stridor) when the patient inhales. Spasms occur for about 30 seconds to 1 minute. Then the seizure enters the second phase, called the clonic phase. The muscles begin to alternate between relaxation and rigidity. After this phase, the patient may lose bowel or urinary control. The seizure usually lasts a total of

2 - 3 minutes, after which the patient remains unconscious for a while and then awakens to confusion and extreme fatigue. A severe throbbing headache similar to migraine may also follow the tonic-clonic phases.^[44]

- **Absence (*Petit Mal*) Seizures:** Absence or petit mal seizures are brief losses of consciousness that occur for 3 - 30 seconds. Physical movement and loss of attention may stop for only a moment. Such seizures may pass unnoticed by others. Young children may simply appear to be staring or walking distractedly. Petit mal may be confused with simple or complex partial seizures, or even with attention deficit. Attention deficit hyperactivity disorder. In petit mal, however, a person may experience attacks as often as 50 - 100 times a day. About 25% of patients with petit mal develop grand mal seizures. An Electroencephalogram (EEG) test that shows a specific brain wave pattern can usually identify these patients.^[45]

Other Seizures:

- **Atonic (*Akinetic*) Seizures:** A person who has an atonic (or akinetic) seizure loses muscle tone. Sometimes it may affect only one part of the body so that, for instance, the jaw slackens and the head drops. At other times, the whole body may lose muscle tone, and the person can suddenly fall. A brief atonic episode is known as a drop attack.
- **Simple Tonic or Clonic Seizure:** Seizures can also be simply tonic or clonic. In tonic seizures, the muscles contract and consciousness is altered for about 10 seconds, but the seizures do not progress to the clonic or jerking phase. Clonic seizures, which are very rare, occur primarily in young children, who experience spasms of the muscles but not tonic rigidity.
- **Myoclonic:** Myoclonic seizures are a series of brief jerky contractions of specific muscle groups, such as the face or trunk.^[46]

1.1.2 Symptoms of seizure:

The main symptom of epilepsy is recurrent seizures. However, if a person experiences one or more of the following symptoms, they should seek medical attention, as it may indicate epilepsy:

- A convulsion with no fever, confused memory and repetitive movements
- Intermittent fainting spells, during which they lose bowel or bladder control, frequently followed by extreme tiredness
- Sudden stiffness and falling for no apparent reason
- Sudden bouts of blinking and chewing without apparent stimuli
- Fearfulness for no apparent reason and panic and anger
- Peculiar changes in senses, such as smell, touch, and sound
- Jerking arms, legs, or body, which will appear as a cluster of rapid jerking movements in babies.

1.1.3 Causes of epilepsy:

A variety of factors can contribute to the development of seizures, such as:

- Traumatic brain injury or other head trauma
- Brain scarring after a brain injury (post-traumatic epilepsy)
- Serious illness or very high fever
- Lack of oxygen to the brain and brain tumour or cyst
- Dementia, including Alzheimer's disease
- Maternal use of some drugs, prenatal injury, brain malformation, or lack of oxygen at birth
- Genetic or developmental disorders or neurological diseases.^[47]

1.1.4 Diagnosis:

Neuroimaging studies play an integral role in evaluation of seizures for the determination of the structural and functional aetiology of seizures. Various diagnostic tools are used to identify and classify the seizure type and aetiology, including Electroencephalogram (EEG), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Magneto Encephalogram (MEG), and

neuropsychiatric testing. The EEG often is critical for identifying specific seizure types. CT scan may help in assessing newly diagnosed patients, but MRI is preferred. MRI may locate brain lesions or anatomic defects that are missed by conventional radiographs or CT scans. Serum prolactin level obtained within 10 to 20 minutes of a tonic-clonic seizure can be useful in differentiating seizure activity from pseudo seizure activity but not from syncope. EEG is mostly useful in the diagnosis of various types of seizures.^[48]

1.1.5 Treatment:

Treatment should be started with a single conventional Anti-Epileptic Drug (AED). The dose should be gradually increased until seizure control is achieved. If the initial treatment is ineffective then second AED can be tried. The dose of the second drug is increased slowly until maximum tolerated dose is achieved.^[49]

➤ *Mechanism of action of antiepileptic drugs* ^[50]

Antiepileptic drugs may act mainly by one of three main mechanisms:

- i.Reducing electrical excitability of cell membranes, particularly (by blocking) the voltage dependent sodium channels which are responsible for the inward current that generates an action potential.
- ii.Enhancing GABA mediated synaptic inhibition, by inhibiting GABA transaminase or by drugs with direct GABA agonist properties; the result is increased membranes permeability to chloride ion, which reduces cell excitability.
- iii.Inhibiting excitatory neurotransmitters. e.g. Glutamate. Inhibiting T-type calcium channels (important in controlling absence seizures) or by inhibitory excitatory neurotransmitters.

Table 2: Antiepileptic Drugs Approved for the Treatment of Seizures in the U.S^[51]

S.No	Seizure type	Conventional anti-seizure drug	Recently developed anti-seizure drug
1.	<i>Partial seizures</i>		
	(i) Simple partial	Carbamazepine Phenytoin Phenobarbital Primidone Valproate	Gabapentin Lamotrigine
	(ii) Complex partial	Carbamazepine Phenobarbital Phenytoin Primidone Valproate	Gabapentin Lamotrigine
	(iii) Partial with secondarily generalized tonic clonic seizure	Carbamazepine Phenobarbital Phenytoin Primidone Valproate	Gabapentin Lamotrigine
2.	<i>Generalized seizure</i>		
	(i) Absence Seizures	Clonazepam Ethosuximide Valproate	
	(ii) Myoclonic Seizure	Valproate	
	(iii) Tonic-clonic Seizure	Carbamazepine Phenobarbital Phenytoin Primidone Valproate	

Lamotrigine: Mechanism of Action: prolongation of Na⁺ channel inactivation and suppression of high frequency firing has been demonstrated. In addition, it may directly block voltage sensitive Na⁺ channels thus stabilizing the presynaptic membrane and preventing release of excitatory neurotransmitters, mainly glutamate and aspartate.

Table 3: Marketed formulation of lamotrigine:

Generic name	Strength	Dosage form	Manufacturer
Lamictal	25,100,150,200mg	Tablets	Glaxo smithkline pharmaceuticals Ltd
Lamictal CD	2,5,25mg	Chewable tablets	
Lamictal ODT	25,50, 100, 200mg	Oral disintegrating tablets	
Lamictal XR	25,50,100,200,250,300mg	Extended-release tablets	

2. Literature Review

1. **Raghavendra Kumar Gunda *et al.*, (2015)**^[52] Formulated a sustained release tablets of lamotrigine were prepared employing different concentrations of HPMC K4M and HPMC K100M in different combinations as a rate retarding polymer by wet granulation technique using 3² factorial design. Totally nine formulations were designed and are evaluated. On the basis of evaluation parameters, the optimized formulation F5 may be used once a day administration in the management of epilepsy.

2. **S. Sangeetha *et al.*, (2011)**^[53] Study was to designed and evaluate oral sustained release tablet of lamotrigine using polymer such as HPMC K 4M, HPMC K 100M and methocel E50 LV at 15%, 25%, and 35% Concentration range. *In-vitro* release profile was studied using HPMC K4M, HPMC K100M and methocel E50 LV at three different concentration. The study proves that fluctuation in the drug release is overwhelmed when lamotrigine is administered in the form of SR tablet.

3. **Noorana tehseen *et al.*, (2013)**^[54] Prepared a minitables of pregabalin. The system comprises of 15 matrix mini-tablets weighing 25 mg encapsulated in HPMC capsule (size1). For achieving the sustain release profile, various viscosity grades of Hydroxy propyl methyl cellulose polymer (HPMC K4M, K15M, K100M) were used. The *in-vitro* performance of our best mini-tablets formulation showed the desired behavior, nearly 99.57 % of drug was sustained for a period of 12 hrs.

4. **B.Ramu *et al.*, (2015)**^[55] Developed fast disintegrating tablets of Lamotrigine. New generation super disintegrates Solutab, Explotab and Polyplasdone XL was selected as super disintegrates. Among all the formulations F4 formulation showed maximum % drug release i.e., 97.54 % in 10 min hence it is considered as optimized formulation. The f4 formulation contains Solutab as super disintegrate in the concentration of 20 mg. F8 formulation also showed maximum percentage drug release i.e., 101.8% in 10 min.

5. **Sagar *et al.*, (2021)**^[56] Study based on conventional compressed tablets and capsules are associated with certain limitations associated to their varying plasma drug concentration, requirement of multiple dosing and difficulty in swallowing. Pharmaceutical Mini-tablets (MTs), seem to circumvent the above-mentioned limitation and can facilitate oral administration in pediatric and geriatric patients with minimal swallowing difficulty which

can be attributed to their small diameter ≤ 4 mm. By reducing the fluctuations in drug release profile, MTs can deliver the therapeutic agent efficiently with desired release pattern.

6. **Suresh Gautam *et al.*,(2020)^[57]** Developed and evaluated a solid dispersions of lamotrigine were prepared with soya lecithin by the solvent method. Solid dispersion with maximum drug content (77.68%) and dissolution rate (91.40%) was formulated as an orodispersible tablet and characterized for its pharmaceutical properties. It can be concluded that the solid dispersion of lamotrigine incorporated with soya lecithin demonstrated enhanced solubility and dissolution rate may have potential clinical application.

7. **Asha Paul, K.M *et al.*,(2017)^[58]** Developed an intranasal mucoadhesive formulation of Lamotrigine (LTG) loaded in-situ gel, for the treatment of epilepsy to avoid possible side effects and first pass metabolism associated with conventional treatment. Lamotrigine was loaded into different polymeric solutions of gellan and xanthan gum. This study was concluded as antiepileptic drug lamotrigine which could enhance nasal residence time with increased viscosity and mucoadhesive character and provided better release profile of drug for treating acute epileptic conditions.

8. **Jeannine M. Conway *et al.*,(2014)^[59]** We developed a stable-labelled IV formulation of lamotrigine (LTG) for studying pharmacokinetics in epilepsy patients. Stable-labeled IV LTG was given to 20 persons with epilepsy (6 men; 14 women) with a mean age of 34.8 years . A 50 mg dose of LTG (stable labeled) was given intravenously and replaced 50 mg of the regular morning oral dose of LTG. No significant changes in blood pressure, heart rate, or adverse events including rash were attributed to administration of a 50-mg dose of the intravenous LTG formulation. Our results showed that LTG base that is complexed with 2-hydroxypropyl- β -cyclodextrin and stable-labeled can be given safely as a tracer replacement dose.

9. **Prasad Rao Manchineni *et al.*,(2020)^[60]** Investigated to study the effect of various super disintegrants on the dissolution characteristics of Lamotrigine by formulating oral disintegrating tablets (ODT). ODT formulations of Lamotrigine were prepared using different quantities of Sodium Starch Glycolate (SSG) & Crospovidone (CP) employed as Super disintegrants by Direct Compression technique as per 32 Factorial Design. Formulation (F4) containing 35 mg of Sodium Starch Glycolate & 40 mg of Crospovidone

was found to be best one among all and also similar to the Marketed product (LAMICTAL-25) & no significant difference to marketed product.

10. **Prashanta Kumar Panda *et al.*,(2021)^[61]** study was formulated and characterized the mucoadhesive tablets of Lamotrigine employing different proportions of natural polymer acquired from the Okra and Hibiscus rosasinensis. The findings showed the formulations containing higher amounts of gum Okra and Hibiscus rosasinensishave better mucoadhesion strength. The mucoadhesive tablets of Lamotrigine enhanced the systemic absorption due to higher permeability with a rich blood supply to mucus layer.

11. **PK Lakshmi *et al.*,(2013)^[62]** study was to developed lamotrigine (LM) bilayered and single layered floating tablets and to compare their release profiles. Drug, hydroxy propyl methyl cellulose K4M, lactose monohydrate and polyvinylpyrrolidone K30 constitute controlled release layer components and floating layer components includes polymers and sodium bicarbonate. The Hydroxypropyl cellulose (hydrophilic polymer) which showed good floating and duration for 16 h. This study demonstrated that the *invitro* development of bilayered gastro retentive floating tablets with controlled drug release profile for LM is feasible.

12. **Shaikh Siraj Nawaj *et al.*,(2018)^[63]** Developed & optimized sustain release Minitablet of Telmisartan. Mini tablets of Telmisartan were prepared by direct compression method using HPMC K 200M and Carbopol 940 release retarding agents. The prepared Mini tablets exhibited satisfactory physic-chemical characterise full factorial design and optimization technique successfully used in the development of Mini tablet. Comparing the all the formulations, formulation H5 was considered as optimized formulation which exhibited 97.87% of drug release in 12 hours also stable in stability.

13. **Nikhil Biswas *et al.*,((2014)^[64]** Study was to develop and internally validate a nonlinear *invitro in vivo* correlation model for a chrono therapeutically programmed HPMC based propranolol HCl(PHCl) mini-tablet. A simple and sensitive HPLC method was developed for the determination of PHCl content in rabbit plasma. The influence of tri-sodium citrate (TSC) on release behaviour was investigated through *in vitro* dissolution and *in-vivo* absorption. Prediction errors were investigated for Cmax and AUC in the light of US FDA

guidelines for average percent prediction error. *In vitro* optimized formulation showed nearly 4.5 h lag time and rapid drug release $97.11 \pm 1.87\%$ in 6 h.

14. **Poonuru R.R et al.,(2014)**^[65] Developed a Gastro retentive bimodal drug delivery systems of lamotrigine using immediate release and extended release segments incorporated in a Hydroxypropyl methylcellulose capsule and *in vitro* and *in vivo* evaluations were conducted. *In vivo* radiographic studies were carried out for the optimized formulation in healthy human volunteers with replacement of drug polymer complex by barium sulphate and the floating time was noted. The results of release studies of formulations shown that as the percentage of polymer increased, the release decreased. Extended its drug release up to 12th hour with 99.59% drug release following zero order kinetics with R² value of 0.989.

15. **Srinija K et al.,(2016)**^[66] Designed to core in cup (In lay) buccoadhesive tablets which aims for controlled, unidirectional release, increased patient compliance and decreased side effects. The present study involves the preparation of core in cup tablets containing release retarding polymers like sodium alginate, xanthan gum and HPMC E 15LV in core and HPMC K 15M in cup for mucoadhesion. The dependent variable studied for L9 orthogonal array Taguchi runs include % drug release from which the formulation with highest S/N ratio was optimized. L1, L2, L4 and L8 formulations showed controlled release for up-to 8 hours with good assay values.

16. **Peter Gieszinger et al.,(2020)**^[67] Investigated with Nanocapsules (NCs) have become one of the most researched nanostructured drug delivery systems due to their advantageous properties and versatility. NCs can enhance the bioavailability of hydrophobic drugs by improving their solubility and permeability. The results indicate that the formulation could be a promising alternative of lamotrigine (LAM) as the NCs were around 305 nm size with high encapsulation efficiency (58.44%). Moreover, the LAM showed rapid and high release from the NCs *in vitro* and considerable penetration to the brain tissues was observed during the *in vivo* study.

17. **Jigar Lalani et al.,(2015)**^[68] Study was to develop surface-engineered Lamotrigine(LTG) nanoparticles (NPs) using transferrin and lactoferrin as ligand to deliver higher amount of drug to brain and improve the biodistribution and pharmacokinetic profile of drug with prolonged duration of action and reduced accumulation in nontarget organs.

The LTG NPs were prepared by nanoprecipitation and optimized by factorial design for high entrapment and optimized particle size. Both biodistribution and pharmacodynamic study in mice confirmed that the approach used for LTG can help to increase clinical applications of LTG due to brain targeting and reduced side effects.

18. **Marilena Vlachou *et al.*,(2017)^[69]** Mono-layered and three-layered minitablets, filled into capsules were prepared using theophylline and dextran or pectin as excipients. Their release behavior was compared with respect to powder filled capsules and the commercially available Theodur® 20mg tablets. Dissolution tests were performed in three pH media (1.5, 7.4 and 6.0) in the presence and absence of the enzyme Pectinex® Ultra SP-L solution, which degrades polysaccharides. The product, Pectinex® Ultra SP-L, was found to give more accurate dissolution results when used as an additive to the media, mimicking the large intestine/colon area especially when the formulations target this region.

19. **Bibaswan Mishra *et al.*,(2017)^[70]** Formulated rapid dissolving films containing lamotrigine using different viscosity grade of HPMC. The prepared films can be used in the treatment of epilepsy and bipolar disorder with a view to improve the onset of action The effect of various viscosities of HPMC alone and in blend on various properties of film was investigated. Hence lamotrigine can be safely incorporated into the film and used as antiepileptic whenever quick on set of action is desired.

20. **Jilby Saju *et al.*,(2018)^[71]** The study was concerned with the development and characterization of a novel nanoparticulate system containing hydrophobic AED, Lamotrigine for brain targeting to improve the bioavailability, patient compliance and reducing the strength of the drug. Using Carboxymethyl chitosan (CMC) nanoparticles as a carrier. Lamotrigine loaded CMC nanoparticles were prepared by a solvent evaporation method. The drug-loaded nanoparticle is mainly integrated into an in-situ gel for active targeting to the brain and for easy administration, thus providing quick action prepared formulation were subjected to characterization *in-vitro* and *in-vivo* drug release studies.

21. **Arshiya Praveen *et al.*,(2018) ^[72]** Lamotrigine nanoliposomes (LTG-NLs) was prepared to using thin film hydration and rehydration method using the phospholipon 90G, cholesterol and tween 80 as main ingredients. The results showed that LTGNLopt shown nano size with high entrapment and drug release. From the study, it was concluded that the

independent variables used to optimize the NLs shown significant effect on the dependent variables and consider effective lipid carrier system for intranasal delivery.

3. Aim of the Investigation

The purpose of this study is to Development and evaluation lamotrigine (LTG) 200 mg extended-release minitablets using HPMCK100 M and HPMC K4 M as release modifiers. The Minitablets, to be produced by direct compression technique. A 3²-full factorial design is planned for two polymers (HPMC) with three different levels. T50 and Tensile strength to be used as dependent variable. The proposed weight of Minitablets is 55 mg. Hence, around 8 minitablets, each contains 25 mg of LTG to be filled in to 0 size Capsule. The optimized formulation to be studied for *in vivo* (pharmacokinetics) animal study using rat model (Approved by IAEC at CL Baid Metha College of Pharmacy) and complete evaluation for capsule dosage for also to be carried out.

4. Plan of work

1. Literature review:

- Selection of drug based on literature
- Selection of polymer based on literature

2. Preformulation study:

- Selection of punches and die
- Raw material analysis of lamotrigine
- Drug and excipient interaction study by FT-IR

3. Formulation and Development:

- Design of experiment 3^2 full factorial design
- Formulation of lamotrigine extended release minitables
- Evaluation of blend
 - Angle of repose
 - Bulk density and tapped density
 - Compressibility index
 - Hausner's Ratio
- Compression of minitables

4. Evaluation:

- Characterization of physical properties of minitables
 - Weight variation
 - Thickness
 - Tensile strength
 - Friability
 - Content uniformity
 - Swelling study
 - *In-vitro* drug release
- Optimization by Stat –Ease
- Development of optimized formulation
- Evaluation of developed minitables formulation
- *In-vivo* study for optimized formulation.

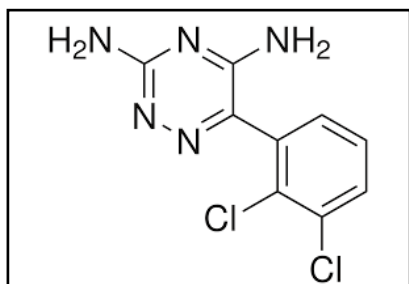
5. Drug Profile

5.1 Drug name: Lamotrigine.^[73]

Synonyms: lamotrigine, lamotriginum, Lamictal

Category: Antiepileptic drug

Structure:



IUPAC name: 6-(2,3- dichlorophenyl)-1,2,4-triazine-3,5-diamine

Molecular formula: C₉H₇Cl₂N₅

5.2 Physical properties:

Appearance: White to pale cream-colored powder

Molecular weight: 256.09

Solubility: In water 0.17 mg/ml and in 0.1 M HCl, 4.1 mg/ml at 25°C and in ethanol is approximately 1 g/L.

PKa: 5.7

Melting point: 216-218°C

5.3 Clinical pharmacology:

5.3.1 Drug indication:

Lamotrigine is indicated as adjunctive therapy for the following seizure types in patients ≥ 2 years of age: partial seizures, primary generalized tonic-clonic seizures, and generalized seizures due to Lennox-Gastaut syndrome. It is also indicated for the process of conversion to drug monotherapy for those at least 16 years of age or older with partial seizures and

currently are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED). In addition to the above, lamotrigine is also indicated for the maintenance treatment of bipolar I disorder, delaying the time to mood episodes (which may include mania, hypomania, depression, mixed episodes) in adults at least 18 years or older, who have been treated for acute mood symptoms with standard therapy. Limitations of use It is important to note that lamotrigine should not be used in the treatment of acute mood episodes, as efficacy has not been established in this context.

5.3.2 Mechanism of action:

The exact mechanism of action of lamotrigine is not fully elucidated, as it may exert cellular activities that contribute to its efficacy in a range of conditions. Although chemically unrelated, lamotrigine actions resemble those of phenytoin and carbamazepine, inhibiting voltage-sensitive sodium channels, stabilizing neuronal membranes, thereby modulating the release of presynaptic excitatory neurotransmitters. Lamotrigine likely acts by inhibiting sodium currents by selective binding to the inactive sodium channel, suppressing the release of the excitatory amino acid, glutamate. The mechanism of action of lamotrigine in reducing anticonvulsant activity is likely the same in managing bipolar disorder.

5.3.4 Dosage and Administration

The initial recommended monotherapy dosage is 25 mg/day orally which is gradually increased to 200 mg/day over 6 weeks. Dosages over 200 mg/day as monotherapy are not recommended, as no additional efficacy has been demonstrated in clinical trials evaluating dosages up to 400 mg/day. For patients taking valproate semisodium, the initial recommended lamotrigine dosage is 25mg every other day and the target dosage is 100 mg/day from week 6.

5.4 Pharmacokinetics:

➤ Absorption:

Lamotrigine is rapidly and entirely absorbed with minimal first-pass metabolism effects, with a bioavailability estimated at 98%. C_{max} is reached in the range of 1.4 to 4.8 hours post-dose, but this depends on the dose administered, concomitant medications, and epileptic status. The rate and extent of lamictal absorption is considered equivalent between

the compressed tablet form taken with water to that of the chewable dispersible tablets, taken with or without water.

- **Plasma protein binding:** 55-68%
- **Metabolism:** Lamotrigine is mainly glucuronidated, forming 2-N-glucuronide conjugate, a pharmacologically inactive metabolite
- **Volume of distribution:** (Vd/F) of lamotrigine following oral administration ranges from 0.9 to 1.3 L/kg and is independent of dose administered
- **Elimination half-life:** The average elimination half-life of lamotrigine ranges from approximately 14-59 hours. The value is dependent on the dose administered, concomitant drug therapy, as well as disease status.
- **Clearance:** 1.6–2.6 L/h

5.5 Pharmacodynamics:

5.5.1 Drug interaction:

Lamotrigine pharmacokinetics appear not to be significantly altered by many commonly used psychotropic agents, nor does lamotrigine alter the pharmacokinetics of lithium. However, enzyme-inhibiting drugs (e.g. valproate semisodium) increase lamotrigine plasma concentrations and enzyme-inducing drugs (e.g. carbamazepine) decrease lamotrigine concentrations. Lamotrigine appears not to have clinically significant reciprocal effects on the pharmacokinetics of these drugs.

5.5.2 Adverse effect:

The side effect profile is different for different patients. The most common side effects associated with LTG are dizziness, nausea, vomiting, headache, stomach pain, diarrhea, fever, sore throat, drowsiness and tired feeling.

5.5.3 Therapeutic uses:

- Anticonvulsants; Calcium Channel Blockers; Excitatory Amino Acid Antagonists; Voltage-Gated Sodium Channel Blockers.
- Lamotrigine has been shown to be an effective maintenance treatment in patients with bipolar I disorder who have had a recent depressive or manic/hypomanic episode.

- Lamotrigine is used alone or with other medications to prevent or control seizures. (epilepsy).
- Lamotrigine as adjunctive therapy for the following seizure types in patients aged 2 years and older: partial-onset seizures, primary generalized tonic-clonic (PGTC) seizures, generalized seizures of Lennox-Gastaut syndrome.
- It indicated for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED).

5.5.4 Toxicity:

Overdose with lamotrigine has been manifested by ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay. Though no known antidote exists for lamotrigine, hospitalization and general supportive measures should be employed in the case of a suspected lamotrigine overdose. Gastric lavage and emesis may be warranted with simultaneous protection of the airway. It is uncertain at this time whether hemodialysis is an effective means of removing lamotrigine from the systemic circulation.

6. Polymer Profile:

6.1 Hypromellose:^[74]

Nonproprietary Names:

BP: Hypromellose

JP: Hydroxypropylmethylcellulose

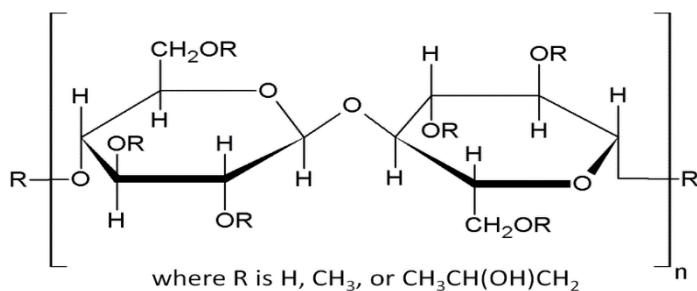
PhEur: Hypromellosum

USP: Hypromellose

Synonyms:

Benecel MHPC, HydroxyPropyl MethylCellulose(HPMC); Methocel; methylcellulose propylene glycol ether, Methyl hydroxypropyl cellulose.

Structure:



Chemical Name and CAS Registry Number:

Cellulose hydroxypropyl methyl ether [9004-65-3]

Description: Odorless and tasteless, white or creamy-white fibrous or granular powder.

Molecular Weight: 86,000

Bulk Density: 0.25-0.75 g/cm³

Functional Category Coating agent:

Film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent

Solubility:

Soluble in cold water forming a viscous colloidal solution, insoluble in alcohol, ether and chloroform, but soluble in mixtures of methyl alcohol and methylene chloride. Certain grades are soluble in aqueous acetone, mixtures of methylene chloride and isopropyl alcohol and other organic solvents.

Grades: Methocel K100 Premium LV, Methocel K4M, K15M, K100M, Metolose 60SH, 65SH, 90SH.

Stability: Stable material, although it is hygroscopic after drying.

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution Density (true) : 1.326 g/cm³

Melting point: Browns at 190–200°C; chars at 225–230°C.

Glass transition temperature is 170–180°C.

Viscosity: Ranges from 3-100000 mPa s.

Methocel K100M (100000 mPa s),

Methocel K15M (15000 mPa s),

Methocel K4M (4000 mPa s)

Stability and Storage Conditions:

Very stable in dry conditions. Solutions are stable at PH 3.0 -11.0. Aqueous solutions are liable to be affected by microorganisms. When used as a viscosity increasing agent in ophthalmic solutions, an anti-microbial agent, such as benzalkonium chloride, should be incorporated. Store in a tight container, in a cool place. Incompatibility: Extreme pH conditions, oxidizing materials.

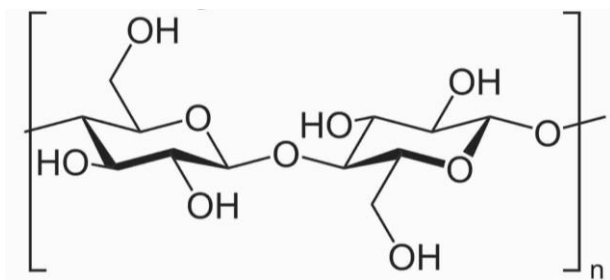
Uses:

It is used as film former (2-10%), binder (2-5%). High viscosity grades are used to retard the release of water- soluble drugs. It is also used as emulsifier, suspending agent and stabilizer in gels and ointments Adhesive in plastic bandages.

6.2 Microcrystalline cellulose:^[75]

Synonyms: Avicel PH, Celex, Cellulose gel, Celphere, Ceolus KG, Crystalline cellulose, E460, Emcocel, Ethispheres, Fibrocel and Pharmacel.

Structural formula:



Functional Category:

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Description:

It is purified, partially depolymerised cellulose, which occurs as white, odorless, tasteless, dry powder composed of porous particles. It is available in various particle size and moisture grades.

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

pH: 5.0 to 7.0

Table 4: Grade of MCC

Grade	Bulk Density	Tapped Density	Nominal Mean Particle Size
PH 101	0.320 g/cm ³	0.386 g/cm ³	50 Micro meter
PH 102	0.307 g/cm ³	0.3709/Cm ³	100 Micro Meter

Melting point: Chars at 260-270°C.

Incompatibilities: Incompatible with strong oxidizing agents.

Stability and Storage:

It is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place

Uses:

It is widely used as a diluent/binder (20 – 90 % w/w). As a tablet disintegrant (5-15% w/w).

It can be used as an adsorbent, antiadherent (20- 90% w/w).

6.3 Pregelatinised starch:^[76]

Nonproprietary Names:

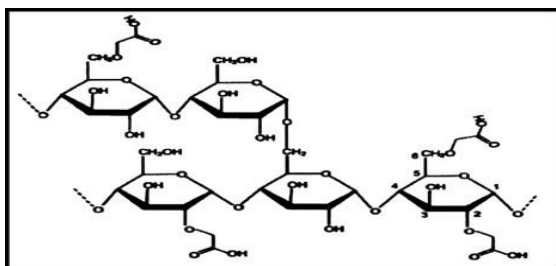
BP: Pregelatinised Starch

PhEur: Starch, Pregelatinised

USP-NF: Pregelatinized Starch

Synonyms: Corn starch, Corn starch (pregelatinized), Corn starch, pregelatinized, Maize starch, Pregelatinize d corn starch 1551 ,Starch 1500, Starch 1500 pregelatinized. Starch, corn (spress B820)

Structure:



Chemical name: Pregelatinized starch

Molecular Formula: C₁₂H₂₂O₁₁

Molecular Weight: 342.295 g/mol

Melting Point: 256-258°C

Functional Category: Tablet and capsule diluents, Tablet and capsule disintegrants, tablets binder

Description:

Pregelatinized starch occurs as a moderately coarse to fine, white to off-white colored powder. It is odourless and has a slight characteristic taste.

Stability and storage condition:

Pregelatinized is a stable but hygroscopic material, which should be stored in a well closed container in a cool, dry place.

Application and Pharmaceutical Technology:

Partially Pregelatinized starch is a modified starch used in oral capsule and tablet formulation as binder, diluents and disintegrant. In comparison to starch, Pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry compression or direct compression process. In such processes, Pregelatinized starch is self-lubricating.

Safety:

Pregelatinized starch and starch are widely used in oral solid-dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and non-irritant excipient. However, oral consumption of large amounts of pregelatinized starch may be harmful.

7. Materials and Instrumentation

7.1 Materials used in the formulation of extended release minitables:

Table 5: List of Ingredients used in formulation

S.No	Ingredients	Manufacturer/supplier	Category
1	Lamotrigine BP/Ph.Eur	CTX Life Sciences Pvt. Ltd. Gujarat, India	Active Pharmaceutical Ingredients (API)
2	Hydroxy Propyl Methyl Cellulose (HPMC) (Methocel-K4M)	DDP Speciality Electronic Materials US, Midland USA	Polymer
3	Hydroxy Propyl Methyl Cellulose (HPMC) (Methocel-K100M)	DDP Speciality Electronic Materials US, Midland USA	Polymer
4	Partially pregelatinized maize starch (1500)	Colorcon, Indiana USA	Binder/ disintegrant
5	Micro crystalline cellulose (Avicel-PH 102)	Dupont Nutrition & Health (N&H), Ireland	Filler/Binder
6	Talc BP/Ph.Eur	Imerys Talc Italy	Glidant
7	Magnesium stearate BP	Nitika Pharmaceutical Specialities Pvt. Ltd, India	Lubricant

7.2 Equipment used in formulation of minitablets:

Table 6: List of equipment used in formulations

S.No	Equipment /Instruments	Manufacturer / supplier
1	Digital Weighing Balance	Sartorius GE 212, Germany.
2	Rotary Tablet Press (8 station)	Kambert KMPC-DB-8, India
3	Vernier caliper	Mitutoyo, Japan
4	Moisture Balance	Sartorius MA 150, Germany
5	Friabilator FT 1020	Labindia, India
6	Tablet Hardness Tester	Sotax MT 50
7	Disintegration Tester DT 1000	Labindia, India
8	Dissolution apparatus TDT-0P	Electrolab, India
9	Ultrasound sonicator	Leela Electronics, India
10	UV-Visible Spectrophotomer UV 1800	Shimadzu, Japan
11	FT-IR Spectrometer 104 MB	ABB Bomem, Canada
12	High Performance Liquid Chromatography (C18 column)	Shimadzu SPD-20A, Japan

8. Methods

8.1 Raw material analysis of lamotrigine:

8.1.1 Physical Appearance:^[77]

Physical appearance of drug was examined by various Organoleptic properties.

8.1.2 Melting point:

Melting point of the lamotrigine was determined by capillary fusion method. One sided closed capillary filled with drug and put into the Melting Point Apparatus. Temperature was noted at which solid drug changed into liquid.

8.1.3 Determination of Solubility:

The solubility of lamotrigine was determined in different solvent systems and buffers. An excess quantity of the drug was mixed with 10 ml of each solvent in screw capped glass tubes and shaken on constant water bath shaker for 24 hours at 25°C. The solutions were examined physically for the absence or presence of drug particles and also by spectrophotometrically for quantitative determination of drug in buffers.

8.1.4 Percentage purity:

8.1.4.1 Assay:^[78]

Lamotrigine standard was accurately weighed (10.0 mg) and dissolved with 10 ml of 0.01 M HCl in a 20 ml volumetric flask. It was kept in an ultrasonic bath for 15 minutes. The volume was completed with the same solvent ($500 \mu\text{g mL}^{-1}$). An aliquot of 2.0 mL of this solution was diluted in a 50 mL volumetric flask, and the volume was completed with the same solvent ($20 \mu\text{g mL}^{-1}$). The absorbance of solution was measured at 267nm using UV-spectrophotometer.

8.2 Preformulation studies:

Preformulation studies is the first step in the rational development of dosage forms. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

8.2.1 Drug- excipient compatibility studies by FT-IR:^[79]

The compatibility between the pure drug and excipients was detected by FT-IR spectra using KBr disc method. 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity of finely powered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The pellet was scanned from 4000 to 400 cm⁻¹. The resultant spectrum was compared for any spectral changes. They were observed in the presence of characteristic peaks for the respective functional group in the compound. The result were shown in the **Table: 18-20** and **Fig :16-18**

8.2.2 Preparation of calibration curve of lamotrigine:^[55]

100 mg of Lamotrigine was accurately weighed and dissolved in little amount of methanol and make up the final volume up to 100 ml with 0.1 M HCl (pH 1.2) to prepare stock solution. The 10 ml of stock solution was further diluted with 0.1 M HCl (pH 1.2) in 100ml to get 100µg/ml (working standard). Then 0.5, 1, 1.5, 2 and 2.5 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1M HCl to prepare 5, 10, 15, 20 and 25µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 244 nm against 0.1 M HCl (pH 1.2) as blank. The absorbance of lamotrigine in different concentration is showed in Table and in Fig.

8.3 Design of Experiment (DOE):^[52]

Experimental design is a systematic and scientific approach to study the relationship and interaction between independent and dependent variables. A 3 level 2 factor full factorial design 3² was used to optimize the lamotrigine Extended release minitables using Design Expert 11.1.2 [stat Ease. Inc.] The concentration of HPMC K4M (A) and HPMC K100M (B) was optimized by using Design of Experiment DoE) at three different levels Low (-1), medium (0) and high (+). Percentage of drug release and Tensile strength were selected as response variables. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the formulation responses. Polynomial equation for 3² full factorial designs is given in Equation

$$Y= b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11} X_1^2+b_{22} X_2^2 \dots\dots\dots(1)$$

Where Y is the response, b_0 is the arithmetic mean response of the 9 runs. The responses in the above equation Y are the quantitative effect of formulation components or independent variables A and B; b_0 is the arithmetic mean response; b_1, b_2, b_3, b_4 and b_5 are the estimated coefficient for the factor A and B.

Table 7 : Coded values of Independent variables

S.No	Factors	Low level (-)	Medium level (0)	High level (+)
1	A (HPMC K4M)	4	8	12
2	B (HPMC K100M)	2	4	6

Table 8 : Full factorial design layout

S.No	Formulation	Factors	
		A (HPMC K4M)	B (HPMC K100M)
1	F1	4	4
2	F2	4	6
3	F3	8	2
4	F4	8	4
5	F5	12	4
6	F6	8	6
7	F7	12	2
8	F8	12	6
9	F9	4	2

8.4 Formulation of lamotrigine extended release minitables:

The minitables was prepared by direct compression method. Lamotrigine, HPMC K4M & K100M, partially pregelatinized starch and Avicel PH-102 were accurately weighed and passed through sieve #30. Each formulation of ingredients as shown in Table were mixed in a polybag. Talc and magnesium stearate were finally added after passing through sieve

number #30 and mixed properly. The powder were then compressed into tablets of 55mg using 5mm punch.

Table 9: Ingredients used for the formulation of minitables

S.No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Lamotrigine	25	25	25	25	25	25	25	25	25
2	HPMC K4M	4	4	8	8	12	8	12	12	4
3	HPMC K100M	4	6	2	4	4	6	2	6	2
4	Partially pregelatinized maize starch	10	10	10	10	10	10	10	10	10
5	Microcrystalline cellulose	11	9	9	7	3	5	5	1	13
6	Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
7	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total weight (mg)		55	55	55	55	55	55	55	55	55

8.5 Evaluation of micromeritics properties:^[55]

The physical properties of pharmaceutical powders were of utmost importance in the pharmaceutical industry. The knowledge of their flow properties was of critical significance in operations such as blending, tablet compression, capsule filling, transportation, and in scale-up operations. Powders flow properties are measured using a number of parameters such as the angle of repose, compressibility index (Carr's index) and Hausner's ratio.

8.5.1 Angle of repose:

The angle of repose is the steepest angle of descent or dip relative to the horizontal plane to which a material can be piled without slumping. The angle of repose can be range from 0 to 90°. When the angle of repose exceeds 50 degrees, the flow is rarely acceptable for manufacturing purposes.

Procedure:

- A Funnel is fixed at a particular height ‘h’ cm on burette stand. A white paper is placed below the funnel on the table.
- The given powdered drug whose angle of repose is to be determined is passed slowly through the funnel, until it forms a pile.
- Further addition on drug is stopped as soon as the drug pile touches the tip of the funnel. Circumference of the pile of the drug is drawn with a pencil without disturbing the pile.
- The radius of the pile is noted as ‘r’ cm. Angle of repose θ of this drug is calculated by using the formula.

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

Where,

θ = angle of repose.

h = height of the cone.

r = radius of the cone base.

Table 10: Angle of repose with flow properties

Flow Properties	Angle of Repose (θ)
Excellent	Upto 20
Good	Upto 30
Fair/reasonable	Upto 40
Flow with difficulty	Above 50

8.5.2 Apparent bulk density:

The bulk density was determined by transferring the accurately weighed sample of powder to the graduated cylinder. The initial volume and weight were noted. Ratio of weight of the sample will be calculated by using the formula.

$$\text{Density} = \text{Mass/Volume}$$

8.5.3 Tapped density:

Weighed powder sample was transferred to a graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (500). The tapped density was determined by the formula.

$$\text{Density} = \text{Mass/Tapped volume}$$

8.5.4 Carr's Index:

Based on the poured density and tapped density, the percentage compressibility of the granules was computed using the Carr's compressibility index by the formula and the Carr's index value and its specifications are given in Table 11.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

Table 11: Carr's Index Values

S.No	% Compressibility	Type of flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	>40	Extremely poor

8.5.5 Hausner,s ratio:

It indicates the flow properties of powder and is measured by the ratio of tapped density to bulk density Table 12.

$$\text{Hausner 's ratio} = \text{Tapped Density} / \text{Bulk Density}$$

Table 12: Hausner's ratio limits

Hausner's ratio	Type of flow
<1.25	Good flow
>1.25	Poor flow

8.6 Evaluation of minitables:

8.6.1 Weight variation:

20 minitables were selected randomly, individually each tablet was weighed in a single pan electronic balance and the average weight was calculated. The uniformity of the tablets was determined according to I.P specifications. As per I.P not more than two of the individual weight should deviate from the average weight by not more than 10%. The limits are given in Table 13.

Table 13: Limits as per monograph

S.No	IP/BP	Limit	USP
1	80 mg or less	±10%	130 mg/less
2	More than 80 mg or less than 250 mg	±7.5%	130 mg to 324 mg
3	250 mg or more	±5%	More than 324 mg
4	80 mg or less	±10%	130 mg or less

8.6.2 Thickness:

The thickness of the minitabket is important for uniformity of tablet size. Thickness was measured using vernier calipers. It was determined by checking the thickness of ten tablets of each formulation. Results are shown in Table 22.

8.6.3 Hardness:

Hardness is termed as the minitabket crushing strength and it is the force required to break a tablet diametrically. Hardness of tablets was measured by selecting 5 tablets randomly and the hardness of each tablet was measured with Hardness tester. The hardness was noted. The hardness is usually measured in terms of kg/cm² or Newton (N).

8.6.4 Tensile strength:^[36]

The tablet hardness tester was used to determine crushing strength(F) of minitabkets. Tensile strength of the mini-tablets was calculated using the standard tensile strength formula,

$$\sigma_t = \frac{2F}{\pi dt}$$

Where,

F- Crushing strength (N)

d - Tablet diameter (mm)

t - Tablet thickness (mm)

8.6.5 Friability:

6.5g of minitabkets were weighed and the initial weight of these tablets was recorded and placed on Roche friabilator and rotated at the speed of 25 rpm for 100 revolution. The tablets were then removed from the friabilator, dusted off the fines and again weighed and the weight was recorded. Percentage friability was calculated by using the formula

$$\% \text{ Friability} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

8.6.6 Content uniformity:^[78]

Twenty tablets were accurately weighed and finely powdered. An amount equivalent to 25 mg of lamotrigine was transferred to a 50 ml volumetric flask with 25 ml of 0.01 M HCl. This volumetric flask was kept in an ultrasonic bath for 15 minutes and shaken by a mechanical shaker for 15 minutes. The volume was completed with the same solvent (500 $\mu\text{g mL}^{-1}$), and the solution was filtered. An aliquot of 2.0 mL of this solution was diluted in a 50 mL volumetric flask, and the volume was completed with 0.01 M HCl (20 $\mu\text{g mL}^{-1}$). The absorbance of solution was measured at 254 nm using UV-visible spectrophotometer.

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labelled drug content can be considered as the test was passed.

8.6.7 Swelling study:

The swelling behaviors of all extended-release formulation were studied. The initial weight of the minitables (W_1) were noted and placed individually into petri dish containing pH 6.8 buffer. The tablet was removed and weight was noted (W_2) after lightly blotted with tissue paper. The swelling index was calculated by the following formula,

$$\text{Swelling index} = \frac{W_2 - W_1}{W_1} \times 100$$

Where

W_1 - Final weight of minitables

W_2 - Initial weight of minitables

8.6.8 *In-vitro* drug release: ^[79]

Dissolution conditions:

Medium 1 : 0.1N HCl; 750 ml

Medium 2 : 0.20M Tribasic sodium phosphate; 250 ml

Speed : 50 rpm.

Type : paddle

Time interval : 2, 4, 6, 8, 10 and 12 hours.

Procedure:

The *in vitro* drug release studies of the tablets were performed using a dissolution test apparatus (USP Type II) with the paddle rotating at 50 rpm in dissolution media maintained at $37 \pm 0.5^\circ\text{C}$. The dissolution media used were 0.1 N HCl/pH 6.8 buffer (1000 ml). The media were 750 ml of 0.1 N HCl for 2 h. After withdrawal of sample then for the remaining intervals 250 ml of 0.20 M trisodium phosphate buffer with preheated (37°C) was added to adjust the pH to 6.8. 10 ml aliquots of dissolution media were withdrawn at time intervals and replaced with the same volume of fresh dissolution media after each withdrawal. Aliquots were filtered through Whatman filter paper and then the absorbance of samples was measured at 306 nm (267 nm in case 0.1 N hydrochloric acid) against the corresponding reagent blank.

8.6.9 Drug release kinetics:^[53]

The release of drug from the tablet can be characterized using various kinetics.

8.6.9.1 Zero order equation:

The zero-order release kinetics can be obtained by plotting cumulative % drug released (vs) time (hours). It is ideal for the formulations to have release (vs) time. It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C = K_0 t \dots \dots \dots (2)$$

Where,

K_0 = zero order constant in conc/time

t = Time in hours

8.6.9.2 First order equation:

The graph was plotted as log % cumulative drug remaining vs time in hours

$$\text{Log } C = \text{Log } C_0 - Kt/2.303 \dots \dots \dots (3)$$

Where,

C_0 = Initial drug concentration

K=First order constant

t= Time in hours

8.6.9.3 Higuchi kinetics:

The graph was plotted with % cumulative drug released (Vs) square root of time.

$$Q = Kt^{1/2} \dots \dots \dots (4)$$

Where,

K= Constant reflecting design variable system (different rate constant)

t= Time in hours

8.6.9.4 Korsemeyer-peppas equation:

To evaluate the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released (vs) log time Table 12.

$$M_t / M_d = Kt^n \dots \dots \dots (6)$$

Where,

M_t / M_d = Fraction of drug released at time t

t= Release time

K=Kinetics constant

n=Diffusional exponent indicature of mechanism of drug release.

Table 14 : Korsemeyer-peppas “n” value

Diffusion component (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomolous (non-Fickian) diffusion
0.89	Case - II transport
n > 0.89	Super case – II transport

Table 15: Dissolution Data modelling

Release mechanism	Y- axis	X- axis
Zero-order kinetics	% cum drug release	Time in min
First order kinetics	Log % cum drug remaining	Time in min
Higuchi kinetics	% cum drug release	Square root at time
Korsemeyer-peppar equation	Log cum% of the drug release	Log time

8.8 Optimization:

Optimization was carried out using Design expert software.

8.9 Development of optimized formulation:^[80]

Mini-tablets were manually filled into capsule shells to demonstrate the flexibility in dosing that can be achieved. The total number and weight of mini-tablets that fit in each capsule shell size were recorded. After capsulation, it was analysed as per IP including content uniformity, weight variation, etc.

8.10 Evaluation of developed minitables:

8.10.1 Physical test:

- **Weight variation:**

For each capsule, the weight of intact capsule was first weighed. Then, the capsule was opened and its content was removed, leaving only empty shell. The empty shell was weighed. By subtracting weight of empty shell from weight of the intact capsule, the weight of content was known.

8.10.2 Chemical test:

- **Dissolution test:**

The capsule was placed in the dissolution medium and paddle caused to rotate at a specified speed. The dissolution medium is held in a covered 1000ml glass vessel and maintained at $37^{\circ}\text{C}\pm 0.5$ by means of a constant temperature suitable water bath.

- **Content uniformity:**

10 capsules are taken and subjected to assay.

- **Moisture permeation:**

The degree and rate of moisture penetration is determined by packaging the dosage unit together with a colour revealing desiccant minitables. The packed unit exposed to known relative humidity over a specified time. The colour change of the minitables was observed, which indicate absorption of moisture.

8.11 In vivo pharmacokinetic study for optimized lamotrigine minitables.^[81]

The study protocol was approved by committee for the purpose of control and supervision of Experiments on animal (CPCSE)/ Institutional Animal Ethical Committee (IAEC). Proposal no. 10/321/PO/Re/01/CPCSEA.

Pharmacokinetics study for Optimized formulation and marketed formulation were carried out using male wistar rats (200-250g) and divided into 2 groups, each contained 3 animals.

8.11.1 Handling and feeding condition:

The rats are handled in accordance with CPCSEA guidelines for the care of laboratory animals and ethical guidelines for the investigation of experimental pain in conscious animals.

The animals were maintained in a clean room at a temperature between 20°C to 25°C with 12h light and dark cycles and controlled humidity.

8.11.2 Experimental design:

Table 16: Grouping of animals

Group	Drug	Dose of Administration	No. of rats
Group 1- Standard	Market Formulation	30mg/kg	6
Group 2- Test	Optimized Formulation	30mg/kg	6

8.11.3 Test procedure:

The animals were kept fasted for 12hrs prior to study. Minitablets with a dose of 30mg/kg body weight of rats were administered by dispersing in distilled water through oral feeding pipe. Blood sample were taken via lateral tail vein of rats at predefined time intervals 1, 2, 3, 4, 5 and 6 hrs with the maximum of 0.5ml collected at each sampling point into heparinized tube. The blood samples were centrifuged at 3000 rpm for 10min and 100 µl of plasma samples were stored at -20⁰ C until analysis.

8.11.4 Analytical procedure:

Plasma concentration of drug was determined by a HPLC methods.

Column : C18 column

mobile phase : 0.01M potassium phosphate-acetonitrile-methanol (70:20:10% v/v/v)

Ph: 6.7

Injection volume : 20µl

Detector wavelength : 214nm

flow rate : 1.3ml/min

8.11.5 Pharmacokinetic analysis:

Most common pharmacokinetic parameters such as peak plasma concentration (C_{max}), time to reach maximum concentration (T_{max}) and total area under the plasma concentration-time curve (AUC) were determined from the plasma concentration time profile of market sample and optimized formulation using pharmacokinetic solution software.

8.11.6 Stability Study:

ICH recommends carrying out stress testing on the drug substance to establish its inherent characteristics and support the solubility of the proposed analytical procedure. Stability study at room temperature is the method of determining the actual shelf life of the product. Unfortunately it is difficult to make an accurate expiration date prediction until 2-3 yrs. Of data are generated, which will require long shelf life conditions. Hence accelerated stability studies were carried out at elevated temperature will help to determine shelf life within a lesser period of time. The prepared tablets were evaluated for a period of one to three months as per ICH Guidelines. Stability studies were conducted on the Optimised Lamotrigine minitables. The stability was assessed with respect to their physical appearance, drug content and drug release by storing at ambient room temperature and 40°C ± 2°C maintained at RH 75% ± 5% for 3 months.

9. Results

9.1 Raw material analysis of lamotrigine:

9.1.1 Physical Property of Lamotrigine were found as per values obtained after analysis:

Table 17: Physio-chemical Characteristics of Lamotrigine

S.No.	Parameter	Inference /Report
1	Nature	Crystalline powder
2	Colour	White to pale cream
3	Melting point	216-218 ⁰ C
4	Solubility -In water -In 0.1M HCL	-Very slightly soluble -Slightly soluble
5	Percentage Purity: (98.0~102.0%)	98.8% by UV method (Complies with IP)

9.2 Preformulation Studies:

9.2.1 Drug –excipient compatibility (FT-IR) study of Lamotrigine:

The FT-IR analysis of the drug and polymer gave thermal profile characteristic of the substances are shown in Fig 16-18. Principal peaks of minitables containing drug and polymer are intact in the formulations.

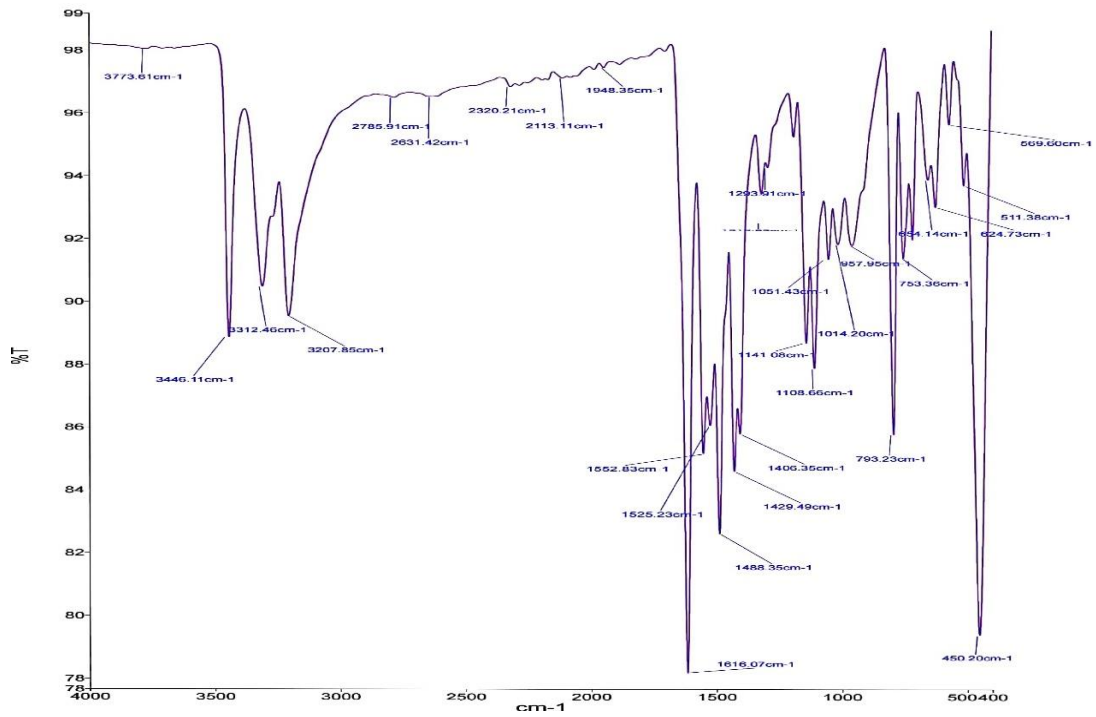


Fig.16: FT-IR spectrum of pure sample of lamotrigine

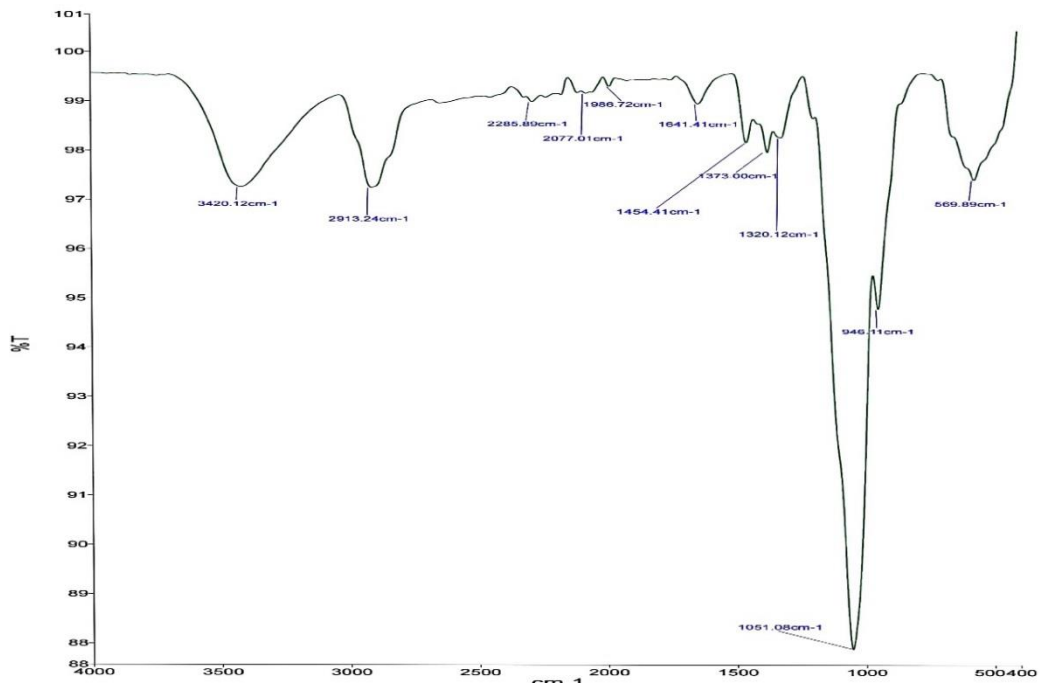


Fig.17: FT-IR spectrum of HPMC

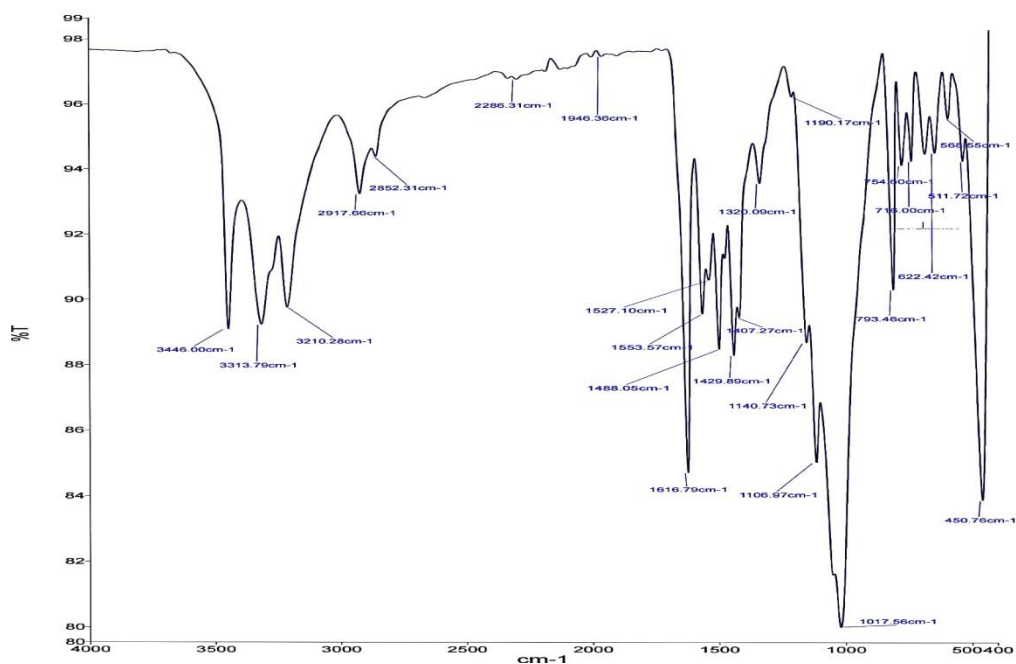


Fig.18: FT-IR spectrum of formulation

Table 18: Interpretation of FT-IR spectrum for Lamotrigine

Materials	Test wave number (cm-1)	Functional group assignment
Lamotrigine	3444.11	N-H Stretching
	3207.85	C-H Stretching
	1616.07	C=N Stretching
	1488.35	C=C Stretching
	1429.49	
	753.26	C-C-C Bending
	624.73	C-Cl stretching

Table 19: Interpretation of FT-IR spectrum for HPMC

Materials	Test wave number (cm-1)	Functional group assignment
HPMC	3420.12	O-H Stretching
	2913.24	C-H stretching
	1641.41	C=O stretching
	1051.08	C-O Stretching

Table 20: FT-IR spectrum of formulation

Materials	Test wave number (cm-1)	Functional group assignment
Minitablet formulation	3446	N-H Stretching
	3313.79	O-H Stretching
	3210.28	C-H Stretching
	2917.66	C-H Stretching
	1616.07	C=N Stretching
	1488.05	C=C Stretching
	754.6	C-C-C Bending
	622.42	C-Cl Stretching

9.2.2 Calibration curve of Lamotrigine:

The drug was analysed by UV spectrophotometer at 244 nm.

Table 21: Preparation of Standard Calibration Curve of Lamotrigine

Conc. ($\mu\text{g/ml}$)	Absorbance (244nm)
0	0
5	0.215
10	0.398
15	0.601
20	0.856
25	0.989

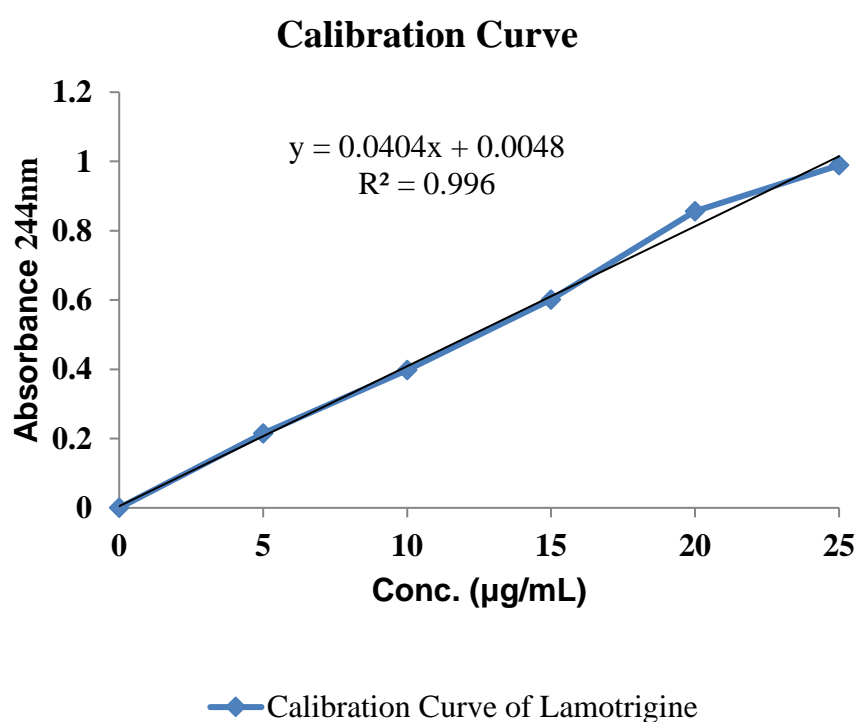


Fig.19: Calibration curve of Lamotrigine

9.3 Evaluation of Micromeritics properties:

Table 22: Evaluation of Micromeritics properties

Formulation number	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio (%)	Angle of repose (θ)
F1	0.464±0.06	0.559±0.02	10.52	1.121	25.7±1.02
F2	0.492±0.05	0.538±0.03	10.42	1.127	23.41±1.08
F3	0.478±0.10	0.551±0.05	14.54	1.172	28.3±1.21
F4	0.477 ±0.08	0.589±0.11	12.74	1.146	27.40±0.10
F5	0.513±0.04	0.584±0.02	13.79	1.162	25.81±1.52
F6	0.544±0.03	0.660±0.04	13.85	1.158	24.15±0.15
F7	0.486±0.13	0.593±0.01	12.07	1.137	26.17±0.03
F8	0.526±0.02	0.662±0.10	14.64	1.181	22.2±1.03
F9	0.565 ±0.01	0.695 ± 0.06	12.95	1.139	28.45±0.05

9.4 Evaluation of Minitablets:

9.4.1 Parameters

Table 23: Evaluation of Lamotrigine Minitablets

Formulation Number	Average weight (mg)	Thickness (mg)	Hardness (N)	Friability (%)
F1	55.8±0.67	2.64±0.06	61.2±2.03	0.36
F2	55.1±0.23	2.61±0.01	65.4±1.23	0.32
F3	55.0±0.75	2.64±0.04	59.8±1.42	0.41
F4	56.1±0.61	2.69±0.08	60.2±2.13	0.36
F5	55.2±0.24	2.59±0.05	66.9±1.60	0.34
F6	55.3±0.43	2.60±0.01	63.6±2.09	0.32
F7	56.2±0.06	2.62±0.02	64.1±2.34	0.35
F8	55.3±0.32	2.58±0.03	69.8±1.32	0.32
F9	55.6±0.66	2.65±0.01	58.2±2.15	0.45

9.4.2 Evaluation of content uniformity and swelling index:

Table 24: Content uniformity of minitables

Formulation	Content Uniformity (%)
F1	98.3±0.56
F2	98.4±0.62
F3	97.6±0.36
F4	98.4±0.46
F5	99.9±0.50
F6	96.2±0.56
F7	98.8±0.65
F8	97.7±0.32
F9	99.2±0.66

Table 25: Swelling study of minitablets

Formulation	Swelling index %	
	2 (hrs)	4(hrs)
F1	8.7	17.2
F2	6.0	18.4
F3	8.1	20.0
F4	9.9	24.1
F5	10.4	29.1
F6	12.6	30.1
F7	9.2	22.8
F8	14.6	32.1
F9	6.7	15.4

9.5 In- Vitro Studies:

The eight minitablets in each basket.

Table 26: *In vitro* dissolution of lamotrigine minitablets F1

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%)
0	0	0	0	0
2	0.5652	94.7	47.3	47.3
4	0.6198	103.8	4.5	51.9
6	0.8852	148.3	22.2	74.1
8	1.0966	183.7	17.7	91.8
10	1.1382	190.7	3.4	95.3
12	1.1542	193.4	1.3	96.7

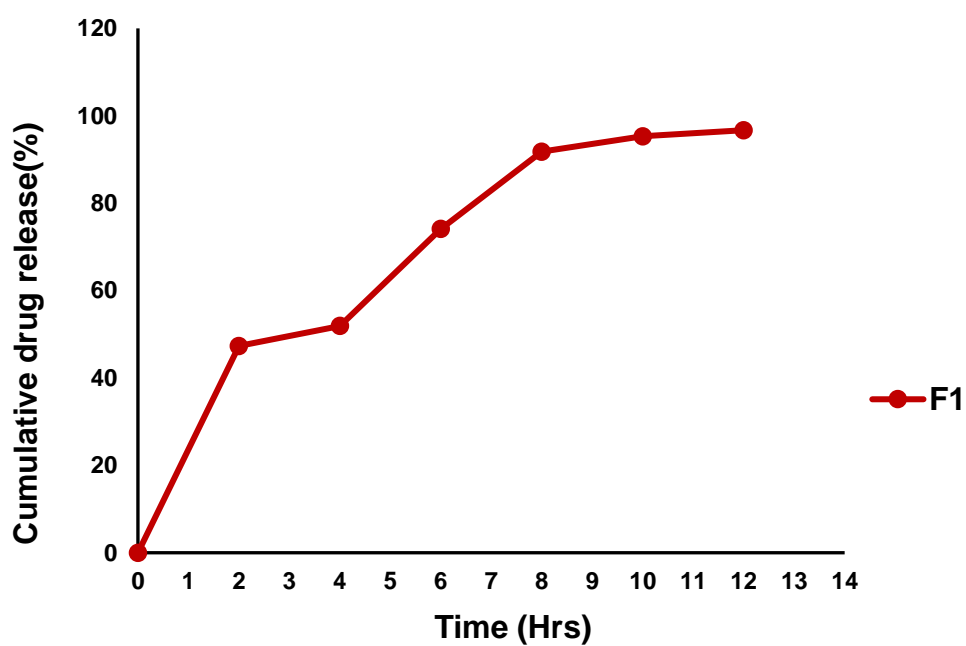


Fig. 20: *In vitro* dissolution of Lamotrigine formulation F1

Table 27: *In vitro* dissolution of lamotrigine minitables F2

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%)
0	0	0	0	0
2	0.5014	84.0	42	42.0
4	0.5756	96.4	6.2	48.2
6	0.6023	100.9	2.2	50.4
8	1.0506	176.0	37.5	88.0
10	1.0856	181.9	2.9	90.9
12	1.1349	190.2	4.1	95.1

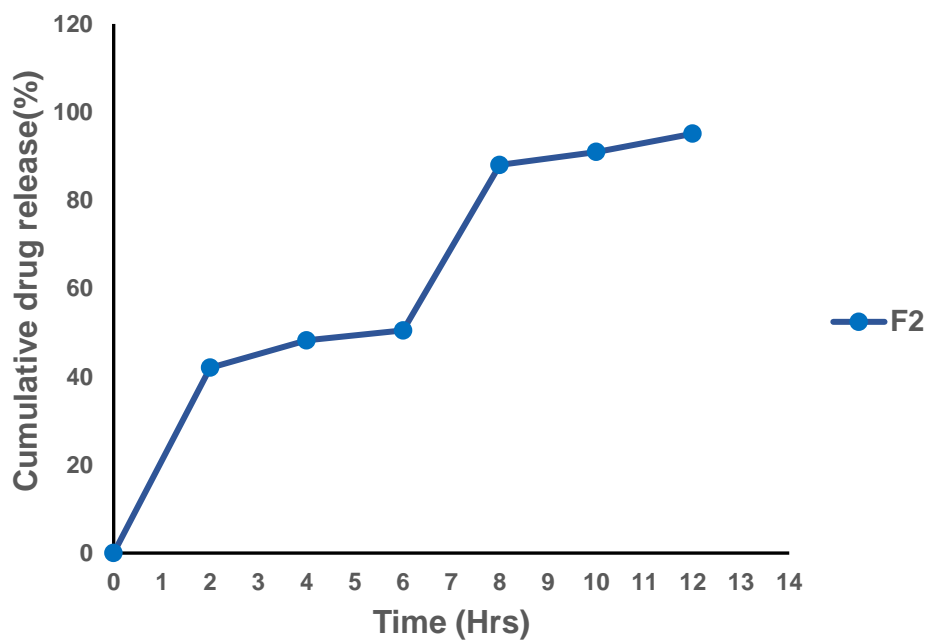


Fig. 21: *In vitro* dissolution of lamotrigine formulation F2

Table 28: *In vitro* dissolution of lamotrigine minitables F3

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%)
0	0	0	0	0
2	0.3612	60.5	30.2	30.2
4	0.5731	96.0	17.7	48.0
6	0.8869	148.6	26.2	74.3
8	0.9652	161.7	6.5	80.8
10	1.0514	176.2	7.2	88.1
12	1.1652	195.2	9.5	97.6

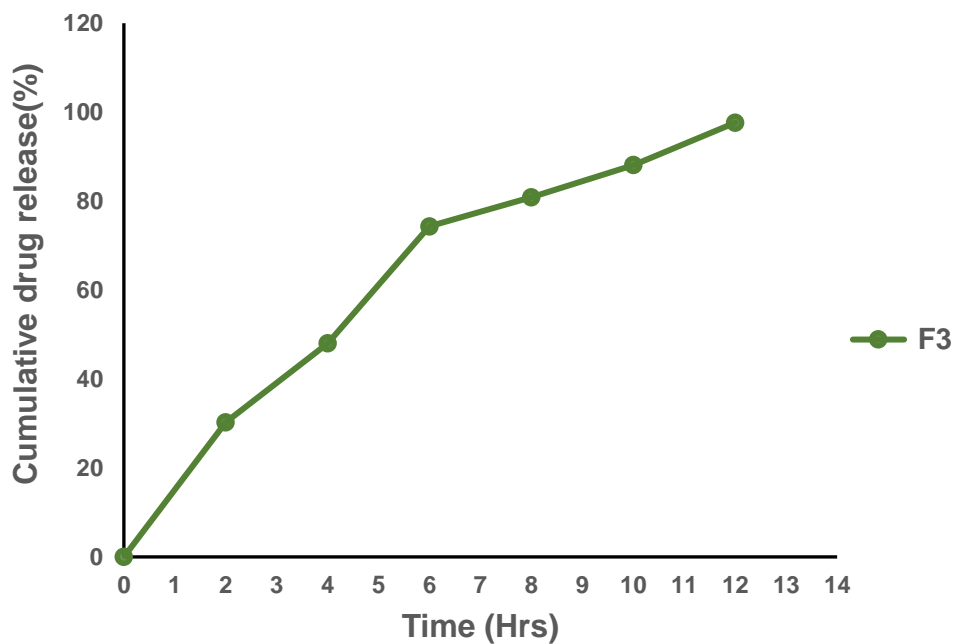


Fig.22: *In vitro* dissolution of lamotrigine formulation F3

Table 29: *In vitro* dissolution of lamotrigine minitables F4

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%)
0	0	0	0	0
2	0.4234	70.9	35.4	35.4
4	0.4681	78.45	3.7	39.2
6	0.7458	124.9	23.2	62.4
8	0.8021	134.4	4.7	67.2
10	1.0505	176.0	20.8	88.0
12	1.1447	191.8	7.8	95.9

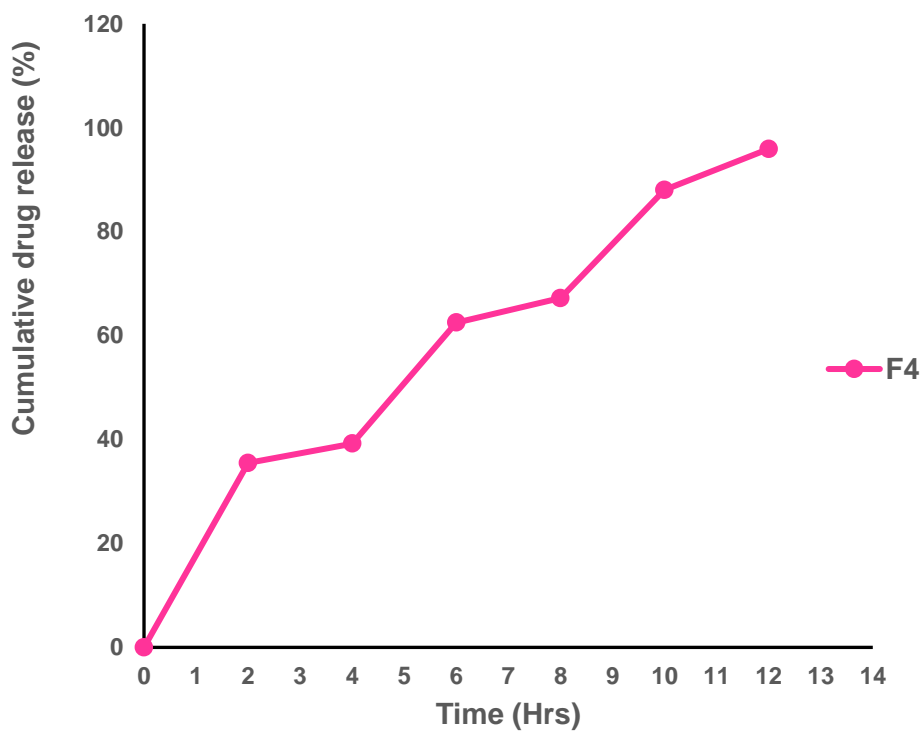


Fig.23: *In vitro* dissolution of lamotrigine formulation F4

Table 30: *In vitro* dissolution of lamotrigine minitables F5

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%)
0	0	0	0	0
2	0.3021	50.6	25.3	25.3
4	0.3251	54.4	1.9	27.2
6	0.6348	106.3	25.9	53.1
8	0.736	123.3	8.4	61.6
10	0.8038	134.7	5.6	67.3
12	1.062	177.9	21.6	88.9

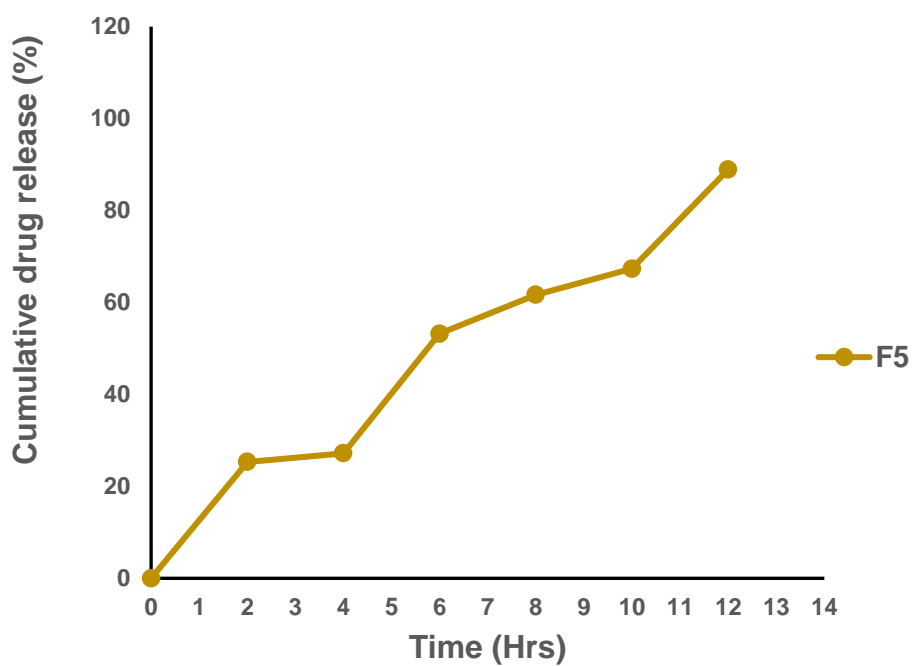


Fig.24: *In vitro* dissolution of lamotrigine formulation F5

Table 31: *In vitro* dissolution of lamotrigine minitables F6

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%)
0	0	0	0	0
2	0.3731	62.5	31.2	31.2
4	0.462	77.4	7.4	38.7
6	0.6242	104.6	13.5	52.3
8	0.7362	123.3	9.3	61.6
10	0.9323	156.2	16.4	78.1
12	1.1032	184.8	14.3	92.4

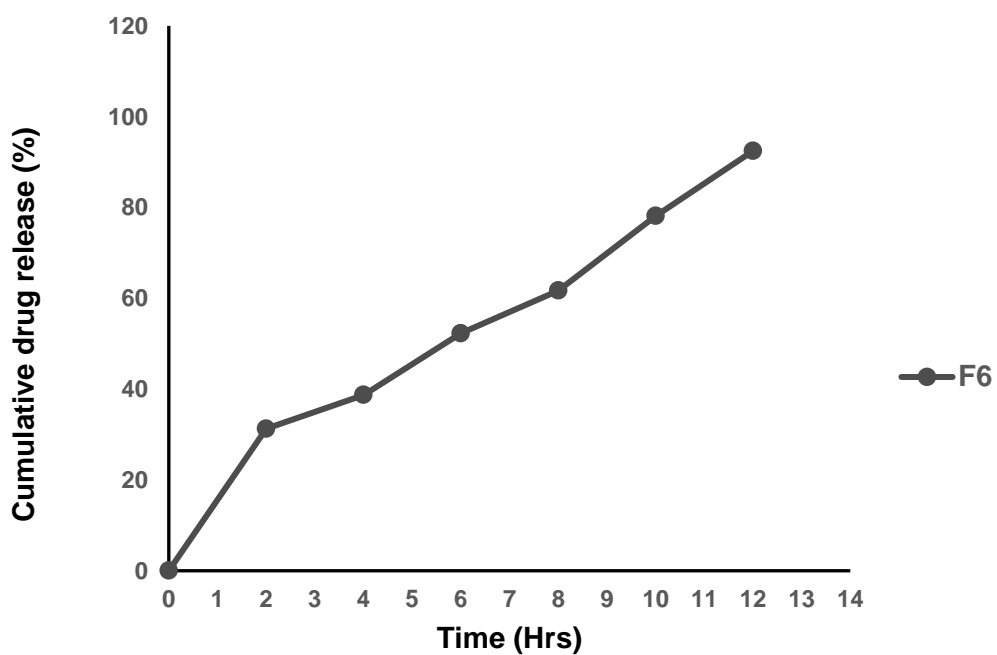


Fig.25: *In vitro* dissolution of lamotrigine formulation F6

Table 32: *In vitro* dissolution of lamotrigine minitables F7

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%)
0	0	0	0	0
2	0.2963	49.6	24.8	24.8
4	0.4623	77.4	13.9	38.7
6	0.6032	101.0	11.	50.5
8	0.6756	113.2	6.0	56.6
10	0.9865	165.3	26.0	82.6
12	1.0625	178.0	6.3	89.0

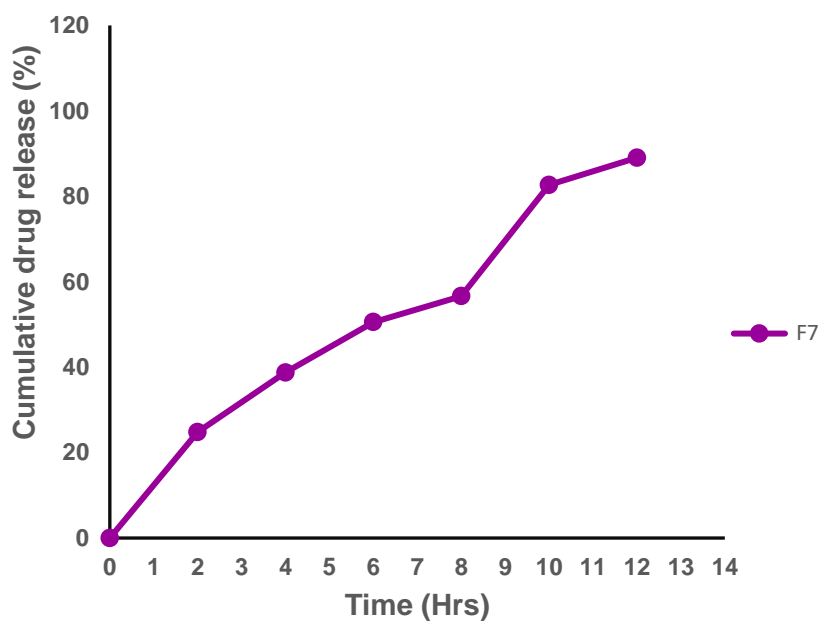


Fig.26: *In vitro* dissolution of lamotrigine formulation F7

Table 33: *In vitro* dissolution of lamotrigine minitables F8

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%)
0	0	0	0	0
2	0.2052	34.3	17.1	17.1
4	0.2521	42.2	3.9	21.1
6	0.7358	123.3	40.5	61.6
8	0.8145	136.5	6.5	68.2
10	0.8651	144.9	4.2	72.4
12	1.0369	173.7	14.3	86.8

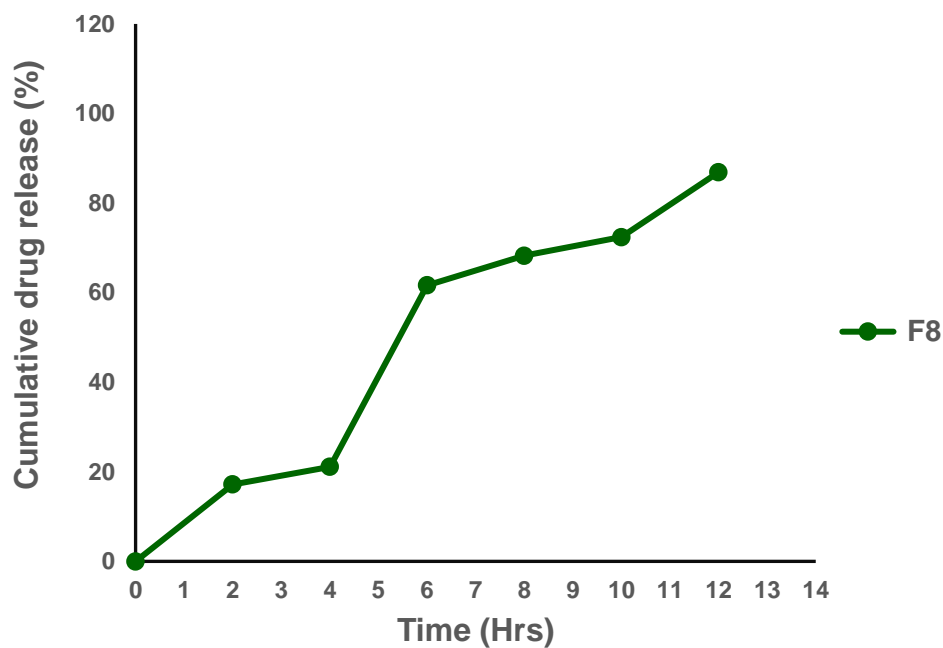


Fig.27: *In vitro* dissolution of lamotrigine formulation F8

Table 34: *In vitro* dissolution of lamotrigine minitables F9

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%)
0	0	0	0	0
2	0.5612	94.0	47.0	47.0
4	0.7334	122.9	14.4	61.4
6	0.8155	136.6	6.8	68.3
8	0.952	159.5	11.4	79.7
10	1.0958	183.6	12.0	91.8
12	1.1812	197.9	7.1	98.9

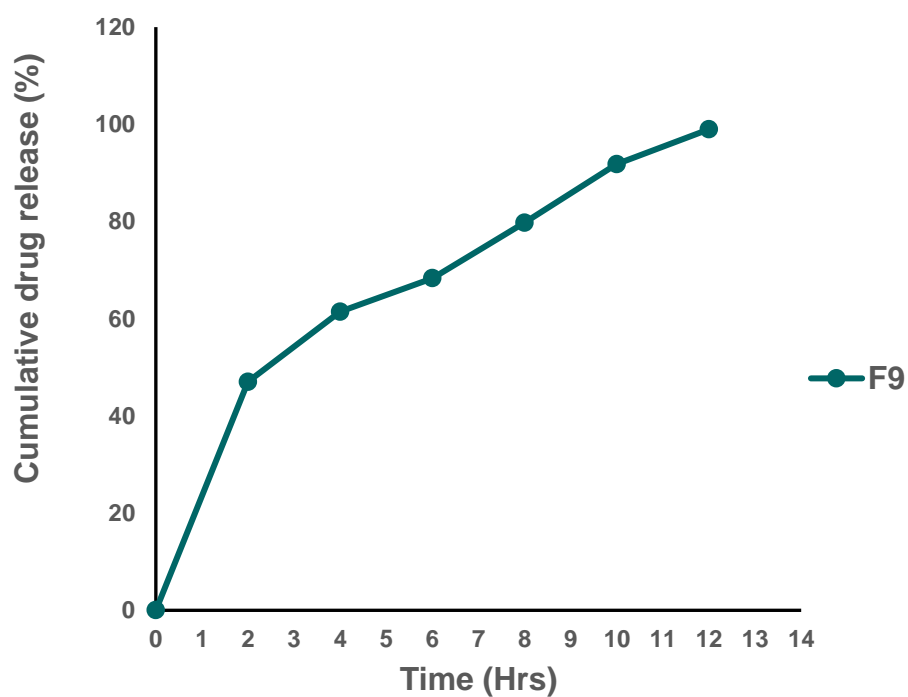


Fig.28: *In vitro* dissolution of lamotrigine formulation F9

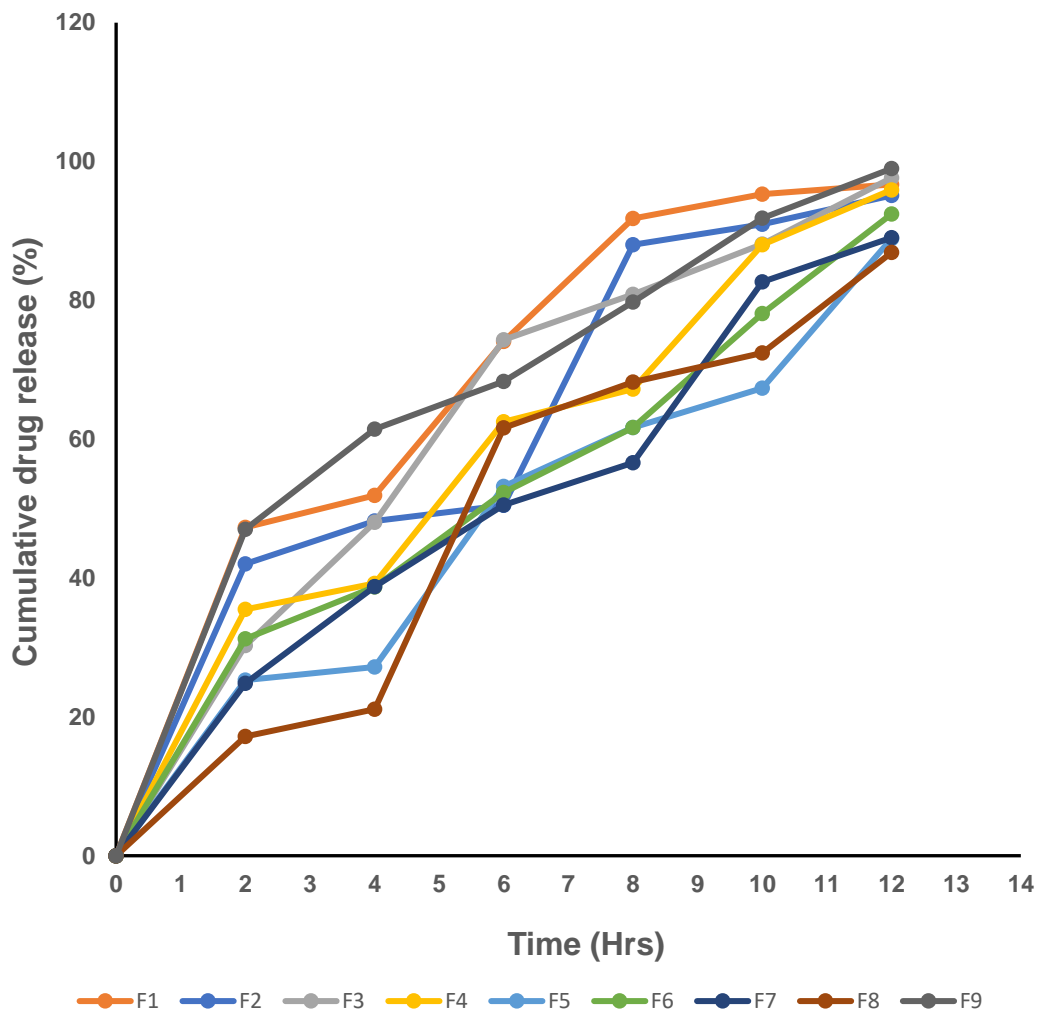


Fig.30: Comparative *In-vitro* Drug release profile of Lamotrigine minitables

9.6 Optimization by 3² Full factorial design:

Table 35: Results of Independent variable and corresponding dependent variable according to the 3² Full factorial design

Std	Run	Factor 1 A: HPMC K4M (mg/tab)	Factor 2 B: HPMC K100M (mg/tab)	Response 1 Drug release (%)	Response 2 Tensile strength (N/m ²)
4	1	4	4	96.7	2.9
7	2	4	6	95.1	3.1
2	3	8	2	97.6	2.8
5	4	8	4	95.9	2.9
6	5	12	4	88.9	3.2
8	6	8	6	92.4	3.0
3	7	12	2	89.0	3.1
9	8	12	6	86.8	3.4
1	9	4	2	98.9	2.7

9.6.1 ANOVA for Response surfaces:

Table 36: Response surface value of Drug release (%)

Source	Sum of Squares	DF	Mean Square	F-Value	P- value
Model	106.07	4	26.52	85.02	0.0004
A-HPMC K4M	66.13	1	66.13	212.03	0.0001
B-HPMC K100M	27.35	1	27.35	87.68	0.0007
AB	2.61	1	2.61	8.36	0.0445
A ²	9.98	1	9.98	31.98	0.0048
Residual	1.25	4	0.3119		
Cor total	107.32	8			

Table 37: Response surface for tensile strength

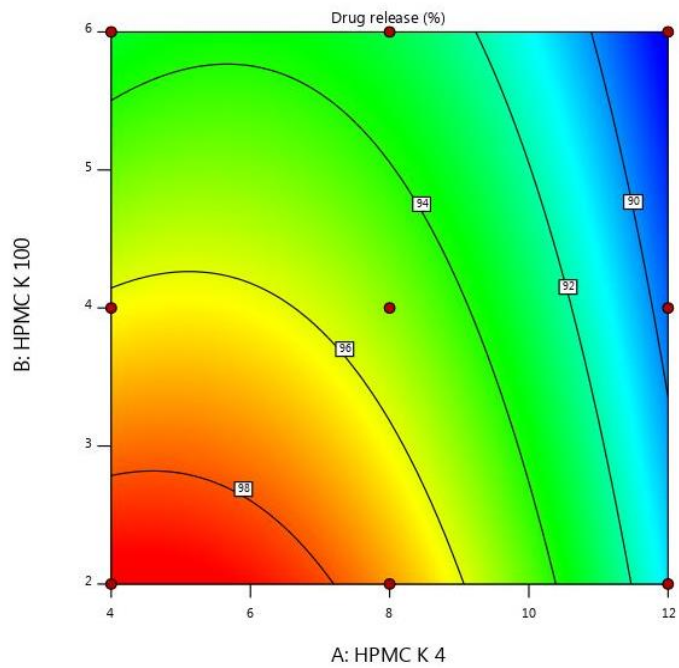
Source	Sum of squares	Df	Mean square	F-value	P- value
Model	0.3335	3	0.1112	44.59	0.0005
A-HPMC K4M	0.138	1	0.138	0.138	0.0007
B-HPMC K100M	0.1411	1	0.1411	56.58	0.0007
A²	0.0544	1	0.0544	21.84	0.0055
Residual	0.0025	5	0.0025		
Cor total		8			

(a)

Design-Expert® Software
Factor Coding: Actual

Drug release (%)
● Design Points
88.54 98.84

X1 = A: HPMC K 4
X2 = B: HPMC K 100



(b)

Design-Expert® Software

Factor Coding: Actual

Drug release (%)

● Design points above predicted value

○ Design points below predicted value

88.54  98.84

X1 = A: HPMC K 4
X2 = B: HPMC K 100

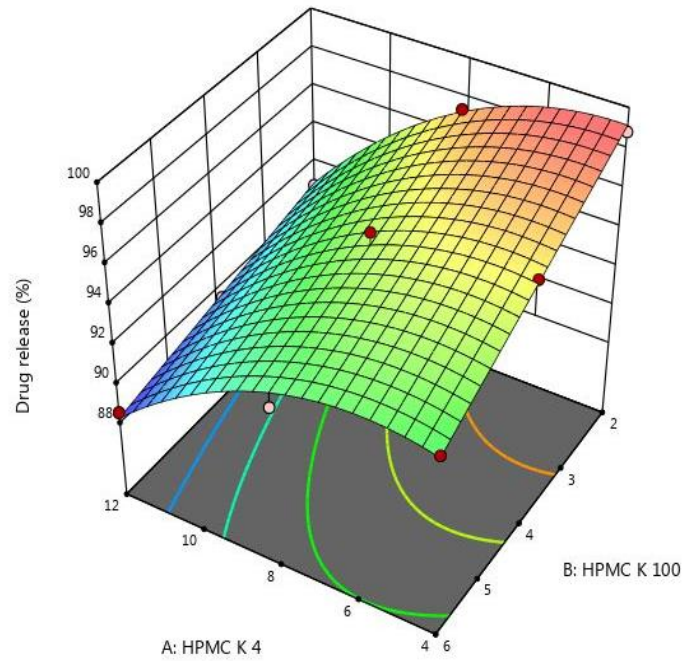


Fig.31: Effect on HPMC K4M & K100M on drug release (%) presented by response surface plot (a), and contour plot (b)

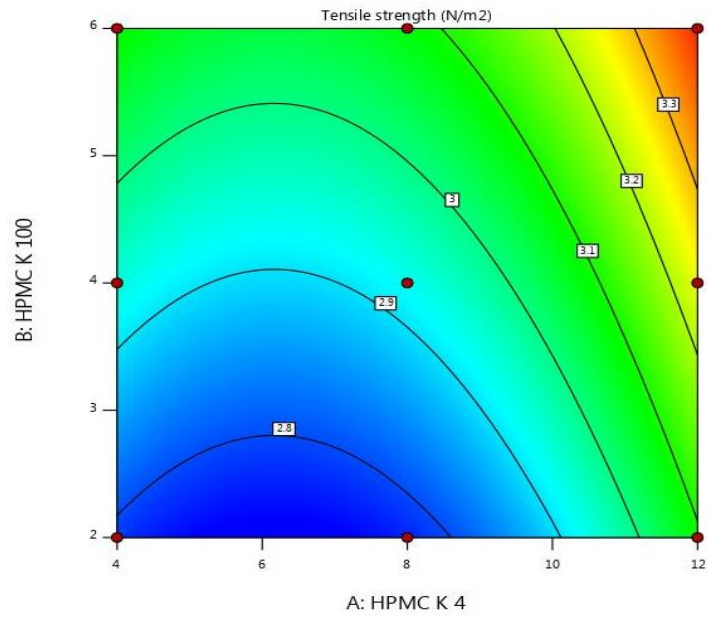
(a)

Design-Expert® Software
Factor Coding: Actual

Tensile strength (N/m²)

● Design Points
2.75 3.42

X1 = A: HPMC K 4
X2 = B: HPMC K 100



(b)

Design-Expert® Software
Factor Coding: Actual

Tensile strength (N/m²)

● Design points above predicted value
○ Design points below predicted value
2.75 3.42

X1 = A: HPMC K 4
X2 = B: HPMC K 100

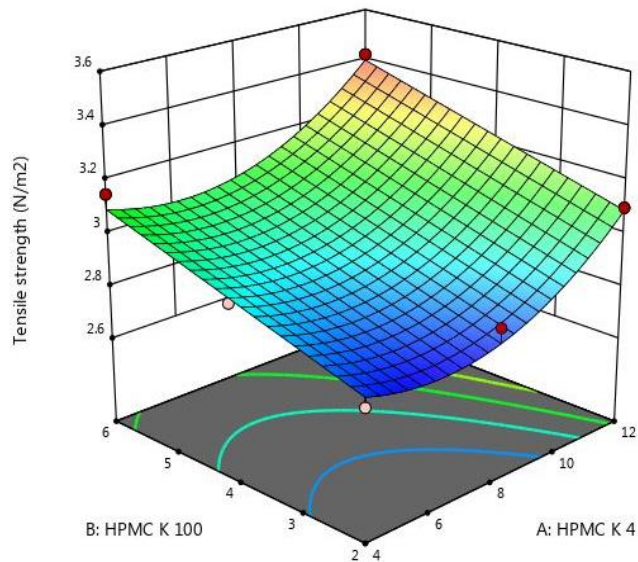


Fig. 32: Effect on HPMC K4M & K100M on Tensile strength (N/m²) presented by response surface plot (a), and contour plot (b).

Table 38: Optimize formulation derived by 3² full factorial design

Factors	HPMC K4M (mg/tab)	HPMC K100M (mg/tab)
Optimized formulation(F10)	11.0	4.5

Table 39: Results of Experiments design

Response	Predicted Mean
Drug release (%)	90.7
Tensile strength (N/m²)	3.18

9.7 Formulation Evaluation of developed Lamotrigine minitables (F10):



Fig.33: Optimized Minitables

Table 40: Flow Properties of Lamotrigine blends

S.No	Parameter	Report
1	Bulk density (gm/ml)	0.534±0.07
2	Tapped density (gm/ml)	0.578±0.02
3	Carr's index (%)	12.42
4	Hausner's ratio	1.021
5	Angle of repose (θ)	23.41±1.52

Table 41: Evaluation of Lamotrigine ER minitables

S.No	Parameter	Report	IP Limit
1	Average Weight (mg)	55.1±0.23	Complies with IP
2	Thickness (mg)	2.53±0.04	Complies with IP
3	Hardness (N)	65.7±1.54	Complies with IP
4	Friability (%)	0.32±0.01	Complies with IP
5	Content Uniformity (%)	99.01±0.54	Complies with IP
6	Swelling index %		
	Time (hrs) 2	9.74	-
	6	23.86	-

**Fig. 34:** Swelling study of optimized minitables

9.7 In- Vitro dissolution of Optimized Formulation (F10):

Table 42: *In vitro* dissolution of lamotrigine minitables F(10)

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%) at 12 hrs
0	0	0	0	0
2	0.203	34.0	17.0	17.0
4	0.361	60.5	13.2	30.2
6	0.6891	115.4	27.4	57.7
8	0.8512	142.6	13.5	71.3
10	1.0628	178.1	17.7	89.0
12	1.1358	190.8	6.1	95.4

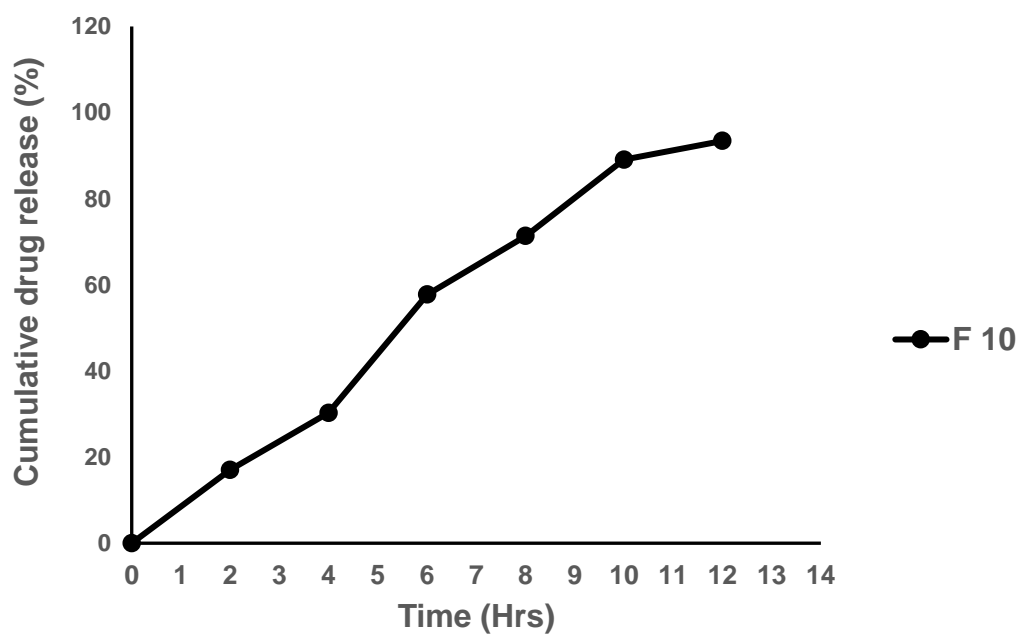


Fig. 35: *In vitro* dissolution of lamotrigine formulation F10

Table 43: Comparative of predicted and Experimental value by DOE

Response	Predicted value	Experimental value
Drug release %	90.7	93.4
Tensile strength N/m ²	3.18	3.21

Table 44: Comparative study with Market product (LAMICTAL XR)

Time (Hrs)	Absorbance (nm)	Cumulative drug release (mg)	Drug release (%)	Cumulative drug release (%) at 12 hrs
0	0	0	0	0
2	0.5348	31.8	15.7	15.7
4	0.7413	53.2	11.1	26.8
6	0.9652	89.6	18	44.1
8	0.8512	124.2	18.1	62.9
10	1.0943	161.7	18	80.9
12	1.1358	183.4	10.4	91.3

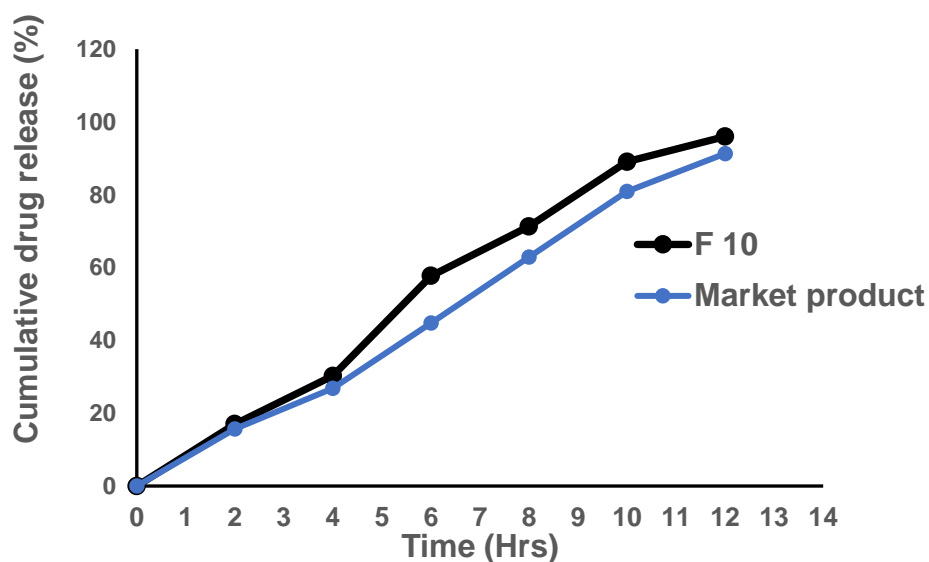


Fig. 36: *In vitro* dissolution of lamotrigine formulation F10

9.8 Drug Release Kinetics:

Table 45: Dissolution parameter for optimized minitables:

	Zero Order	First order	Higuchi	Korsmeyer Peppas
Slope	16.649	0.117	16.372	0.3517
R value	0.9615	0.5278	0.9389	0.7862
R²	0.9806	0.7265	0.969	0.8867

9.8.1 Zero Order Kinetics Parameter for Lamotrigine minitables:

Table 46: Analysis of curve fitting for Zero- Order Kinetics

Time (h)	F (%)	Mean	F (%) pre	Mean
0	0	0	0	0
2	17.02	17.02	19.46	19.46
4	30.51	30.51	36.55	36.55
6	57.6	57.6	52.84	52.84
8	71.2	71.2	68.65	68.65
10	89.48	89.48	84.09	84.09
12	93.1	93.1	99.26	99.26

Table 47: Best- fit values

Parameter	Mean
k0	8.484

Table 48: Secondary Parameter

Parameter	Mean
T25	2.947
T50	5.893
T75	8.84
T80	9.429
T90	10.608

Table 49: Goodness of Fit

Parameter	Report
N_observed	7
DF	6
R_obs-pre	0.9794
Rsqr	0.9302
Rsqr_adj	0.9302
MSE	74.5922
MSE_root	8.6367
Weighting	1
SS	447.5531
WSS	447.5531
AIC	44.7266
MSC	2.377

9.9 In vivo studies:

Table 50: Plasma concentration of Optimized Formulation F10 And Market Formulation

Time (hr)	Optimized formulation (F10) Conc (µg/ml)	Market formulation Conc (µg/ml)
0	0	0
1	151	114
2	241	209
3	306	298
4	375	312
5	41	26
6	19	14

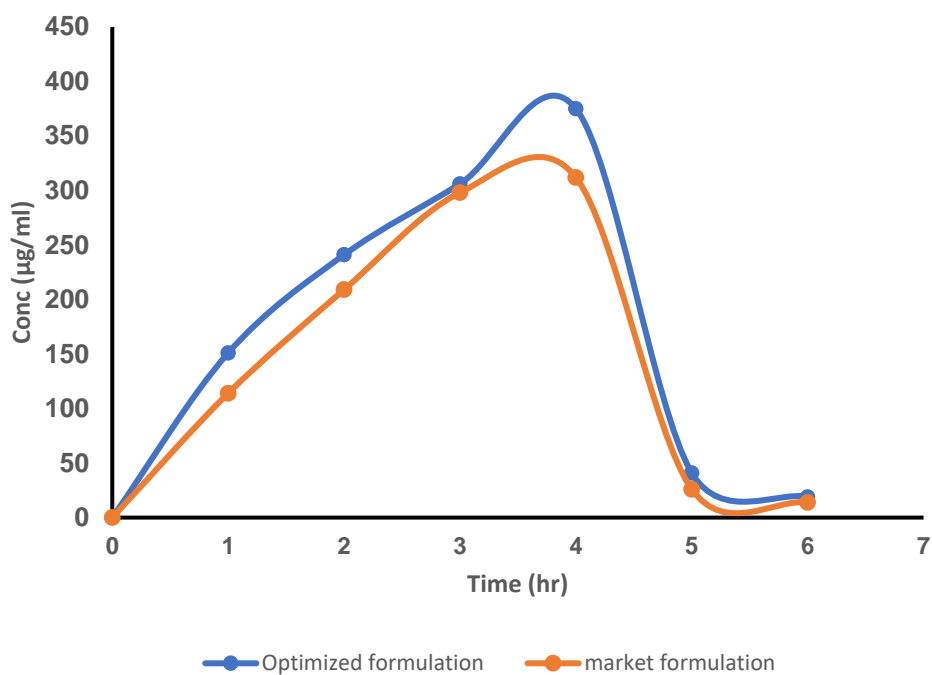


Fig. 37: Plasma concentration Optimized Formulation F10 And Market Formulation

Table 51: Pharmacokinetic Parameter of Optimized formulation

Trapezoid Calculation of AUC ($\mu\text{g}\cdot\text{hr}/\text{ml}$)				Trapezoid Calculation of AUMC ($\mu\text{g}\cdot\text{hr}^2/\text{ml}$)			
Time (hr)	Conc ($\mu\text{g}/\text{ml}$)	Partial	Cumulative	Time (hr)	Time x Conc	Partial	Cumulative
0	0	0	0	0	0	0	0
1	151	75.5	75.5	1	151	75.5	75.5
2	241	196	271.5	2	482	316.5	392
3	306	273.5	545	3	918	700	1092
4	375	340.5	885.5	4	1500	1209	2301
5	41	208	1093.5	5	205	852.5	3153.5
6	19	30	1123.5	6	114	159.5	3313

Table 52: Pharmacokinetic parameters of optimized F10 and market product

Parameters	Optimized F10	MARKET PRODUCT
C max ($\mu\text{g}/\text{ml}$)	375.0	312
T max (hrs)	4.0	4.0
AUC ($\mu\text{g}\cdot\text{hr}/\text{ml}$)	1123.5	997.8
AUMC ($\mu\text{g}\cdot\text{hr}^2/\text{ml}$)	3313	3108.6

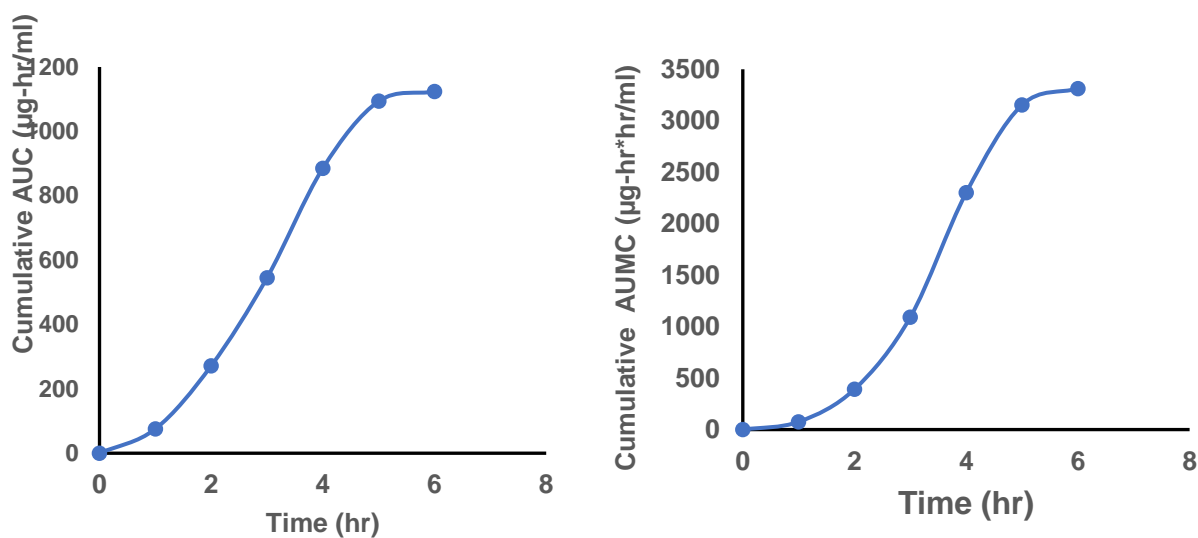


Fig.38 : Cumulative AUC and AUMC

9.10 Accelerated Stability Study:

Table 53: Stability testing parameters for optimized minitables

Parameter	Storage condition 40°C±2°C & 75%±5% RH		
	Initial	1 st month	2 nd month
Average Weight (mg)	55.8	55.6	55
Drug content (%)	99.0	98.9	98.8

10. Discussion

10.1 Formulation and development of Lamotrigine minitablets:

The study started with the selection of disease and the epilepsy was found to be most common neurological diseases. Different formulation for the treatment of epilepsy is available. Minitablets represent a new trend in solid dosage form design and main goal of overcome some therapeutic barrier. Minitablets with extended drug delivery system is to reduce the frequency of the dosing and to increase the effectiveness of the drug and alternative solution for single unit dosage form. Dose dumping and local irritation can be avoided by the use of minitablets. So study moved to the development of Lamotrigine extended release minitablets to treat epilepsy.

API weighed and mixed with other excipients as a part of the manufacturing process. The Formulation developed for lamotrigine ER minitablets by using 3^2 full factorial design. Minitablets were prepared by adding the two grades of HPMC K4M & K100M using direct compression technique. Lamotrigine and polymers were added in the proportions shown in **Table 9**. HPMC were added to provide extended duration of action in therapeutic range without reaching toxic levels as in the case of conventional dosage forms. Lamotrigine is the better choice to patients for its safety, efficacy and many other benefits.

10.2 Selection of Drug and Excipients:

Formulation development begins with the selection of the API, the challenging aspects of cost, efficiency, availability, and selection of the drug properties of lamotrigine. Then, the excipients were selected based on the compatibility.

10.3 Selection of punch and tools:

We have selected the punches based on the surface area to volume ratio (mm^{-1}). The surface area to volume ratio gradually increases as we use punch sizes of 5.00, 5.16, 5.25 and 5.45mm. Therefore, 5mm punch was chosen for the entire study.

10.4 Raw Material Analysis:

10.4.1 Description and Solubility:

The description of the Active Pharmaceutics Ingredient Lamotrigine was found to be complies with IP. Solubility of the Lamotrigine was found with the different solvents. The results were shown in **Table:17**.

10.5 Preformulation Study:

10.5.1 Determination of Interaction:

A comprehensive understanding of physicochemical interactions in dosage forms is expected under quality design prototypes for drug development. The analytical methods into the initial steps of preformulation studies have contributed significantly to early prediction, monitoring, and characterization of the API incompatibility to avoid costly material wastage and considerably reduce the time required to arrive at an appropriate product formulation. The drug and the excipients chosen for the formulation was screened for its interaction by physical methods. This study would suggest the excipients to be avoided and form a part of the preliminary assessment. The Drug-Excipients compatibility study was carried out by FTIR with their physical mixture of formulations.

10.5.2 Fourier Transformer Infrared spectroscopy (FT-IR) studies:

The FT-IR spectra of Lamotrigine are presented in (**Fig.16**). The characteristic absorption of the Lamotrigine was the band at 3444.11 cm^{-1} , which is assigned to the stretching vibration of N-H group of Lamotrigine and 3207.85 cm^{-1} assigned to stretching vibration of C-H group and 1616.07 cm^{-1} assigned to the stretching vibration C=N group and another band at 624.72 cm^{-1} assigned to the stretching vibration of C-Cl group. The Lamotrigine minitabket formulation was band at 3444 cm^{-1} , which assigned to the stretching vibration of N-H stretching vibration and 3210.28 cm^{-1} assigned to starching vibration of C-H group. 1616.07 cm^{-1} assigned to the stretching vibration C=N group and another band at 622.42 cm^{-1} assigned to the stretching vibration of C-Cl group. While comparing both Lamotrigine (API) and Lamotrigine minitabkets dosage form results that the absence of drug- excipients interaction and the stability of the drug in the minitabket were confirmed.

10.6 Evaluation of Micromeritics properties:

The prepared core granules were physically evaluated with several parameters and suggested that they are suitable for compression into tablets.

The flow properties of lamotrigine powder blend were checked by studying the angle of repose, compressibility index, and Hausner's ratio. The powder blends were found to be free flowing with good flow properties as shown in **Table 22**.

Bulk density was found to be in the range of 0.464-0.565 (g/ml) and tapped density between 0.555-0.695 (g/ml) for all the formulations. The % compressibility index was calculated using the density data. The obtained values 10.42–14.64% which were found to be good flow and Hausner's ratio values were in the range of 1.121–1.172 for all powder blends. This was further supported by the angle of repose values between 22.2 and 28°. As it was below 30° it indicated good flow properties of powder blend.

10.8 In Vitro Dissolution study:

The release profile of Lamotrigine ER minitables from different Formulation (F1, F2, F3, F4, F5, F6, F7, F8, and F9) were tabulated in **Table:(26-34)** and plotted in **Fig (20-28)**.

10.8.1 Effect of HPMC K4M on Drug release:

All formulation showed extended drug release over 12 hrs. The cumulative drug release for formulations were found within the range of 86.89 – 98.98 %. The drug release directly depends on the concentration HPMC K4M. The concentration levels are 4 mg (low), 8 mg (medium) and 12 mg (high).

While comparing percentage drug release in formulation F5, F7 and F8 was found to be 86.8 to 89 % due to high concentration of polymer. The release rate was found moderate in formulation F3, F4 and F6 gave 92.4, 95.9 and 97.6 % respectively and these formulations showed moderate drug release. Where else, while comparing the formulation F1, F2 and F9 the percentage drug release was found to be 96.7, 95.1 and 98.9 % respectively. These formulations showed higher dissolution rate due to the incorporation of low concentration of the HPMC and these formulations does not retard the release rate and found unsatisfactory.

10.8.2 Effect of HPMC K100M on *in vitro* dissolution:

All formulations showed prolonged drug release over 12 hours. The cumulative drug release for formulations was found within the range of 86.89 – 98.98 %. The drug release directly depends on the concentration HPMC K4M which kept as 4 mg (low), 8 mg (medium) and 12 mg (high). While comparing percentage drug release in formulation F5, F7 and F8 was found to be 86.8 to 89 % due to high concentration of polymer. The release rate was found moderate in formulation F3, F4 and F6 gave 92.4, 95.9 and 97.6 % respectively and these formulations showed moderate drug release. Where else, while comparing the formulation F1, F2 and F9 the percentage drug release was found to be 96.7, 95.1 and 98.9 % respectively. These formulations showed higher dissolution rate due to the incorporation of low concentration of the HPMC and these formulations does not retard the release rate and found unsatisfactory. The optimized formulation gave 93.4% and these showed extended-release rate.

10.9 Effect of HPMC K4M & K100M on Tensile strength of minitablets:

Minitablets tensile strength (N/m^2) depends on the hardness, thickness and diameter. The tensile strength of the tablet was varied according to the HPMC concentration. In F8 tensile strength was found to be 3.42 N/m^2 due to high concentration of HPMC K4 (12 mg) and K100M (6 mg). In the case of formulation F9, the tensile strength was found to be 2.75 N/m^2 . Compare the all formulation lower concentration of HPMC K4M (4 mg) and K100M (2 mg) gave lower tensile strength.

10.10 Optimization

A total of 9 ER minitablet formulations were proposed through a 3^2 full factorial design for two dependent variables: percent drug release and tensile strength were investigated as optimised response parameters in the current study. The results of the ANOVA indicated that these models were significant for all response parameters (**Table 37-38**). The Design-Expert.11.1.2 software provided suitable polynomial model equations involving individual main factors and interaction factors after fitting these data. The model equation relating dissolution as a response becomes. ANOVA study was performed and the final equation of best yield was found to be.

Model equation relating drug release as response became:

$$Y=+100.333+0.999A-1.875B+0.1009AB-0.139A^2 \dots\dots\dots (7)$$

Model equation relating tensile strength as response became:

$$Y=+2.976-0.012A+0.076B+0.010A^2 \dots\dots\dots (8)$$

The influences of main effects (factors) on responses investigated (here, dissolution) were further elucidated by response surface methodology. Response surface methodology is a widely proficient approach in the development and optimization of drug delivery devices. In order to evaluate the optimization capability of these models generated according to the results of 3² full factorial design, optimized Lamotrigine ER minitabets were prepared using one of the selected optimal process variable settings proposed by the experimental design. The selected optimal process variable settings used for the optimized formulation were A = 11 and B = 4.5. Gunda RK *et al* ^[52] performed dissolution parameters related to controlled release tablets formulation and similarly optimization carried out for coating process parameter to acquire the optimal values of responses based on desirability criterion with the help of Design expert software (Version 11.1.2, Stat-Ease Inc., Minneapolis, MN), which led to develop optimized minitabets (F10).

10.10.1 Response surface and contour:

Three-dimensional response surface plots and their corresponding contour plots to estimate the effects of the independent variables (factors) on each response investigated were presented in **(Fig:31-32)** A 3D response surface plot details the main and interactive effects and effects of independent variables (factors), while a 2D contour plot gives a visual representation of the response values. The three -dimensional response surface plots and corresponding contour plots relating to dissolution indicates the decreased values of % drug release with increases HPMC concentration. Thereby, increasing the concentration of HPMC in turn increase the tensile strength of the minitabets. The probability (p value) of the models was less than 0.05 and the p value of the lack of fit was greater than 0.05, indicating that the selected model could well describe the relationship between the independent and dependent variables.

10.11 Drug release kinetics:

Dissolution data of the optimized formulation was fitted to various mathematical models (zero-order, first-order, Higuchi and Korsmeyer-Peppas) in order to describe the kinetics of drug release. Regression coefficient and slope (rate) were compared in all the formulations to study their effect on drug release. Further, optimized formulation fitted with selectively zero order and Peppas model to calculate the value of sum of squared residuals (SSR) and Akaike information criterion (AIC), best goodness-of-fit test (R^2). High value of Mean selection criterion (MSE) was taken as criteria for selecting the most appropriate model. Accordingly, optimized formulation fitted with all dissolution model and the values found to be (**Table:45**) values found to be followed zero-order and Korsmeyer-Peppas kinetics (**Table:46-49**). The release exponent of peppas model ($n=0.3$) indicate Quasi-Fickian) diffusion and rates as a function of time follows zero order release. Similarly, adjusted R^2 Values - 0.9910, AIC - 44.7266, some of square residues (SSR) and mean selection criterion - 2.377 were satisfied with korsmeyer-peppas model.

10.12 In vivo studies:

This method has been used to assess lamotrigine in plasma following a single oral dose of the 30 mg/kg formulation in rats. Plasma Concentration, profile of test and standard shows in **Table 50**. After the administration of formulation, where as in test, Area Under Plasma Concentration (AUC 0-t) was found to be 1123.4 $\mu\text{g} \cdot \text{hr}/\text{ml}$ and (AUMC 0-T) was found to be 3313 $\mu\text{g} \cdot \text{hr}^* \text{ hr}/\text{ml}$ and its C_{max} was found to be 375.0 $\mu\text{g}/\text{ml}$, T_{max} is 4 hrs. (AUC 0-t), AUMC 0-T, C_{max} and T_{max} was found to be 997 $\mu\text{g} \cdot \text{hr}/\text{ml}$, 3108.6 $\mu\text{g} \cdot \text{hr}^* \text{ hr}/\text{ml}$, 312.0 $\mu\text{g}/\text{ml}$ and 4 hrs for market formulation. (**Table 52**).

10.13 Stability study:

The colour and shape of the minitablets were found to be unchanged even at the end of 2nd month stability study in all conditions. The results are shown in Tables:41 and Fig: . In order to perform the stability study, the minitablets were placed with packing material and then placed into the stability chamber. At the end of the month, one set of the capsule was analysed for shape average weight and drug content. There was no change in the colour and shape of the minitablets. Also, no change absorbed in release behaviour up to two months when compared to optimized formulation.

11. Summary

Chapter I:

In this introduction chapter discussed about epilepsy, types and treatment, extended- release drug delivery system and their approaches. Also, Multi particulate drug delivery system, minitabets, types, advantages and method of manufacturing.

Chapter II:

In this Chapter the literature related to this work was surveyed and a brief discussion had been given on each literature.

Chapter III:

The objective of present investigation was to formulated and developed lamotrigine (200mg) extended-release minitabets using HPMC K4M and K100M as a release modifier. Minitabets were prepared by direct compression technique.

Chapter IV:

This Chapter gives an idea for the proposed plan of work that has to be carried out.

Chapter V & VI:

In this chapter information about the drug and the polymers used in the study was given.

Chapter VII & VIII:

This chapter deals with the materials and methods used in the study. This chapter covers the details of experimental methods, Design of experiment, including evaluation of pre formulation, *in vivo*, *in-vitro* evaluation, and release kinetics finally stability studies.

Chapter IX:

This chapter depicts the results for the all tests indicated in the chapter VIII. The results for all the parameter to be evaluated for the prepared Lamotrigine minitabets forms were given in this chapter. The *In-vitro* evaluation of the optimized formulation were available.

Chapter VIII & X:

These chapters deal with the optimization of the formulation among the 9 formulation of Lamotrigine ER minitablets. In it, the best values for different evaluation tests are found and presented. Dissolution studies of different formulation is tabulated and stability study was given. The chapter discussion involves in discussion of the better fit values of the different evaluation test to optimize the best fit values A total of 9 ER minitabulet formulations were proposed by the 3^2 full factorial design for two independent Variables. percent drug release and tensile strength were investigated as optimised response parameters in the current study. The results of the ANOVA indicated that these models were significant for all response parameters (**Table 36-37**). The Design- Expert 11.1.2 software provided suitable polynomial model equations involving individual main factors and interaction factors after fitting these data. The influences of main effects (factors) on responses investigated optimized formulation fitted with selectively zero order and Peppas model to calculate the value of sum of squared residuals (SSR) and Akaike information criterion (AIC), best goodness-of-fit test (R^2). High value of Mean selection criterion (MSE) was taken as criterion for selecting the most appropriate model. Accordingly, optimized formulation fitted with all dissolution model and the values found to be followed Zero-order, First order, Higuchi' s model Korsemyer-peppas kinetics (Table 44). The release exponent of peppas model ($n=0.3$) indicate Quasi-Fickian) diffusion and rates as a function of time follows zero order release. Similarly, adjusted R^2 Values - 0.9910, AIC - 44.7266, some of square residues (SSR) and mean selection criterion - 2.377 were satisfied with korsemyer-peppas model.

12. Conclusion

In this study, lamotrigine extended-release mini-tablets were successfully developed by filling 8 mini-tablets into empty capsule shells (size 0), releasing almost the full dose within 12 hours. 3^2 full factorial design and optimization technique successfully used in the development and formulation of Minitablet. Mini tablets of lamotrigine were prepared by the direct compression method using HPMC K4 M and K100M as a release modifiers. The different formulations containing HPMC with different viscosity grades have shown differences in drug release profiles.

The blend of all the formulations showed good flow properties such as the angle of repose, bulk density, tapped density. The prepared tablets showed good post-compression parameters and they passed all quality control evaluation parameters according to I.P limits. From the results it was clearly understand that as the polymer concentration increases the release rate of drug was retarded and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired extended release of the drug for longer periods treatment of epilepsy.

Lamotrigine can be used in a minitabket sustained-release drug delivery system and prolong the duration of action in the therapeutic range without reaching toxic levels as in conventional dosage forms. a valuable tool for achieving improved adherence and seizure control, and reduced toxicity.

Optimum formulation F(10) was suggested by the software. Formulation F (10) were exhibited satisfactory physio-chemical characteristics and prepared with HPMC K4M (11 mg) and K100M (4.5 mg) gave 95.4 % of desired drug release in 12 hrs also stable in stability. Marketed formulation (LAMICTAL XR) showed 91.3% drug release. when compared with the optimized formulation decrease release profile. The maximum plasma concentration C_{max} was 375.0 $\mu\text{g/mL}$ and the time needed to reach T_{max} was 4 hrs for Lamotrigine ER minitabkets.

The optimized formulations followed zero order kinetics while the drug release mechanism was found to be Quasi Fickian. On the basis of evaluation parameters, the formulation F10 used once a day administration in the management of epilepsy. These dosage forms have the ability to reduce the dosing frequency.

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