FORMULATION AND *IN-VITRO* EVALUATION OF GABAPENTIN CONTROLLED RELEASE TABLETS USING NATURAL POLYMERS

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI - 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I – PHARMACEUTICS

Submitted by

NAME: V.ARUNKUMAR

REG.No.261810251

Under the Guidance of

Dr S.BHAMA, M. Pharm., Ph. D

PROFESSOR & HEAD

DEPARTMENT OF PHARMACEUTICS

J.K.K.NATTARAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

TAMILNADU.

APRIL – 2020

CERTIFICATES

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION AND *IN VITRO* EVALUATION OF GABAPENTIN CONTROLLED RELEASE TABLETS USING NATURAL POLYMERS",** submitted by the student bearing **Reg. No: 261810251** to **"The Tamil Nadu Dr M.G.R. Medical University – Chennai",** in partial fulfilment for the award ofDegree of **Master of Pharmacy** in Pharmaceutics was evaluated by us during the examination held on……..…….

Internal Examiner External Examiner

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"FORMULATION AND *IN VITRO* EVALUATION OF GABAPENTIN CONTROLLED RELEASE TABLETS USING NATURAL POLYMERS",** submitted to "**The Tamil Nadu Dr M.G.R. Medical University, Chennai**", in partial fulfilment and requirement of university rules and regulation for the award of Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by the student bearing Reg. No**. 261810251** during the academic year 2019-2020, under the guidance and supervision of **Dr S.BHAMA, M. Pharm., Ph. D.,** Professor & Head, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy,Kumarapalayam.

Dr. S. Bhama, M. Pharm., PhD.,
Professor & HOD,
Department of Pharmaceutics

Dr. R. Sambathkumar, M. Pharm., PhD.,
Professor & Principal,

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"FORMULATION AND *IN VITRO* EVALUATION OF GABAPENTIN CONTROLLED RELEASE TABLETS USING NATURAL POLYMERS",** submitted to "**The Tamil Nadu Dr. M.G.R. Medical University**, **Chennai**", in partial fulfilment and requirement of university rules and regulation for the award of Degree of **Masterof Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by the student bearing, **Reg.No. 261810251** during the academic year 2019-2020, under my guidance and direct supervision in the Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Kumarapalayam.

Place: Kumarapalayam,
Date:

Dr. S. Bhama, M. Pharm., PhD.,
Professor & HOD,
Department of Pharmaceutics

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"FORMULATION AND *IN VITRO* EVALUATION OF GABAPENTIN CONTROLLED RELEASE TABLETS USING NATURAL POLYMERS",** submitted to "**The Tamil Nadu Dr. M.G.R. Medical University**, **Chennai**", in partial fulfilment and requirement of university rules and regulation for the award of Degree of **Master of Pharmacy** in **Pharmaceutics**, is a bonafide work carried out by the student bearing, **Reg. No: 261810251**during the academic year 2018-2020, under the guidance and supervision of **Dr. S. BHAMA, M. Pharm., Ph. D.,** Professor & Head, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

Place: Kumarapalyam
Date:

Dr. R. Sambathkumar, M.Pharm., PhD.,
Professor & Principal,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam.

DECLARATION

I do hereby declare that the dissertation **"FORMULATION AND *IN VITRO* EVALUATION OF GABAPENTIN CONTROLLED RELEASE TABLETS USING NATURAL POLYMERS"** submitted to "**The Tamil Nadu Dr. M.G.R Medical University - Chennai",** for the partial fulfilment of the degree of **Master of Pharmacy** in **Pharmaceutics,** is a bonafide research work has been carried out by me during the academic year 2019-2020, under the guidance and supervision of **Dr S.BHAMA, M. Pharm., Ph. D.,** Professor & Head, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam. I further declare that this work is original and this dissertation has not been submitted previously for the award of any other degree, diploma, associateship, and fellowship, or any other similar title. The information furnished in this dissertation is genuine to the best of my knowledge.

Place: Kumarapalayam

Date:

Mr. ARUN KUMAR. V

Reg. No. 261810251

Dedicated to Parents,
Teachers & My Family

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

I am proud to dedicate my deep sense of gratitude to the founder, (Late) Thiru **J.K.K. Nattaraja Chettiar,** providing the historical institution to study.

My sincere thanks and respectful regards to our reverent Chairperson **Smt.N.Sendamaraai, B.Com.,** and Director **Mr.S.OmmSharravana,B.Com., LLB.,** J.K.K. Nattraja Educational Institutions, Kumarapalayam for their blessings, encouragement, and support at all times.

It is a most pleasant duty to thank my beloved guide **Dr. S. Bhama, M.Pharm., Ph.D.,** Professor & Head Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam for ensuring all the facilities were made available to me for the smooth running of this project and tremendous encouragement at every step of this dissertation work, without her critical advice and deep-rooted knowledge, this work would not have been a reality.

It is my privilege to express the deepest sense of gratitude towards**, Dr. R. Sambathkumar M.Pharm., Ph.D.,** Principal & Professor for his valuable suggestions and inspiration.

My sincere thanks to **Mr. R. Kanagasabai, B.Pharm, M.Tech.** Associate Professor, **Dr. V. Kamalakannan, M.Pharm., Ph.D.,** Associate Professor, **Mr. K. Jaganathan, M.Pharm.,** Associate Professor, **Mr. C. Kannan, M.Pharm.,** Associate Professor, Department of Pharmaceutics, **Ms. S. Manodhini Elakkiya, M.Pharm.,** Assistant Professor, and **Mr. M. Subramani, M.Pharm.,** Lecturer, Department of pharmaceutics for their invaluable help during my project.

My sincere thanks to **Dr. V. Sekar, M.Pharm., Ph.D.,** Professor and Head, Department of Analysis, **Dr. Ananda Thangadurai, M.Pharm., Ph.D.,** Professor, **Dr. I. Caolin Nimila, M.Pharm., Ph.D.,** Associate Professor, **Mr. D. Kamalakannan,** Assistant Professor, **Mrs. P. Devi, M.Pharm.,** Assistant Professor and **Ms. V. Devi, M.Pharm.,** Lecturer, Department of Pharmaceutical Analysis for their valuable suggestions.

My sincere thanks to **Dr. R. Shanmugasundaram, M.Pharm., Ph.D.,** Vice Principal & HOD, Department of Pharmacology, for his valuable suggestions during my project work.

I greatly acknowledge the help rendered by **Mrs. K. Rani,** Office Superintendent, **Miss. S. Sudhalakshmi,** Typist, **Mrs. V. Gandhimathi, M.A., M.L.I.S.,** Librarian, **Mrs. S. Jayakala B.A., B.L.I.S.,** and Asst. Librarian for their co-operation. I owe my thanks to all the technical and non-technical staff members of the institute for their precious assistance and help.

My sincere thanks to **K. Gangaiamaran. M.Pharm., G. Ramachandran. B.Pharm.,** and **Nijanthan, M.Pharm.,** and **K. Sundarrajan, M.Pharm., C. Yogananth B.Pharm,** for his help during the project.

I am thankful to all my classmates, friends, and juniors. It is a very difficult task to acknowledge the services to thank all those gentle people. So I would like to thank all those people who have helped me directly or indirectly to complete this project work successfully.

V.ARUN KUMAR,
REG.NO:261810251

CONTENTS

CONTENTS

LIST OF ABBREVIATIONS USED

API	Active Pharmaceutical Ingredient
C	Centigrade
CDDS	Controlled drug delivery system
CRDDS	Controlled release drug delivery system
CO_2	Carbon dioxide
HCL	Hydrochloric acid
FT-IR	Fourier transform infra-red
GFDDS	Gastric floating drug delivery system
GI	Gastrointestinal
GIT	Gastro intestinal tract
HPLC	High-performance liquid Chromatography
IP	Indian pharmacopoeia
SA	Sustained action
SR	Sustained release
USP	United States Pharmacopeia
UV	Ultraviolet

1. INTRODUCTION

The United States Pharmacopoeia (USP) defines the modified-release (MR) dosage form as "the one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms". One class of MR dosage form is an extended-release (ER) dosage form and is defined as the one that allows at least a 2-fold reduction in dosing frequency or a significant increase in patient compliance or therapeutic performance when compared with that presented as a conventional dosage form (a solution or a prompt drug-releasing dosage form). The terms "controlled release (CR)", "prolonged release", "sustained or slow-release (SR)" and "long-acting (LA)" have been used synonymously with "extended-release".

Controlled drug delivery systems can include the maintenance of drug levels within the desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations. The ideal drug delivery system should be inert, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize. The goal of many of the original controlled-release systems was to achieve a delivery profile that

would yield a high blood level of the drug over a long period of time. With traditional drug delivery systems, the drug level in the blood level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective.[1]

These difficulties have prompted researchers to design a drug delivery system which can remain in the stomach for a prolonged and predictable period. Attempts are being made to develop a controlled drug delivery system, which can provide drug release at a pre-determined, predictable and controlled rate. The De novo design of an oral CDDS should be primarily aimed at achieving more predictable and increased bioavailability of drugs[2.] For the successful performance of oral CRDDS, the drug should have good absorption throughout the GIT, preferably by passive diffusion.

The controlled release dosage form is a dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or locally to a specified target organ. Greater attention is paid on the development of oral controlled release drug delivery systems due to flexibility in designing of the dosage form. The main challenges to oral drug delivery systems are to deliver a drug at a therapeutically effective rate to the desired site, modulation of GI transit time and minimization of first-pass elimination. Control release dosage form provides better maintenance of optimal and effective drug level for a prolonged duration with less dosing frequency and side effects. [2]

The modified release oral drug delivery systems classified as are:

- Controlled release
  - Sustained release
  - Extended-release
  - Prolonged-release
- Delayed-release

1.1. CONTROLLED RELEASE DRUG DELIVERY SYSTEM

The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutics, pharmacokinetics, and pharmacodynamics properties of a drug in such a way that its utility is maximized through a reduction in side effects and cure or control of disease condition in the shortest possible time by using the smallest quantity of the drug, administered by the most suitable route. The immediate-release drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. An ideal drug delivery system should deliver the drug at a rate dictated by the need of body over a specified period of treatment.

A controlled release drug delivery system is capable of achieving the following benefits over conventional dosage forms [3].

- The total dose is low.
- Reduced GI side effects and other toxic effects.
- Reduced dosing frequency.
- Better patient acceptance and compliance.

- Less fluctuation in plasma drug levels.
- More uniform drug effect.
- Better stability of the drug.

1.2. FACTOR INFLUENCING THE FORMULATION OF ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEM[2, 3, 4, and 5]

Physicochemical factors

1.2.1. Solubility:

Low aqueous solubility drugs have low oral bioavailability [5].Drugs having good solubility in the stomach are a poor choice for controlled/sustained oral dosage forms.The water solubility limits the loading efficiency of the drug into a variety of carrier systems such as liposome and microparticles, where highly water-soluble drug tend to leach fast from the carrier. The pH-dependent solubility, particularly in the physiological pH range, would be another problem for controlled release formulation because of the variation in pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system allowsestimatingthe contribution of three major factors solubility, dissolution and intestinal permeability which affect oral absorption. Class III (High solubility-Low permeability) and Class IV (Low solubility-Low permeability) drugs is a poor candidate for the controlled release dosage form.

1.2.2. Drug Stability

A drug in a solid-state undergoes degradation at a much slower rate than a drug in suspension or solution [6, 7]. Drugs that are unstable in gastric pH can be developed as slow-release dosage form and the drugs can be delayed till the dosage form reaches the

intestine. Drugs that undergo gut-wall metabolism and show instability in the small intestine are not suitable for oral controlled drug delivery systems.

1.2.3. Molecular Size and Diffusivity[8, 9, 10]

Diffusivity defined as the ability of a drug to diffuse through the membrane, is inversely related to molecular size. Diffusivity depends on the size and shape of the cavities of the membrane. More than 95% of drugs are absorbed by passive diffusion. The upper limit of drug molecular size for passive diffusion is 600 Dalton. The examples of the drugs which are difficult to control the release rate of medicament from dosage form are proteins and peptides.

1.2.4. Partition coefficient[9, 10]

The partition coefficient is defined as the fraction of drug in an oil phase to that of an aqueous phase. It governs the permeation of drug particles through biological membrane. Drugs with high partition coefficient value easily permeate through biological membrane. The diffusion of drug molecules across rate controlling membrane or through the matrix system essentially relies on partition coefficient. Drugs that have lower partition coefficient are not suitable for oral controlled release drug delivery system and drugs that have higher partition coefficient are also not suitable for oral controlled drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane.

1.2.5. Drug pKa and ionization at physiological pH [5, 11]

Drugs existing largely in ionized form are poor candidate for oral controlled release drug delivery system because absorption rate of ionized drug is 3-4 times less than that of unionized form. The pKa range for acidic drug whose ionization is

pH sensitive is around 3.0- 7.5 and for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption.

Biological factors

1.2.6. Absorption [1, 4]

The aim of formulating controlled release product is to place control on delivery system. The desirable quality of oral controlled delivery system is that it should release complete drug and the release drug should be completely absorbed. The fraction of drug absorbed from the system can be lower than the expected due to degradation of drug, protein binding, site-specific, dose-dependent absorption, poor water solubility and small partition coefficient.

1.2.7. Distribution [1, 4, 11]

Drugs with high apparent volume of distribution, which influence the rate of elimination of drug, are poor candidate for oral drug delivery system. The apparent volume of distribution is one of the important parameter of drugs that describes the magnitude of distribution as well as protein binding within the body. The distribution of drug can be determined by the volume of distribution at steady state and T/P ratio.

$$T/P=K12/ (K21-b)$$

T = Amount of drug in peripheral compartment,

P = Amount of drug in central compartment,

K12 = Constant for distribution of drug from central to peripheralCompartment,

K21 = Constant for distribution of drug from peripheral to central Compartment,

B = Slow disposition constant.

1.2.8. Metabolism [4, 12]

Metabolism of a drug is either an inactivation, of an active drug or conversion of an inactive drug to an active metabolite. There are two factors related to metabolism of drug whichrestrict the design of sustained/controlled drug delivery. For chronic administration, drugs that are capable of either inducing or inhibiting enzyme synthesis, they are poor candidates for controlled delivery systems due to difficulty in maintaining uniform blood levels. Drugs possessing variations in bioavailability due to first-pass effect or intestinal metabolism are not suitable for sustained/controlled drug delivery.

1.2.9. Half- life [4, 5]

The duration of action is dependent on the biological half- life. Drugs with short half-life (greater than 2 hrs) are most suitable for controlled drug delivery system. Factors influencing the half-life of a drug are elimination, metabolism, and distribution.

1.2.10. Therapeutic index [5]

The margin of safety can be described by considering therapeutics index, which is the ratio of median toxic dose and median effective dose**.**

Therapeutic index = TD50/ED50.

Drugs with low therapeutics index are unsuitable for drug incorporation in controlled release formulation**.** The side effects can be minimized by controlling the concentration within therapeutic range.

1.2.11. Size of dose [5]

If the dose of a drug in conventional dosage form is high, then it is less suitable candidate for CRDDS. This is because the size of a unit dose controlled release oral formulation would become too big to administer without difficulty.

1.2.12. Absorption window [5, 11]

Certain drugs when administered orally are absorbed only from a specific part of GI tract. This part is known as 'absorption window'. These kinds of drugs are not suitable for CRDDS.

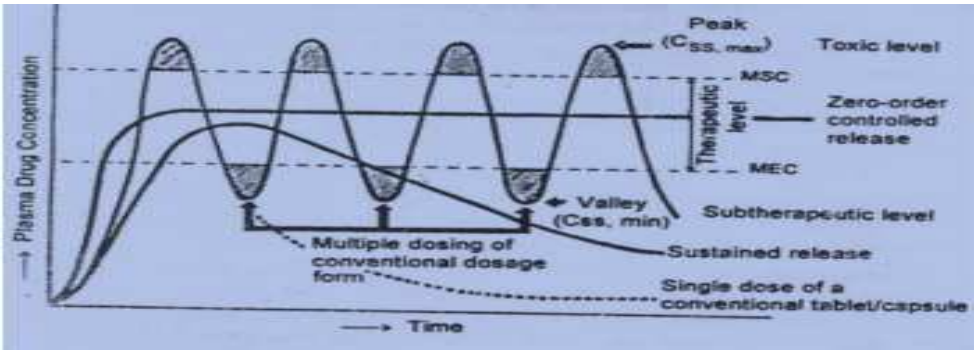
1.2.13. Plasma concentration response relationship [1, 5, 11, 12]

Plasma drug concentration is more responsible for pharmacological response than dose. But the drugs having pharmacological activity independent of plasma concentration are poor candidate for oral CR drug delivery system.

1.2.14. Concentration dependency on transfer of drug

If transfer of drug from one compartment to other follows zero order kinetic process then such drugs are poor candidate for oral CR delivery system [1, 13]. It should be first order kinetics. The following figure represents various formulation strategies for oral CR drug delivery system.

Figure 1: **Concentration dependency on transfer of drug**



1.3. MECHANISTIC ASPECTS FOR ORAL CONTROLLED RELEASE DRUG DELIVERY FORMULATION

1.3.1. Dissolution controlled release [8. 14]

Dissolution is defined as solid substance solubilized in a given solvent. It is a rate determining step when liquid is diffusing from solid. Several theories explain dissolution: Diffusion layer theory, Surface renewal theory, Limited solvation theory.

Noyes Whitney Equation

Dc/dt = kD.A (Cs – C) dc/dt = D/h A. (Cs – C)

Dc/dt = Dissolution rate,

k = Dissolution rate constant (1st order),

D = Diffusion coefficient/diffusivity,

Cs = Saturation/ maximum drug solubility,

C = Conc. of drug in bulk solution,

Cs-C = concentration gradient,

H = Thickness of diffusion layer.

Two common formulation systems rely on dissolution to determine release rate of drugs are:

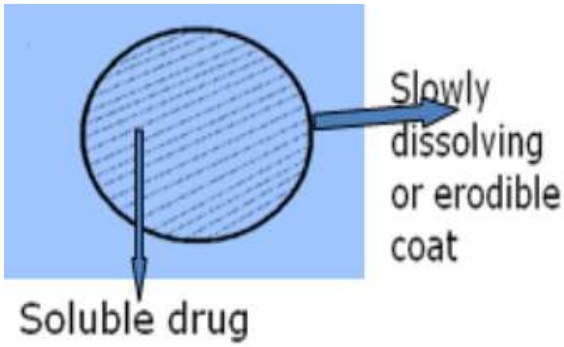
(i) Encapsulated dissolution system

(ii) Matrix dissolution system

(i) Encapsulated dissolution system [8, 15]

This is also known as coating dissolution controlled system. The dissolution rate of coat depends upon stability & thickness of coating. It masks color, odor, and taste and minimize GI irritation. Controlled release products by decreasing the dissolution rate of drugs which are highly water soluble can be formulated by preparing appropriate salt or derivatives, by coating the drug with a slowly dissolving material, or by incorporating the drug into a slowly dissolving carrier. Examples: Ornadespansules.

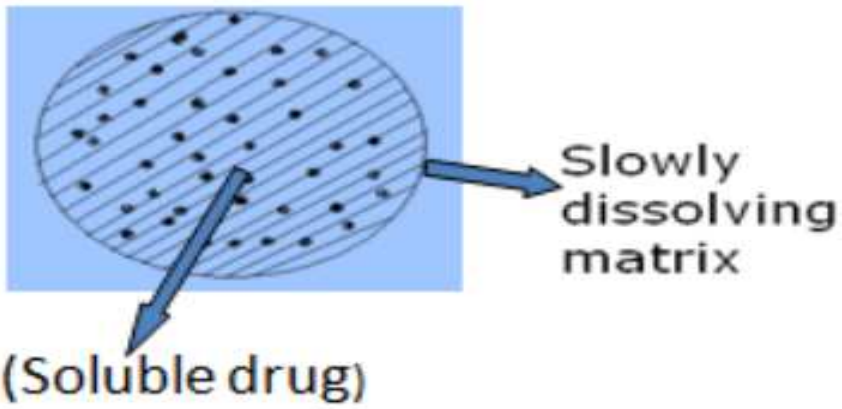
Figure 2: Encapsulated dissolution system



(ii) **Matrix dissolution system** [15, 16]

It is also known as monolithic dissolution controlled system. In this dissolution is controlled by Altering porosity of tablet, decreasing its wettability, dissolving at slower rate. It follows first order drug release. The drug release can be determined by dissolution rate of polymer. Examples: Demeaned extencaps, Dimetapp extencaps.

Figure 3: Matrix dissolution system



a) Diffusion controlled system

It is a major process for absorption in which no energy required. In this drug molecules diffuse from a region of higher concentration to lower concentration until equilibrium is attained and it is directly proportional to the concentration gradient across the membrane. In this system release rate is determined by its diffusion through a water-insoluble polymer.

There are two types of diffusion devices:

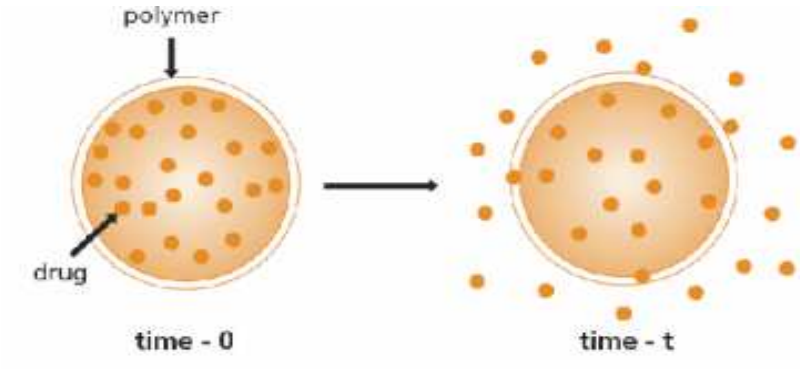
(i) Reservoir diffusion system

(ii) Matrix diffusion system

(i) Reservoir diffusion system [17, 18]

It is also called as laminated matrix device. It is a hollow system containing an inner core surrounded by water insoluble membrane and polymer can be applied by coating or micro encapsulation. The Rate controlling mechanism is that drug will partition into membrane and exchange with the fluid surrounding the drug by diffusion. Commonly used polymers are HPC, ethyl cellulose & polyvinyl acetate. Examples: Nico-400, Nitro-Bid.

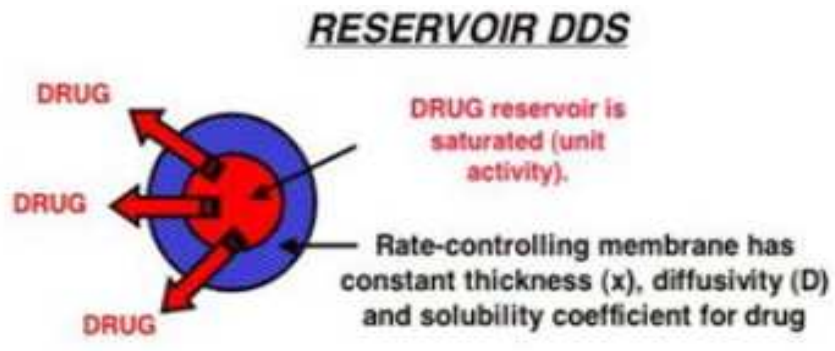
Figure 4: Reservoir diffusion system



Rate controlling steps:

Polymeric content in coating, thickness of coating, hardness of microcapsule.

Figure 5: Rate controlling DDS



(ii) **Matrix dissolution system**

(a) Rigid Matrix Diffusion: Materials used are insoluble plastics such as PVP & fatty acids.

(b) Swellable Matrix Diffusion: it is also called as Glassy hydro gels and popular for sustaining the release of highly water soluble drugs.

Materials used are hydrophilic gums [19].

Examples: Natural- Guar gum, Xanthan gum, Acacia, Agar-Agar.

Semi synthetic -HPMC, CMC

Synthetic -Polyacrilamides.

Examples: Glucotrol XL, Procardia XL

The Higuchi Equation describing the drug release from this system,

$Q = [D\varepsilon/T\ (2A-\varepsilon\ Cs.t)]\ ½$

Where,

Q = amount of drug release per unit surface area at time t,

D = diffusion coefficient of drug in the release medium,

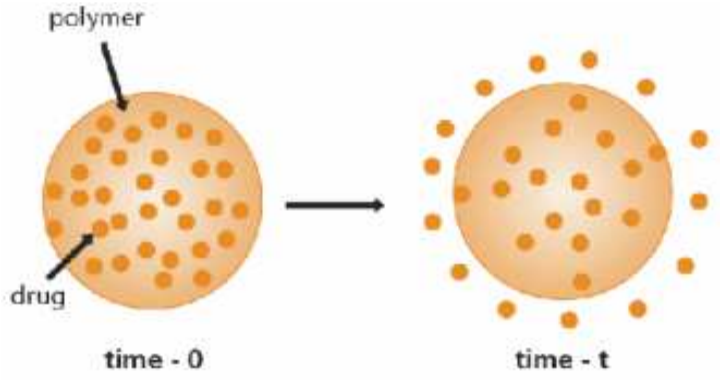
ε = porosity of the matrix,

Cs = solubility of drug in release medium,

T = tortuosity of matrix,

A = concentration of drug present in matrix per unit volume.

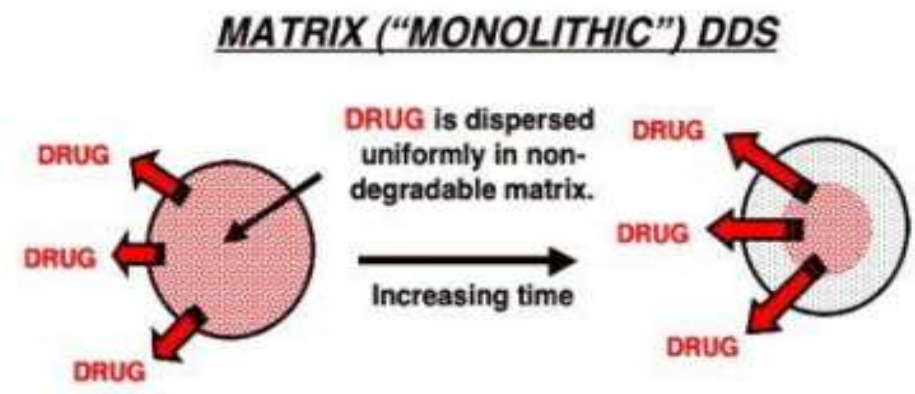
Figure 6: Matrix dissolution system



Rate controlling step:

Diffusion of dissolved drug in matrix.

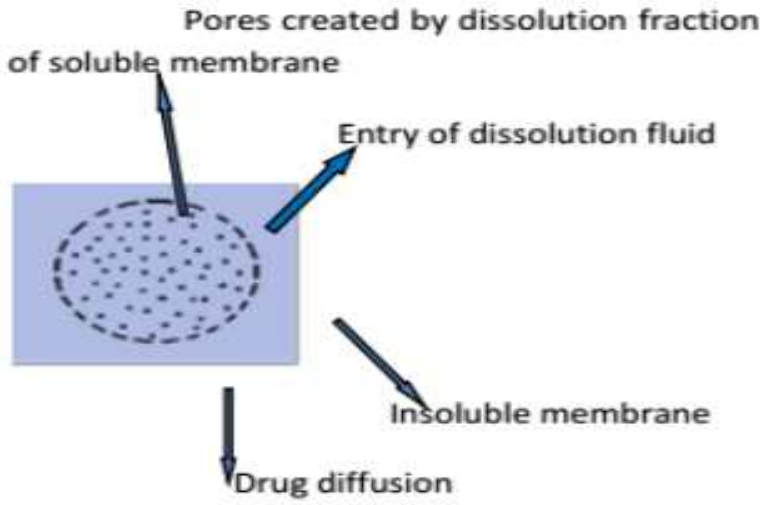
Figure 7: Rate controlling DDS



1.3.2. Dissolution & Diffusion Controlled Release system [20]

In this drug is encased in a partially soluble membrane and pores are created due to dissolution of parts of membrane. It permits entry of aqueous medium into core & drug is dissolved or diffused out of the system. Ex- Ethyl cellulose & PVP mixture dissolves in water & creates pores of insoluble ethyl cellulose.

Figure 8: Dissolution & Diffusion Controlled Release system



1.3.3. Ion exchange resins controlled release system [21, 22, and 23]

Ion exchange resins are cross-linked water-insoluble polymers carrying ionizable functional groups. These resins are used for taste masking and controlled

release system. The formulations are developed by embedding the drug molecules in the ion-exchange resin matrix and this core is then coated with a semi permeable coating material such as Ethyl Cellulose. This system reduced the degradation of drug in GIT. The most widely used and safe ion-exchange resin is divinyl benzene sulphonate**.** In tablet formulations ion-exchange resins have been used as disintegrant.

1.3.4. Osmotically controlled release system [24, 25, 26, 27]

Osmosis is defined as the movement of solvent from lower to higher concentration through semi permeable membrane. Osmotic pressure is the hydrostatic pressure produced by a solution in a space divided by a semi permeable membrane due to difference in concentration of solutes. This technology provides zero order release used for hydrophilic drugs. The drug may be osmotically active, or combined with an osmotically active salt (e.g., NaCl). Semi permeable membrane is usually made from cellulose acetate. Examples: Glucotrol XL, Procardia XL.

The volume flow of water into core reservoir dv/dt is expressed as:

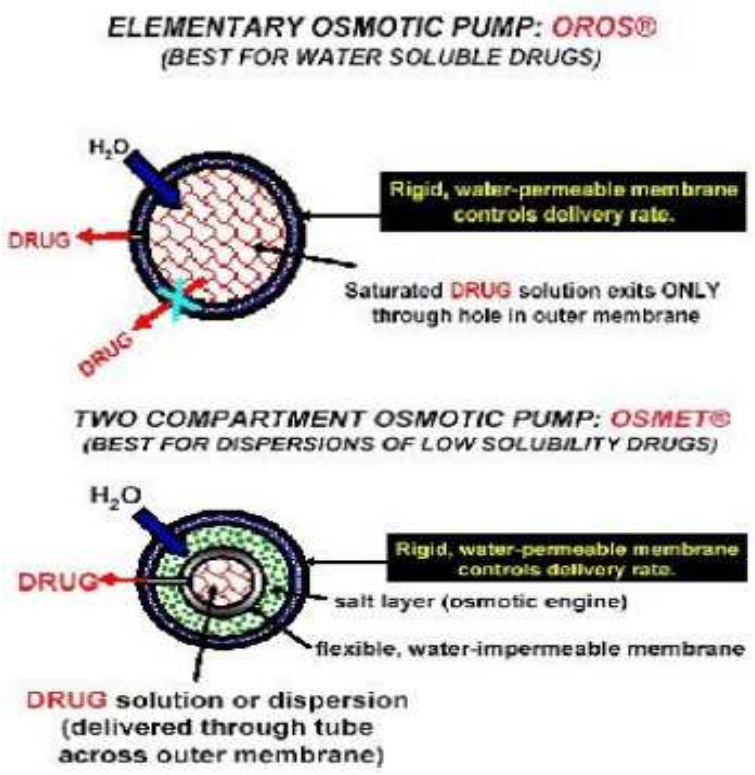
$Dv/dt = K A/ h (\Delta\pi-\Delta p)$

K, A & h= Membrane permeability, effective surface, area & thickness of semi permeable membrane,

$\Delta\pi$= osmotic pressure difference,

Δp= hydrostatic pressure difference.

Figure 9: Osmotically controlled release



1.3.5.P^{H} independent formulation [4, 5, 28]

Most drugs are either weak acids or weak bases. The release from controlled release formulation is pH dependent. However buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to formulation to maintain a constant p^{H} thereby rendering p^{H} independent drug release. A buffered formulation is prepared by mixing a basic or acidic drug with appropriate pharmaceutical excipient and coating with GI fluid permeable film forming polymer. When GI fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant p^{H} thereby rendering a constant rate of drug release.

1.3.5. Altered density formulation [29, 30]

Several approaches have been developed to prolong the residence time of drug delivery system in the GI tract. One such approach is the bio adhesionapproach which is based on the adherence of bio adhesive polymer to mucin/epithelial surface of GI tract. The other approach is to alter the formulation's density by using either high or low density pellets.

(I) **High density approach:**In this density of pellets must exceed that of normal stomach content and should therefore be at least 1.4g/cm^3. In preparing such formulations, drugs can be coated on heavy core or mixed with heavy inert materials such as barium sulphate, titanium dioxide, iron powder and zinc oxide. The weighted pellets can be covered with a diffusional controlled membrane.

(II) **Low density approach*:*** In this apparent density lower than that of gastric fluid can be used as a carrier of drug for controlled release purposes. Polystyrol, pop rice and even popcorn are all candidate as carrier. The surface of these empty shells is undercoated with sugar or a polymeric material such as meth acrylic polymer and cellulose acetate phthalate. The undercoated shell is then coated by a mixture of drug with polymers such as ethyl cellulose and hydroxypropyl cellulose. The final product floats on gastric fluid for a prolonged period, while slowly releasing drug.

1.4. EPILEPSY:

1.4.1. INTRODUCTION: [31]

- Epilepsy is a chronic noncommunicable disease of the brain that affects people of all ages.
- Around 50 million people worldwide have epilepsy, making it one of the most

common neurological diseases globally.

- Nearly 80% of people with epilepsy live in low and middle-income countries.
- It is estimated that up to 70% of people living with epilepsy could live seizure-free if properly diagnosed and treated.
- The risk of premature death in people with epilepsy is up to three times higher than for the general population.
- Three quarters of people with epilepsy living in low-income countries do not get the treatment they need.
- In many parts of the world, people with epilepsy and their families suffer from stigma and discrimination.

Rates of disease:

Epilepsy accounts for a significant proportion of the world's disease burden, affecting around 50 million people worldwide. The estimated proportion of the general population with active epilepsy (i.e. continuing seizures or with the need for treatment) at a given time is between 4 and 10 per 1000 people.

Globally, an estimated five million people are diagnosed with epilepsy each year. In high-income countries, there are estimated to be 49 per 100 000 people diagnosed with epilepsy each year. In low- and middle-income countries, this figure can be as high as 139 per 100 000. This is likely due to the increased risk of endemic conditions such as malaria or neurocysticercosis; the higher incidence of road traffic injuries; birth-related injuries; and variations in medical infrastructure, the availability of preventive health programmes and accessible care. Close to 80% of people with epilepsy live in low- and middle-income countries.

Causes:

Epilepsy is not contagious. Although many underlying disease mechanisms can lead to epilepsy, the cause of the disease is still unknown in about 50% of cases globally. The causes of epilepsy are divided into the following categories: structural, genetic, infectious, metabolic, immune and unknown. Examples include:brain damage from prenatal or perinatal causes (e.g. a loss of oxygen or trauma during birth, low birth weight);congenital abnormalities or genetic conditions with associated brain malformations; a severe head injury; a stroke that restricts the amount of oxygen to the brain;an infection of the brain such as meningitis, encephalitis or neurocysticercosis, certain genetic syndromes; and a brain tumors.

1.4.2. DISEASE PROFILE

Epilepsy is a brain disorder in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally. Neurons normally generate electrochemical impulses that act on other neurons, glands, and muscles to produce human thoughts, feelings, and actions. In epilepsy, the normal pattern of neuronal activity becomes disturbed, causing strange sensations, emotions, and behavior, or sometimes convulsions, muscle spasms, and loss of consciousness[32]. During a seizure, neurons may fire as many as 500 times a second, much faster than normal. In some people, this happens only occasionally; for others, it may happen up to hundreds of times a day.

The risk of premature death in people with epilepsy is 2-3 times higher than the general population. The exact cause of the increased risk is not known in most cases i.e. the cause of sudden unexpected death in some patients[33]. However, some deaths are related to the circumstances around a seizure such as a serious accident during a seizure.

1.4.3. CLASSIFICATION OF EPILEPTIC SEIZURES

Epilepsy can broadly be divided into two categories: idiopathic where there is no known cause, and secondary seizures where there is known cause. Seizures can be either generalized or partial (or focal). In generalized seizures, both halves of the brain are simultaneously affected. In partial seizures, the abnormal electrical discharge starts from a focus in one side of the brain. Later, this may spread to the other side. This spread is called secondary generalization.

- **Generalized Seizures**

In generalized seizures, patients suddenly stop what they are doing, the eyes and head turn to one side and the body becomes stiff. This is usually followed by several jerks of the hands and legs, groaning and frothing from the mouth[34].Generalized seizures consist of many different seizure types, of which the primary generalized tonic-clonic seizure (GTCS) is the most common.

- **Tonic-clonic seizure**

In a generalized tonic-clonic seizure the patient loses consciousness, falls down, sometimes with a scream, and develops a generalized stiffness[35]. Breathing stops, as all the muscles of the trunk are in spasm, the head is retracted, the arms flexed and the legs extended. After a while, this tonic phase is followed by the clonic phase, when the muscles alternately contract and relax, resulting in clonic movements. Either the tonic phase or the clonic phase can predominate in the seizure generalized tonic-clonic seizures can also occur due to secondary generalization in partial epilepsies.

- **Clonic seizures**

These seizures are generalized seizures, where the tonic component is not present, only repetitive clonic jerks (clonic jerks are repetitive rhythmic flexing and stretching of limbs). When the frequency of jerks diminishes the amplitude of the jerks does not diminish.

- **Tonic seizures**

Tonic seizures are sudden sustained muscle contractions, fixing the limbs in some strained position. There is immediate loss of consciousness. Often there is deviation of eyes and head towards one side, sometimes rotation of the whole body.

- **Absence seizures**

These are short periods of loss of consciousness lasting only a few seconds (not more than half a minute). They are of sudden onset, there are usually no, or only minimal motor manifestations. There is a blank stare, brief upward rotation of the eyes and an interruption of ongoing activity. The child is unresponsive when spoken to. It is suddenly over, and the child continues what he was doing before the seizure. People are unaware that these absences are epileptic seizures[36]. Absences are easily provoked by hyperventilation.

- **Myoclonic seizures**

These seizures consist of sudden, brief, shock-like muscle contractions, either occurring in one limb, or more widespread and bilateral. They may be single jerks, or jerks repeated over longer periods. They are often seen in combination with other seizure types occurring in special epileptic syndromes.

- **Infantile spasms**

Patients have flexor spasms of the head, bending of the knees and flexion with abduction of the arms. They occur in the first year of life, and are very difficult to treat.

- **Partial Seizures**

Partial seizures are divided into two groups, simple partial seizures where consciousness is maintained and complex partial seizures where there is an impairment of consciousness.

- **Simple partial seizures**

In simple partial seizures, some patients may experience either motor or sensory phenomena. Such seizures arise from a specific area of the brain, with the patient being fully or partly aware of the event. In motor seizures, the focus is in the primary motor cortex. The psychic symptoms may consist of changes in mood, memory, or thought. May be distorted perceptions or problems with language. Structured hallucinations could occur. These simple partial seizures are usually only recognized as epileptic seizures when they develop into generalized seizures[37].

- **Complex partial seizures**

Here the patient has impaired consciousness, but not complete loss of consciousness. He is slightly aware of what is going on, but he cannot respond to anything, neither can he change his behavior during an attack. The seizure usually starts with an aura which can be of many types such as, a strange feeling in the stomach rising up to the throat and head, or a sensation of light, smell, sound or taste or with changes in perception. After the attack, there is complete amnesia regarding the attack.[38]

1.4.4. CLASSIFICATION OF ANTI EPILEPTIC DRUGS:

Antiepileptic drugs may be classified based on chemistry into different classes. These include:

1. **Hydantoin derivatives**
   - Phenytoin
   - Fosphenytoin
2. **Iminostilbenes**
   - Carbamazepine
   - Oxcarbamazepine
3. **Valproic acid derivatives**
   - Sodium valproate (valproic acid)
4. **Long acting barbiturates**
   - Phenobarbitone
   - Methobarbitone
5. **Deoxy barbiturate**
   - Primidone
6. **Succinimides**
   - Ethosuximide
   - Methsuximide
   - Phensuximide
7. **Benzodiazepines**
   - Clonazepam
   - Nitrazepam
   - Diazepam

8. **Carbonic anhydrase inhibitors (CAI)**
    - Acetazolamide
    - Sulthiame
9. **GAMA- vinyl – GABA**
    - Vigabatrin
10. **Phenyltriazine**
    - Lamotrigine
11. **Amino acid derivatives**
    - GABA pentin
12. **Monosacharide derivatives**
    - Topiramate
13. **Nicotinic acid derivatives**
    - Tiagabine
14. **Sulphonamide derivatives**
    - Zonisamide
15. **Miscellaneous**
    - Paraldehyde

1.4.4. SYMPTOMS

Symptoms vary from person to person. Some people may have simple staring spells, while others have violent shaking and loss of alertness. The type of seizure depends on the part of the brain affected and cause of epilepsy[39].

Most of the time, the seizure is similar to the previous one. Some people with epilepsy have a strange sensation (such as tingling, smelling an odor that isn't actually there, or emotional changes) before eachseizure.[40]

1.4.5. DIAGNOSIS OF EPILEPSY

It is essential that patients with episodes such as described above be accompanied by a witness who can describe the episodes in detail. More often than not, epilepsy can be diagnosed on the basis of reports of patients and eyewitnesses. No laboratory test can replace a clear description provided by theeyewitness.[41]Those who develop epilepsy for the first time require investigations to identify the underlying cause. These investigations include EEG, and imaging tests such as CT scan or MRI of the brain.

1.4.6. TREATMENT

Treatment for epilepsy may involve surgery or medication. If epilepsy seizures are due to a tumor, abnormal blood vessels, or bleeding in the brain, surgery to treat these disorders may make the seizures stop[42].

Medication to prevent seizures, called anticonvulsants, may reduce the number of future seizures.

a. Dosage may need to be changed from time to time. The patient may need regular blood tests to check for sideeffects.

b. Always take medication on time and as directed. Missing a dose can cause the patient to have a seizure. Never not stop taking or change medications without talking to doctor.

c. Many epilepsy medications cause birth defects[43]. Women wishing to become pregnant should tell the doctor in advance in order to adjust medications.

d. Epilepsy that does not get better after two or three anti-seizure drugs have been tried is called "medically refractory epilepsy."

1. Surgery to remove the abnormal brain cells causing the seizures may be helpful for some patients.

2. Surgery to place a vagus nerve stimulator (VNS) may be recommended. This device is similar to a heart pacemaker. It can help reduce the number of seizures.

1.4.7. PREVENTION

Generally, there is no known way to prevent epilepsy. However, proper diet and sleep, and staying away from illegal drugs and alcohol, may decrease the likelihood of triggering seizures in people with epilepsy. Reduce the risk of head injury by wearing helmets during risky activities; this can help lessen the chance of developing epilepsy[44].

Persons with uncontrolled seizures should not drive. Each state has a different law that determines which people with a history of seizures are allowed to drive[45]. If you have uncontrolled seizures, you should also avoid activities where loss of awareness would cause great danger.

2. REVIEW OF LITERATURE

Dhanalakshmi P, et al., (2012), formulated solid lipid nanoparticles of gabapentin for delivery of drugs to the brain. The solid lipid nanoparticles (SLNs) of hydrophilic drug gabapentin is partial seizuresdrugs are developed and the entrapment efficiency of drug in the SLN has been improved. The hydrophilic drug is the problem associated with the incorporation in to SLN**.**[46]

Swati Jagdale, et.al.,(2010), developed gabapentin tablets, pharmaceutically equivalent to the brand-name pioneer product Neurontin® (marketed in USA). Gabapentin 800mg tablets were produced by wet granulation with a constant concentration of intragranular binder and a varying concentration of extra granular binders (A = polyvinylpyrrolidone K30, B = hydroxyl propylmethyl cellulose 15 cps, C = Kollidon VA64, D =Klucel EXF).[47]

Cheng-hung Hsu, et.al., (2010) developed polymorphic transformation of gabapentin polymorphs by Hot stage FTIR microscopy. Four polymorphs (Forms I, II, III and IV) of GBP were well characterized. The GBP form I was proven to be a monohydrate, but other GBP forms II-IV were anhydrous.[48]

Cowels, et.al., (2012), studied pharmacokinetics of gabapentinafter administration of a novel gastroretentive extended release formulation in postmenopausal women with vasomotor symptoms. Gastro retentive extended-release formulation of gabapentin (gabapentin-ER) has recently been demonstrated to be efficacious in the treatment of postmenopausal hot flashes.[49]

Yun-Seok Rhee, et.al., (2012), studied the *Invivo/Invitro* relationship of gabapentin from a sustain release tablet formulation. The dissolution test was employed using pH 1.2, 4.0, or 6.8 buffer solution, or water, to determine the *in vitro* release behaviors of gabapentin tablets.[50]

AbdollahYari, et.al.,(2011), studied aboutantiepileptic gabapentin with a silver nanoparticle modified multiwalled carbon nanotube. A novel carbon nanotube bed electrode impregnated with silver–nanoparticles (AgNPs) for the determination of trace amounts of gabapentin (GBP) was described. The voltammetric behavior of the electrode was investigated by cyclic voltammetry.[51]

Butch KuKanich, et.al., (2011), studied the pharmacokinetics of gabapentin in healthy Greyhound dogs after single oral doses targeted at 10 and 20 mg/kg PO. Six healthy Greyhounds were enrolled (3 males, 3 females). Blood was obtained at predetermined times for the measurement of gabapentin plasma concentrations were determined by liquid chromatography / mass spectrometry. Pharmacokinetic parameters were determined with computer software.[52]

Zhixin Zong, et.al., (2011) determined the stabilizing effect of moisture on the solid state degradation of gabapentin.. Gabapentin was milled in a planetary mill for 15–60 min. The Unmilled and milled gabapentin were stored at 50°C with relative humidity ranged between 5% and 90%. The unmilled and milled samples were assayed for gabapentin and gaba-L by reversed phase-high-performance liquid chromatography and also subjected to powder X-ray diffraction, solid-state nuclear magnetic resonance and surface area analyses.[53]

Ben Achrai, et.al., (2011) reported on the solubilization of gabapentin (GBP) into lyotropic hexagonal mesophases composed of monoolein, tricaprylin,

and water. It was demonstrated that the hexagonal structure remained intact up to 2 wt % gabapentin, whereas the lamellar phase coexisted with the hexagonal one in the concentration range of 3-4 wt % of the drug. At gabapentin content of 5-6 wt %, only lamellar phases containing defects such as dislocations and multilamellar vesicles were detected.[54]

Ahmed N, et.al., (2011) prepared and evaluated floating microsphere of gabapentin.A controlled drug delivery system with prolonged residence time in the stomach can be of great practical importance for drugs with an absorption window in the upper small intestine. The floating microspheres were prepared by the solvent evaporation methods (W/O/W double emulsification- solvent evaporation method, O/O and O/W single emulsion solvent evaporation) using polymers like ethyl cellulose, cellulose acetate, HPMC, HEC, PVP, PVA and chitosan.[55]

Argoft CE, et.al., (2012), developed an once daily gastro retentive formulation of gabapentin tablets for the treatment of post therapeutic neuralgia. Gabapentin immediate-release formulations (G-IR) administered three times a day is an efficacious treatment for postherpetic neuralgia (PHN), but its potential benefits may not be fully realized due to tolerability issues as well as its pharmacokinetic (PK) properties such as its short half-life, and regional and saturable absorption in the proximal small intestine.[56]

Pfizer, et.al., (2009), demonstrated thebioequivalence study of gabapentin between tablet and liquid formulation and the food effect study of liquid formulation.[57]

David Sandercock, et.al., (2009) studied aboutgabapentin for the treatment of painful diabetic peripheral neuropathy.A randomized, double-blind, placebo-

controlled study was conducted in 147 patients to determine the efficacy and safety of gabapentin extended release (g-ER) in treating pain associated with diabetic peripheral neuropathy (DPN). Gabapentin, an immediate-release formulation, has demonstrated clinical efficacy in DPN patients but also a relatively high incidence of somnolence and dizziness at the doses required for effective treatment of DPN pain.[58]

P M Ramdas Bhandarkar, et.al., (2009) carried out the kinetics of oxidative degradation of gabapentin with N-bromosuccinimide in $HClO_4$ medium at 308 K. The experimental rate law obtained was -d(NBS)/dt =NBS]GBP](x)H+](y), where x and y are less than unity. The reaction was subjected to changes in concentration of succinimide, the reduction product of NBS, concentration of the added neutral salt, dielectric permittivity and ionic strength of the medium. Solvent isotope effect has been studied using D_2O.[59]

Taksande, et.al., (2017) formulated and investigatedlamotrigine microspheres and the nasal route has been established as valuable therapeutic alternatives. This study was designed with the basic objective to formulate mucoadhesive microspheres of anticonvulsant drug, lamotrigine (LT) for intranasal delivery and to carry out its pharmacodynamic investigations to benefit the emergency cases of epileptic seizures.[60]

Narasimha S. Managoli, et.al., (2012) prepared crosslinked chitosan hydrogelmatrix tablets for controlledrelease of gabapentin.The hydrogels were prepared by crosslinking chitosan using four different crosslinking agents namely, anhydrous dextrose (DXT), sodium tripolyphosphate (TPP), urea-formaldehyde (UF) and acetaldehyde (AL).They were characterized by differential screening

calorimetry (DSC), thermogravimetricanalysis (TGA) and X-ray diffraction (XRD) analysis.[61]

Issam B. Rimawi, et.al., (2019) developed gabapentin expandable gastroretentive controlled drug delivery system.Expandable systems were usually folded in a capsule and expand to dimensions greater than the pyloric sphincter upon contact with gastric fluid. This prevents them from being evacuated by gastric emptying.[62]

Dembla NM, et.al., (2015) formulated and evaluated gabapentin controlled release tabletsusing different grades of controlled release polymer.[63]

Samar M. Abouelatta, et.al., (2018) developed gastroretentive raft liquid delivery system for carrier mediated drug. Gabapentin (GBP), an antiepileptic and anti-neuropathic agent, suffers from short half-life (5–7 h), hasnarrow absorption window, and is absorbed via carrier-mediated mechanism resulting in frequent dosing,poor compliance, and poor bioavailability (<60%).[64]

Md Tausif Alam, et.al., (2014) studied about FDA-approved natural polymers for oral route.[65]

3. AIM AND OBJECTIVE

AIM:

The aim of the work is to formulate and evaluate the controlled release tablets of gabapentin using natural polymers such as acacia, agar agar, guar gum & xanthan gum with various ratios.

OBJECTIVES:

Gabapentin is an anti-epileptic drug and also used now-a-days to treat neuropathic pains. It is rapidly absorbed from GIT and plasma half-life is about 5-7 hours. Maintaining steady state concentration of gabapentin is difficult due to its short biological half-life. Conventional dosage forms reside in stomach and intestine for only short period. So there is a need of dosage form that increases residence time of drugs in absorption site.

Naturally occurring polymers is preferred for controlled formulation because of its low cost, naturally available, biocompatible and better patient tolerance as well as public acceptance.

To overcome this problem the present work is proposed for the controlled release of Gabapentin.

The objectives which were destined to achieve during the work are:

- To release the drug in a controlled manner with good physical strength.
- To obtain the tablets with optimum content of active pharmaceutical ingredients without variation in the content unit/tablet.

- To study the effect of polymer grade or viscosity: In the present investigation natural polymers such as Acacia, Agar-agar, Guar-gum and Xanthan gum were used to increase duration release rate.
- To evaluate the rate of drug release and mechanism of drug release from the designed tablets.
- To maintain the drug concentration within the therapeutic range.
- To improve the patient compliance and avoid frequency of dosing intervals.
- To provide effective, safe and stable pharmaceutical oral formulation containing controlled release of antiepileptic drugs.

4. PLAN OF WORK

The present work was to formulate and evaluate the controlled release tablets of gabapentin. The following experimental protocol was therefore designed to all systematic approach to the study.

Phase-I:

1. Selection of drug and excipients.
2. Pre-formulation study of gabapentin.
3. Drug exicipient compatibility study of gabapentin by Fourier transform infrared spectroscopy (FT-IR).
4. Preparation of standard curve of gabapentin.

Phase-II:

Formulation and *in vitro* evaluation of controlled release tablets of gabapentin.

1. Formulation of controlled release tablets of gabapentinusing different natural polymers.
2. Evaluation of controlled release tablets of gabapentin
    a) Physical evaluation
    b) *Invitro* dissolution study
    c) Kinetic study

Phase-III:

Accelerated stability study of the optimized formulation as per ICH Guidelines.

5. DRUG AND EXCIPIENTS PROFILE

5.1. DRUG PROFILE

GABAPENTIN

Drug information[66]

Generic name **:** Gabapentin

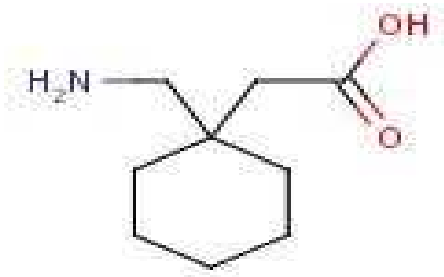
Trade name : Neurontin

Chemical name : 2-[1-(amionmethyl) cyclohexyl] acetic acid

Empirical formula : $C_9H_{17}NO_2$

Molecular weight : 171.24

Structure:



Physico chemical profile

Description **:** White or partially white amorphous powder

Melting point : 162-166°C

Solubility : Freely soluble in water, acidic, alkaline Solutions

Partition co-efficient : log p equal to1.4

Pharmaceutical profile:

1. **Dosage forms and dose:**

   Tablets 100, 300, 400, 600, 800 mg Capsules –100, 300, 400 mg

2. **Pharmacopoeial status:**

   Official in USP and IP

3. **Analytical profile:**

   Chromatographically analyzed by HPLC at 210 nm.

Pharmacokinetic profile:

Oral absorption	:	60%Food has slight effect on the rate and absorption (14% increases in AUC)
Plasma half-life	:	5-7 hours
Volume of distribution	:	58±6 L
Protein binding	:	less than3%
Metabolism	:	not apparently metabolized
Clearance	:	140 ml/min
Excretion	:	renal
Pharmacological		
Profile:		Antiepileptic

5.2. EXCIPIENTS PROFILE

5.2.1. XANTHAN GUM[67]

Nonproprietary Names

BP : Xanthan gum.

USPNF : Xanthan gum

Synonyms : Keltrol; Com sugar gum; Rhodigel; Xantural;

Polysaccharide B-1459

Empirical formula and molecular weight

Formula : (C35H49O29) n

Molecular weight : Approximately 2 X 106

Functional category

Stabilizing agent, suspending agent, viscosity increasing agent.

Applications in pharmaceutical formulation or technology:

Xanthan gum is widely used in oral and topical formulations, cosmetics and Foods as a suspending agent and stabilizing agent. It is also used as a thickening agent and emulsifying agent. It is nontoxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over a wide PH and temperature range. Xanthan gum gels show pseudo plastic behavior, the shear thinning being directly proportional to the shear rate. The viscosity returns to normal immediately on release of shear stress.

Recent studies have revealed that Xanthan gum can also used as excipientsfor spray drying and freeze drying processes for better results.

Although primarily used as a suspending agent, xanthan gum has also beenused to prepare sustained release matrix tablets. Xanthan gum has been incorporated in an ophthalmic liquid dosage form, which interacts with mucin there by helping inprolonged retention of the dosage form in the precorneal area.

Xanthan gum can be used to increase the bio adhesive strength in vaginalformulations and as a binder in colon specific drug delivery systems. Xanthan gumalso used as a hydrocolloid in the food industry and in cosmetics it has been used athickening agent in shampoos.

Description

Xanthan gum occurs as a cream or white colored, Odourless, free-flowing, fine powder.

Typical properties

Acidity/alkalinity **:** pH =6.0-8.0 for a l%w/v aqueous solution

Freezing point **:** 0°C for al% w/v aqueous solution

Heat of combustion **:** 4.6 j/g (3.5 cal/g)

Melting point **:** chars at 270°C

Solubility:

It is practically insoluble in ethanol and ether; soluble in cold or warm water.

Viscosity:

1200-1600 mPas (1200-1600 Cps) for a 1% w/v aqueous solution at 25°C.

Specific gravity:

1.600 At 25°C

Xanthan gum is a stable material aqueous solutions are stable over a wide P H range (PH 3-12), although they demonstrate maximum stability at (PH 4-10) and temperatures of 10-60°C. Xanthan gum solutions of less than 1% w/v concentration may be adversely affected by higher than ambient temperatures: for example, viscosity is reduced. Solutions are also stable in the presence of enzymes, salts, acids and bases.

Storage conditions:

The bulk material should be stored in a well-closed container in a cool, dry Place.

Incompatibilities:

Xanthan gum is incompatible with oxidizing agents, some tablet film coatings, carboxyl methylcellulose sodium, dried aluminium hydroxide gel and some active ingredients such as amitriptyline, tamoxifen and verampil.

Safety:

Xanthum gum is widely used in oral and topical pharmaceuticalformulations, cosmetics and food products and is generally regarded as nontoxic andnonirritant at the levels employed as a pharmaceutical excipient. The estimated acceptable daily intake for xanthan gum has been set by the WHO at up to 10 mg/kg body weight.

Related substances:

Guar gum; ceratonia

5.2.2. GUAR GUM[67]:

Nonproprietary names

BP **:** Guar galactomannan;

PhEur **:** Guar galactomannanum;

USPNF **:** Guar gum.

Synonyms **:** Galactosol; Guar flour; Jaguar gum; Meyprogat; Meyprodor; Meyprofin.

Molecular weight **:** **2,20,000**

Structural formula

Guar gum consists of linear chains of (1:4)-13-d-mannopyranosyl units with a D-galactopyranosyl units attached by (1:6) linkages. The ratio of d-galactose to dMannose is between 1: 1.4 and 1: 2.

Functional category

Suspending agent, tablet binder, tablet disintegrate, and viscosity increasingagent.

Applications in pharmaceutical formulation or technology

Guar gum used in the preparation of sustained release matrix tablets in theplace of cellulose derivatives such as methylcellulose. It is used in solid dosage forms as a binder and disintegrates, in oral and topical products as a suspending,thickening, and stabilizing agent; and also as a controlled release carrier. Guar gum has also been examined for use in colonic drug delivery**.**

Table No.1: Uses of guar gum:

Use	Concentration (%)
Emulsion stabilizer	1
Thickener for lotions and creams	Up to 2.5
Tablet binder	Up to 10

Description

Guar gum obtained from the ground endosperms of Cyamopsistetragonolobus (L.) Taub. (Leguminosae). It consists chiefly of a high-molecular- weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages, which may be described chemically as a galactomannan. Guar gum occurs as an odorless or nearly odorless, white to yellowish-white powder with a blend taste**.**

Typical properties:

pH = 5.0—7.0(1% w/v aqueous dispersion)

Solubility:

It is practically insoluble in organic solvents. It swells almost immediately to form a highly viscous and thixotropic solution in cold or hot water.

Viscosity:

1.86 Pa s (4860 CP) for 1% w/v dispersion.

Stability and storage conditions:

Guar gum powder should be stored in a well closed container in a cool and dryplace.

5.2.3. ACACIA[67]

Scientific Name(s) : Acacia senegal (L.) Willd.

Common Name(s) : Acacia arabica, Acacia gum, Acacia vera, Egyptian thorn, Gum Senegal, Gummaemimosae, Gummiafricanum, Kher, Somali gum, Sudan gum arabic, Yellow thorn.

Empirical Formula and Molecular Weight:

Molecular Formula: $C_{24}H_{34}O_5$

Synonyms: 3b,7b-Dihydroxy-4,4,14-trimethyl-5a-pregn-8-ene-11,15,20-trione, 9CI
3b,7b-Dihydroxy-22,23,24,25,26,27-hexanorlanost-8-ene-11,15,20-trione

Molecular Weight: 402.5 g/mol

Botanic characteristics:

Acacia— Spheroidal tears up to 32mm in diameter or in angular fragments of white to yellowish white colour.Is translucent or somewhat opaque from the presence of numerous minute fissures; very brittle, the fractured surface glassy and occasionally iridescent. Is almost odourless and produces a mucilaginous sensation on the tongue.

Packaging and storage:

Preserve in tight containers.

Solubility and reaction:

Dissolve 1g in 2 mL of water; the resulting solution flows readily and is acid to litmus.

Functional Category: Emulsifying agent (10-20%); stabilizing agent; suspending agent (5-10%); tablet binder (1-5%); viscosity-increasing agent.

Advantages:

Naturally available excipients.

Disadvantages:

Have a chance for microbial growth.

% Weight Loss

Amount retained (R) = W3-W1

Weight loss = S-R

% Weight loss = (S-R/S) X100

Applications in pharmaceutical formulation or technology

Acacia, also known as gum Arabic, is used in the pharmaceutical industry as an emulsifier, stabilizing agent, suspending agent, tablet binder, and viscosity-increasing agent.

Acacia is the dried gummy exudation from Acacia senegal and other species of Acacia (family Leguminosae), prepared as a mucilage and syrup. It is also used in the cooking industry to give body and texture to processed food.

5.2.4. AGAR-AGAR[67]

Scientific names : Gelidiumcorneum

Synonyms : A**gar-agar, agal-agal, E406, gellingagent, stabilizer.**

IUPAC Name **:** (2R, 3S, 4S, 5R)-2-(hydroxymethyl)-6-[[(4R,5S)-4-hydroxy-3-methyl-2,6-dioxabicyclo[3.2.1]octan-8-yl]oxy]-4-methoxyoxane-3,5-diol

Empirical Formula and Molecular Weight

Molecular formula : **$C_{14}H_{24}O_9$**

Molecular Weight : 336.33g/mol

Color/Form

Transparent strips or coarse or fine powder.

Odour:

Odourless.Thin, translucent, membranous pieces, or pale buff powder

Taste:

Tasteless

Solubility:

Less than 1 mg/mL at 63° F (NTP, 1992)

Decomposition:

When heated to decomposition, it emits acrid smoke and fumes.

Absorption, Distribution and Excretion:

It passes through the intestinal tract mostly unabsorbed.

Mechanism of Action:

These substances dissolve or swell in water to form an emollient gel or viscous solution that serves to maintain the feces soft & hydrated. The resulting bulk promotes peristalsis, & transit time is reduced/bulk-forming laxatives.

Uses

Food additives

Uses Classification:

EU food improvement agentsingredient of culture media in microbiology; antitackiness & antistalling agent in baked goods; ingredient in desserts & beverages, laxatives & health foods, pet foods, impression materials; ingredient in pharmaceutical preparations, wave set preparations; laboratory agent in chemical& biological applications.

5.2.5. CALCIUM CARBONATE[67]

Molecular Formula : $CaCO_3$.

Molecular Weight : 100.09.

IUPAC Name **:** calcium; carbonate

Synonyms : Calcite, Calcium carbonate,Calcium milk

Functional category:

Buffering agent, Diluent, Therapeutic agent.

Description:

Occurs as an odorless and tasteless, white powderedcrystals.

Applications:

a. Employed as a pharmaceutical excipient.

b. Also used as a base for medicated dental preparations.

c. Used as bulking agent in tablet sugar coating processes.

d. Used as an opacifier in tablet film coating.

e. Used as a food additive.

f. Used as an antacid and calcium supplement.

Typical Properties:

1. Bulk density -- 0.8 g/cm

2. Tapped density – 1.2 g/cm

3. Flow ability—cohesive.

4. Melting point – 825°C.

Solubility:

Soluble in ethanol, water, insoluble in mineral oil and vegetable oil.

Stability and storage conditions:

It's stable. Stored in well-closed container.Protected from light.

Decomposition

When heated to decomposition it emits acrid smoke and irritating vapors**.**

Safety:

Nontoxic and Non- mucosal irritant.

Refractive Index

Index of Refraction: 1.7216 (300 nm); 1.6584 (589 nm); 1.6503 (750 nm) / Calcite.

Drug Indication

For relief of heartburn and acid indigestion.May also be used as a nutritional supplement or to treat hypocalcemia.

5.2.6. MAGNESIUM STEARATE[67]

Nonproprietaryname : BP: magnesium stearate,

JP: magnesium stearate,

Pheur: magnesiistearas,

USPNF: magnesium stearate.

Synonyms : Magnesium octsdecanoate; octadecanoicacid,

magnesium salt; stearic acid, magnesium salt

Chemical name and CAS registry number:

Octadecanoic acid magnesiumsalt [557-04-0Functionalcategory:

Tablet and capsule lubricant

Description:

Magnesium stearate is a very fine, light white, precipitated or mild, implantable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greesy to the touch and readily adheres to the skin.

Meltingrange **:** 117-150^{o}C(commercial samples); 126-130^{o}C

(high purity magnesium stearate)

Application in pharmaceutical formulation or technology

Magnesium stearate is widely used in cosmetics, foods and in pharmaceutical formulation. It is primarily used as a lubricant in capsule and tablet manufacture.

6. MATERIALS AND METHODS

MATERIALS

The list of materials used was illustrated in the table no 2.

Table 1: List of Materials

S.NO.	MATERIALS	SUPPLIER
1	Gabapentin	Madras Pharmaceuticals, Ltd
2	Acacia	S.D. Fine chemical Pvt Ltd, Mumbai
3	Agar-agar	Merck Specialties Pvt. Ltd
4	Guar gum	S.D. Fine chemical Pvt Ltd, Mumbai
5	Xanthan gum	S.D. Fine chemical Pvt Ltd, Mumbai
6	Calcium carbonate	Nice laboratories
7	Magnesium stearate	S.D. Fine chemical Pvt Ltd, Mumbai

Equipment:

The list of equipmentused in the project was illustrated in table no.3

Table 2: List of Equipment

S.NO.	INSTRUMENTS	MANUFACTURER
1	Electronic Balance	Shimadzu ELB-300
2	Rotary tablet punching machine	Proton Mini press
3	Hardness Tester	Pfizer hardness tester
4	Friability Test Apparatus	Roche Friabilator
5	pH meter	Systronic 335
6	Tablet Dissolution apparatus USP	Lab India
7	Double beam UV Spectrophotometer	Lab India UV 3000
8	FTIR spectrophotometer	Bruker Alpha-T

METHODS

6.1.PREFORMULATIONSTUDIES[68]:

To formulate an intelligent formulation, the pre-formulation studies are usually the quantitative assessment of chemical stability of drug as well as stability in the presence of other excipients for a formulation.

The detailed physical and chemical properties of a drug substance, alone and in combination with excipients were evaluated in Preformulation studies.

6.1.1. Organoleptic properties:

i) Color:

A small quantity of pure gabapentin powder was taken in a paper and viewed in a well-illuminated place.

ii) Taste and odour:

Very less quantity of gabapentin was used to get a taste with the help of tongue as well as smell to get the odour.

6.1.2. **Loss on drying:**.

Determined on 1.000 g by drying in an oven at 100°C to 105°C for 3 hours.Accurately weighed the substance to be tested.If the sample is in the form of large crystals, reducing the particle size to about 2 mm by quickly crushing.Tared a glass stopper, a shallow weighing bottle that had been dried for 30 minutes under the same conditions to be employed in the determination. Put the sample in the bottle, replaced the cover, and accurately weighed the bottle and the contents. By gentle, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. Placed the loaded bottle in the drying chamber. Dried the sample at the

specified temperature from constant weight[68]. Upon opening the chamber, closed the bottle promptly, and allowed it to come to room temperature in desiccators before weighing.

The difference between successive weights should not be more than 0.5mg.

The loss on drying is calculated by the formula:

$$\%LOD=\frac{(W2-W3)}{(W2-W1)} x100$$

Where,

W1 = Weight of empty weighing bottle

W2 = Weight of weighing bottle +sample

W3 = Weight of weighing bottle + dried sample

6.1.3. Solubility analysis[69]:

Solubility is important pre-formulation parameter because it affects the dissolution of drugs, bioavailability of the drug.

Method:

Weigh the appropriate quantity of drug and added to the suitable volume of solvent.

6.1.4.Melting point:

The melting point of gabapentin was determined by the capillary method, using a small quantity of gabapentin was taken and placed in apparatus and determined the melting point and matched with standards[70].

6.1.5. Angle of repose: The angle of repose is the maximum angle of a stable slope determined by friction, cohesion, and the shapes of the particles. The internal angle between the surface of the pile and horizontal surface is known as the angle of repose and is related to the density, surface area, and coefficient of friction of the raw material.

Method: Angle of repose was determined by using the funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. The accurately weighed blend is allowed to pass through the funnel freely on the surface. The height and diameter of the powder cone were measured and the angle of repose was calculated using the following equation.

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

Where, h = height of heap, r = radius of the heap, Θ = angle of repose.

Table3: Limits

Angle of repose	**Flow property**
<25°	Excellent
25-30°	Good
30-40°	Passable
>40°	Very poor

6.2. CALIRATION CURVE OF GABAPENTIN

6.2.1.Preparation of standard curve in 0.1 N Hcl

Preparation of 0.1N HCl:

8.5ml of concentrated hydrochloric acid was diluted up to 1000ml with distilled water.

Accurately weigh one hundred mg of Gabapentin was taken in a 100 mlvolumetric flask and dissolved in 20 ml of methanol. Then the abovesolution was further diluted up to 100 ml with 0.1 N HCl. The resultingsolution of 10 ml was taken and diluted up to 100ml to give a stock solutionof 100 µg/ml with 0.1NHCl to get drug concentration2,4,6,8,10 µg/ml.

The absorbance of the solutions wasmeasured against 0.1 N HCl as a blank at 270 nm using a double beam UV visible spectrophotometer. The plot of concentration (µg/ml) v/s absorbance was plotted and data were subjected to linear regression analysis in Microsoft excel®.

6.2.2.Preparation of standard curve in 6.8 pH buffer

Preparation of Phosphate buffer pH 6.8:

Accurately weighed quantity of 6.8 g of potassium dihydrogenphosphate and 0.89 grams of sodium hydroxide pellets were dissolved indistilled water and diluted with distilled water up to 1000 ml.

Accurately weigh one hundred mg of Gabapentin was dissolvedina 100 ml volumetric flask and dissolved in 20ml of methanol. Then theabove solution was further diluted up to 100ml with a 6.8phosphate buffer.

The resulting solution of 10ml was taken and diluted up to 100ml to give astock solution of 100µg/ml with 6.8phosphate buffer to get a drugconcentration of 2,4,6,8,10µg/ml. The absorbance's of thesolutions were measured against 6.8phosphate buffer as a blank at 270nmusinga double beam UV visible spectrophotometer. The plot of absorbancev/s concentration (µg/ml) was plotted and data were subjected to linear regression analysis in Microsoft excel®

6.3. DRUG AND EXCIPIENT COMPATIBILITY STUDY:

One of the requirements for the selection of suitable excipients or carriers for the pharmaceutical formulation is its compatibility. Therefore in the present work, a study was carried out by using the FTIR spectrometer to find out if, any possible chemical interaction of Gabapentin with Acacia, Agar-agar, Xanthan gum, Guar gum. Compatibility with polymers was confirmed by FTIR studies.

The compatibility study of drug with the excipients was determined by F.T I.R. Spectroscopy (FTIR) using Bruker spectrometer. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The FT-IR spectra were recorded using KBr pellet method in the region 400-4000 cm^{-1}. Spectra were recorded for pure drug, pure excipients, and physical mixture of drug and polymer, drug, polymer, and excipients.

6.4. FORMULATION OF GABAPENTIN CONTROLLED RELEASE TABLETS[71, 72]:

Method of preparation of tablets:

Accurately weigh the active (Gabapentin) and all other ingredients, were individually passed through sieve no.60, and then all the ingredients were mixed thoroughly by triturating upto 15 min. The mixed powder was lubricated and the powder was again mixed thoroughly for punching to tablets by the Direct compression method. The composition of different batch of tablets was given in table no.5.

FORMULATION OF GABAPENTIN TABLETS:

Table 4: Ingredients used and their role

S.NO.	MATERIALS	CATEGORY
1	Gabapentin	Active ingredient
2	Acacia	Polymer
3	Agar-Agar	Polymer
4	Guar gum	Polymer
5	XanthanGum	Polymer
6	CalciumCarbonate	Lubricant
7	Magnesium stearate	Lubricant

FORMULATION OF GABAPENTIN TABLETS:

Table 5: Quantity of Raw Materials per Tablet (In mg)

Ingredients	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**	**F9 (mg)**	**F10 (mg)**	**F11 (mg)**	**F12 (mg)**
Gabapentin	300	300	300	300	300	300	300	300	300	300	300	300
Acacia	125	150	175	_-___	-	-	-	-	-	-	-	-
Agar-agar	_	_	_	125	150	175	_	_	_	_	_	_
Guar gum	_	_	_	_	_	_	125	150	175	_	_	_
Xanthan gum	-_	-	-	-	-	-	-	-	-	125	150	175
Magnesium stearate	25	20	15	25	20	15	25	20	15	25	20	15
Calcium carbonate	50	30	10	50	30	10	50	30	10	50	30	10
Total weight	500	500	500	500	500	500	500	500	500	500	500	500

6.5. EVALUATION OF GABAPENTIN TABLETS

6.5.1.Precompression parameters:

i) Angle of repose[74]:

The frictional forces in loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane and is related to the density, surface area, and coefficient of friction of the rawmaterial.

Method:

The angle of repose was determined by using the funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. The accurately weighed blend is allowed to pass through the funnel freely on the surface[82]. The height and diameter of the powder cone were measured and the angle of repose was calculated using the following equation.

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

Where, h = height of heap, r = radius of the heap, Θ = angle of repose.

Table6: Limits

Angle of repose	Flow property
$<25^{o}$	Excellent
25-30 ^{o}	Good
30-40 ^{o}	Passable
>40 ^{o}	Very poor

ii) Bulk density:

Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle becomes morespherical, bulk density is increase. Also as the granule size increases bulk density decreases.

Method:

The weighed quantity of active powder ingredient (API) was transferred into a 100 ml measuring cylinder without tapping during transfer. The volume occupied by the API was measured. Bulk density was measured by using the formula

Bulk Density = Bulk Mass / Bulk Volume

iii) Tapped density:

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes are observed the mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weigh a specific distance. A device that rotates device during tapping may be preferred to minimize any possible separation of the mass during tappingdown.

Cylinder dropping distance:

14 ± 2mm at a normal rate of 300 drops/minute.

Unless otherwise specified, tab the cylinder 500 times initially and measure the tapped volume Va, the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, Vb, to the nearest graduated unit. If the

difference between the two volumes is less than 2%, Vb is the final tapped volume, Vf. Repeat in increments of 1250 taps, as needed, unit the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per ml, by the formula:

Tapped Density = $\frac{m}{V_f}$

Where,

m = initial weight of material in gm,

V_f= volume of material after tapping.

Generally, replicate determinations are desirable for the determination of this property.

The formulated tablets were evaluated for the following physicochemical parameters.

iv) Measurement of powder compressibility:

The compressibility index and Hausnerratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing power, such interactions are generally less and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility Index and the Hausner Ratio Calculated by the formula:

Compressibility index: = $100\frac{(V_0 - Vf)}{V_0}$

Where,

Vf = final tapped volume,

Vo = initial untapped volume.

Table 7: Limits

S.No.	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	>40	Extremely poor

v) Hausner Ratio:

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. It is named after the engineer Henry H. Hausner. The Hausner ratio is calculated by the formula where is the freely settled bulk density of the powder and is the tapped bulk density of the powder.

Hausner Ratio: = $\frac{V_0}{V_f}$

Where,

Vf = final tapped volume,

Vo = initial un tapped volume.

Table8: Limits:

S. No.	Hausner' ratio	Flow
1	1-1.2	Free-flowing
2	1.2-1.6	Cohesive powder

6.5.2: Post compression parameters:

6.5.2.1. Weight variation test:

Twenty tablets were randomly selected from each batch andindividually weighed. The average weight and standard deviation of 20tablets were calculated. The batch passes the test for weight variation test ifnot more than two of the individual tablet weight deviates from the averageweight by more than the percentage shown in table no.9, and none deviate by more than twice the percentage shown. Weight variation tolerance for Tablet (USP)

Table 9: Weight variation

Average weight (mg)	% Deviation allowed
l30 or less	10
130-323	7.5
More than 324	5

6.5.2.2. Hardness of tablet:

The hardness of the tablets was determined by using Pfizer Hardness Tester.Twenty tablets from each batch were randomly selected. The force requiredto break the tablet is recorded. The unit is Newton. The hardness of IP limitsis NLT 5-8 kg/cm^2.

6.5.2.3.Friability of tablet:

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

6.5.2.4. Drug content:

Five tablets of each formulation were weighed and powdered. The quantity of powder was the equivalent weight of Gabapentin was transferred into 100ml volumetric flask and by using methanol as the extracting solvent and the samples were analyzed by spectrophotometrically.

***6.5.2.5. In vitro* dissolution of tablets:**

Dissolution parameters:

Apparatus – USP-II.

Dissolution medium – 0-2hrs (0.1HCl) 3-12hrs (6.8 phosphate buffer)

RPM-----50.

Sampling Interval-----1,2,3,4,5,6,7,8,9,10,11,12hrs.

Temperature---------37 ±0.5ºc.

Dissolution study:

As the preparation was for prolonged-release given through oral route ofadministration, different receptor fluids are used for evaluation of thedissolution profile.

Procedure:

900ml of 0.1HCl solution was placed in the vessel and the USP—II apparatus (paddle Method) was assembled. The medium was allowed toequilibrate to a temperature of 37±0.5ºc.The tablets of each batch were placedin the vessels and the vessels are covered. The apparatus was operated for2hrs and the medium Phosphate buffer 6.8 was taken for the continuedprocess from 3-12hrs at 50 rpm. At a definite time intervals of 5ml of thereceptor fluid was withdrawn, filtered again 5ml of receptor fluid wasreplaced. Suitable dilutions were done with receptor fluid and analyzedspectrophotometrically at 270nm using U.V-Spectrophotometer.

6.5.2.6.Drug release kinetics–Model fitting of the dissolution data drug release kinetics

Whenever a new solid dosage form is developed or produced, it isnecessary to ensure that drug dissolution occurs appropriately.Drug dissolution from solid dosage forms has been described by kineticmodels in which the dissolved amount of drug (Q) is a function of the testtime, t, or Q=f (t). Some analytical definitions of the Q (t) function arecommonly used, such as Zero order, First order, and Higuchi and Korsmeyer–Peppas models.

Table 10 : drug release kinetics - model fitting of the dissolution data drug release kinetics

Kinetic model	Relation	Systems Following the Mode
First-order	lnQt = lnQo + Kt (release is proportional to the amount of drug remaining)	Water-soluble drugs in porous matrix
Zero-order	Ft= Kot (independent of drug concentration)	Transdermal systems Osmotic systems
Higuchi	Ft=KHt1/2 (proportional to the square root of time)	Matrix formulations
Peppas – Korsmeyer Mt / Mα = Kst	Erodible isometric matrices	Ft= Fraction of dose released at time‘t’; KH, Ko, and Ks = releaserate constants characteristic of respective models; Qo = The drug amount remaining to be released at zero hours; Qt = The drug amount remaining to be released at time‘t’; Mt = Initial amount of drug present in the matrix at time‘t’, Mα = Amount of drug released at time ‘α’.

Mechanisms of the drug release

To find out the drug release mechanism due to swelling (upon hydration)along with gradual erosion of the matrix, first, 60% drug release data can be fittedinKorsmeyer–Peppas model which is often used to describe the drug release

behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomenon is involved.

$$\mathbf{Log\ (Mt / M\infty) = Log\ KKP + n\ Log\ t}$$

Where,

Mt is the amount of drug release at time t,

M∞ is the amount of drug release after infinite time;

KKP is a release rate constant incorporating structural and geometrical Characteristics of the tablet and n are the release exponent indicative of the Mechanism of drug release.

Table 11 : Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

Diffusion exponent(n)	Overall solute diffusionmechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

6.6. Stability studies:

The purpose of stability testing was to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. And to establish shelf life for the drug product and recommended storage conditions.

The storage conditions used for stability studies were accelerated condition (40°C±2°C/75% RH). A stability study was carried out for the optimized formulation. Tablets of optimized formulation were striped packed and kept in the humidity chamber for 90 days on above mention temperature.

The following tests were performed at a regular interval.

Tests performed:

- Drug content
- Dissolution profile
- Test for other physical parameters (hardness, weight variation, friability)

7. RESULTS AND DISCUSSION

7.1. Preformulation studies:

The tests were performed as per procedure given in 7.1. The results were illustrated in tables.

7.1.1. Organoleptic properties:

i) Colour:

TEST	SPECIFICATION	OBSERVATION
Colour	White or almost white powder	White powder

ii) Odour and taste:

TEST	SPECIFICATION	OBSERVATION
Odour	Odourless	Odourless
Taste	Bitter	bitter

7.1.2.Loss on drying:

Loss on drying was determined as per the procedure and the results were illustrated.

Drug	Specification	Observation
Gabapentin	Not more than 0.5%	0.2% ± 0.0334

The loss on drying for the drugs is within pharmacopoeial limits.

7.1.3. Solubility:

Gabapentin was found to be freely soluble in water, soluble in methanol, sparingly soluble in ethanol, slightly soluble in dichloromethane, and 2-propanol, insoluble in ethyl acetate, acetone diethyl ether, and heptane.

7.1.4. Melting point of the drug:

The melting point of active ingredient was determined by capillarymethod.

Drug	Specification	Observation
Gabapentin	162-166^{0}C	165^{0}C

The overall objective of preformulation studies is to generate useful information to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

7.1.5.Angle of repose:

Material	Angle of repose
Gabapentin Raw material	27.57

The results indicating that the raw material had good flow property.

Material	Bulk density	Tapped density	Carr's index (%)	Hausner ratio (%)
Gabapentin raw material	0.33	0.36	16	1.23

7.2. CALIBRATION CURVE OF GABAPENTIN

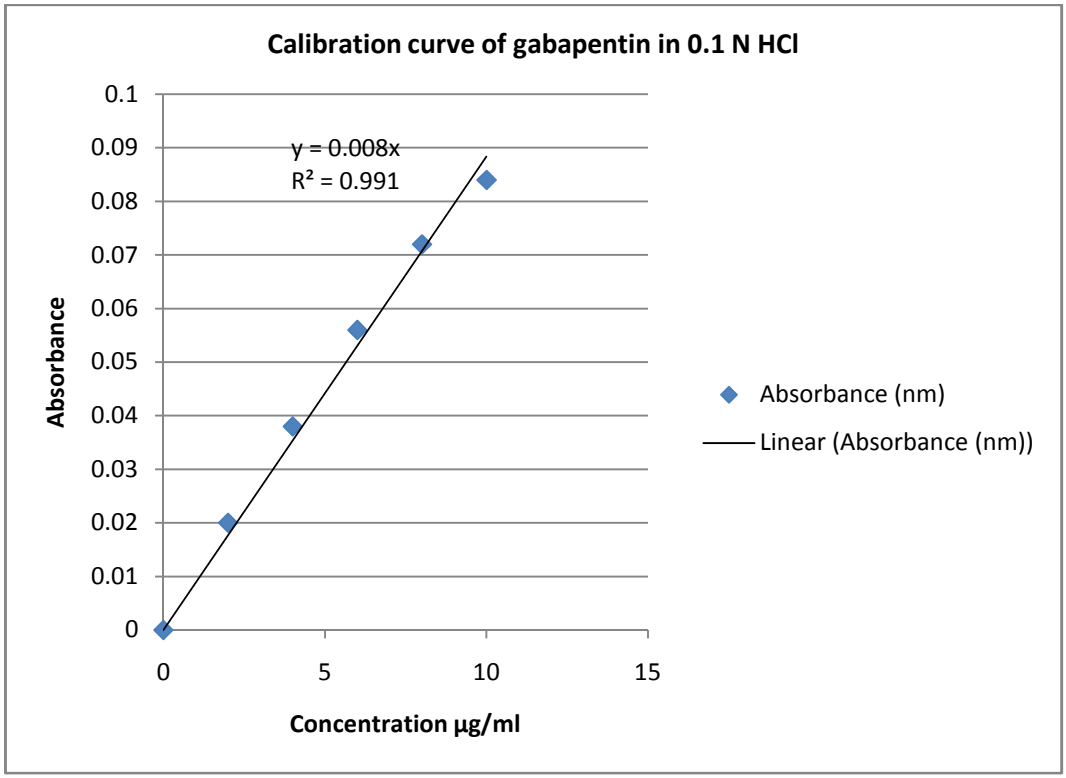
7.2.1. Preparation of standard curve in 0.1 N HCl

The calibration curve of gabapentin was determined by plotting concentration (µg/ml) versus absorbance (nm) at 270 nm. The results were obtained as follows.

Table 12: Calibration curve of Gabapentin in 0.1 N HCl at 270nm

Sample No.	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	2	0.02
3	4	0.038
4	6	0.056
5	8	0.072
6	10	0.084

Figure 10: Calibration curve of Gabapentin in 0.1 N HCl



The standard calibration curve of drug in 0.1 N HCl depicted. The data of absorbance was shown in Table 14. The data had a correlationco-efficient of 0.9917 and the equation of regressed line depicted in figure 10R^2= 0.9917.

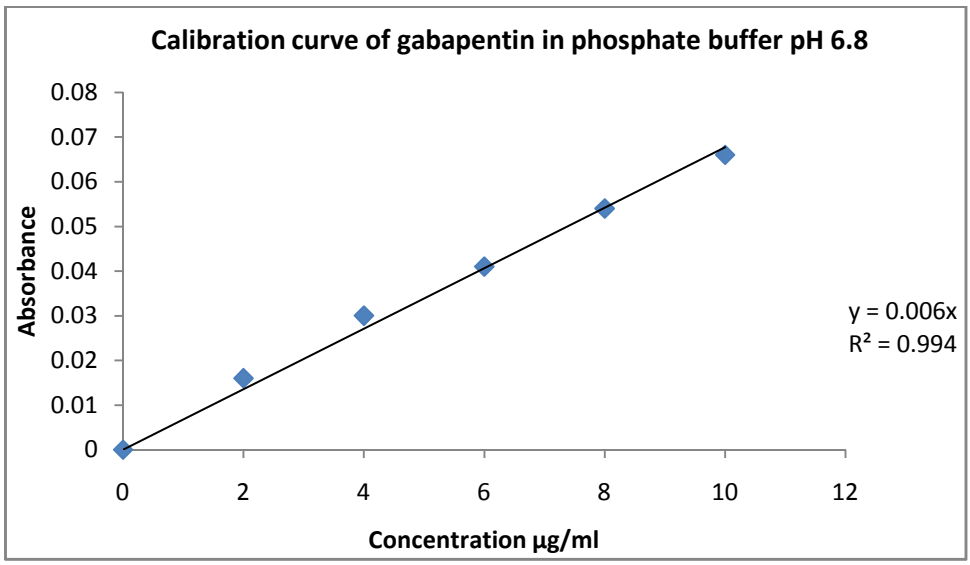
6.2.2.Preparation of standard curve in 6.8 pH buffer

The calibration curve of gabapentin was determined by plotting concentration (µg/ml) versus absorbance (nm) at 270 nm. The results were obtained as follows.

Table 13: Calibration curve of Gabapentin with 6.8 phosphate buffer at 270nm.

Sample No	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	2	0.016
3	4	0.03
4	6	0.041
5	8	0.054
6	10	0.066

Figure11: Calibration curve of Gabapentin with phosphate buffer pH6.8



The standard calibration curve of drug in phosphate buffer pH 6.8depicted as Fig.11. The data of absorbance was shown in Table 15. The data hada correlation coefficient of 0.9941 and the equation of a regressed line withR^2= 0.9941.

7.3.DRUG AND EXCIPIENT COMPATIBILITY STUDY:

Compatibility study of drug with the excipients was determined by F.T.I.R. Spectroscopy (FTIR) using Bruker spectrometer**.** The FTIR spectra of the pure drug, excipient and physical mixture of drugand excipients used in controlled release tablet formulations shown in table no16 Fig no 12-18 were recorded in between 400-4000 wave number (cm^{-1}).

Table 14 : Characteristic peaks of drug and physical mixture

S.No.	Pure drug(wave number cm^{-1})	Physicalmixture(wave number cm^{-1})	Types of vibration	Functional groups
1	2931.4 cm^{-1} (2850-2960)	2922.92 cm^{-1}	C-H stretch	Alkanes
2	2151.45 cm^{-1} (2100-2140)	2150.48 cm^{-1}	-C=C- stretch	Alkynes
3	1545.84 cm^{-1} (15001700)	1625.27 cm^{-1}	N-H bend	Amines
4	1399.26 cm^{-1} (1300-1500)	1399.26 cm^{-1}	C-H bend	Alkanes
5	1299.93 cm^{-1} (1300-800)	1274.86 cm^{-1}	C-C stretch	Alkanes
6	1091.63 cm^{-1} (-1100cm^{-1})	1080.60 cm^{-1}	C-O stretch	Secondary alcohol
7	617.18 cm^{-1} (610-650)	617.18 cm^{-1}	C-H bend	Alkynes

Figure 12: FTIR Spectrum of gabapentin

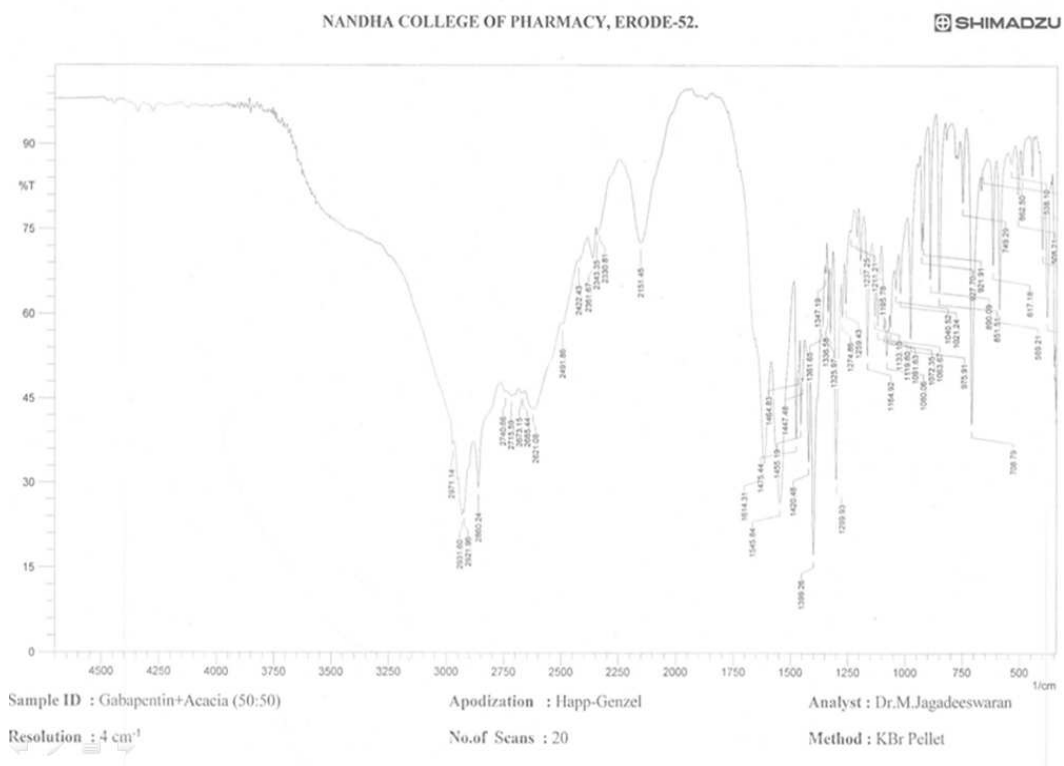


Figure 13: FTIR Spectrum of acacia

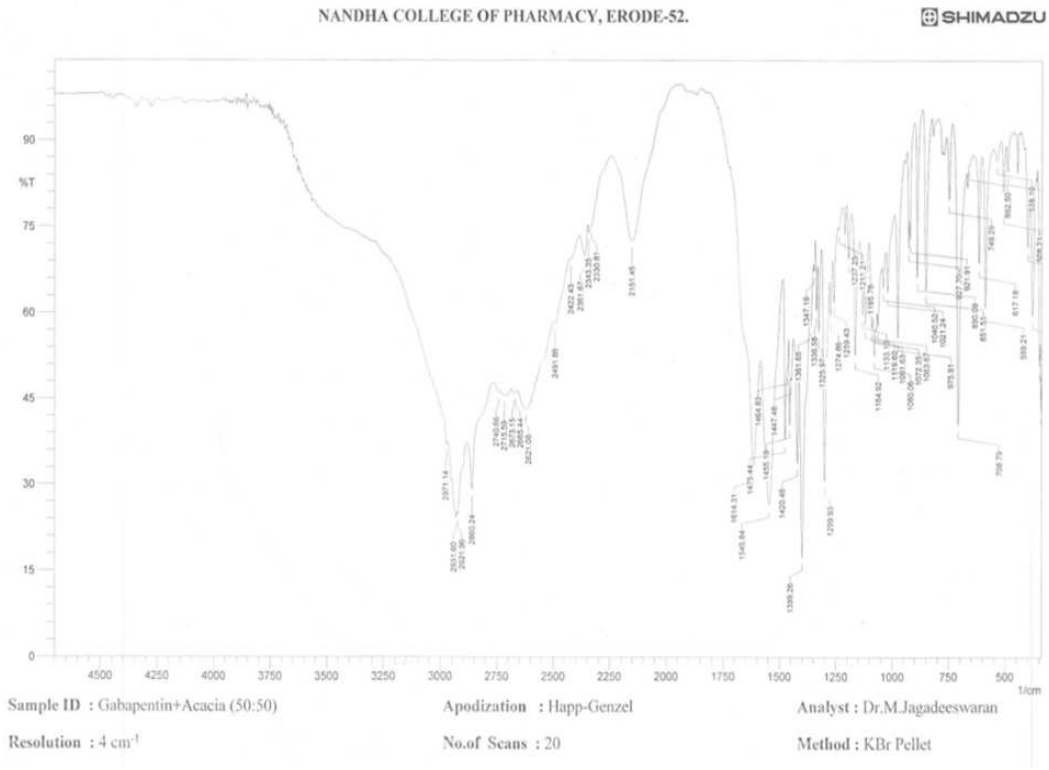


Figure 14: FTIR spectrum of agar-agar

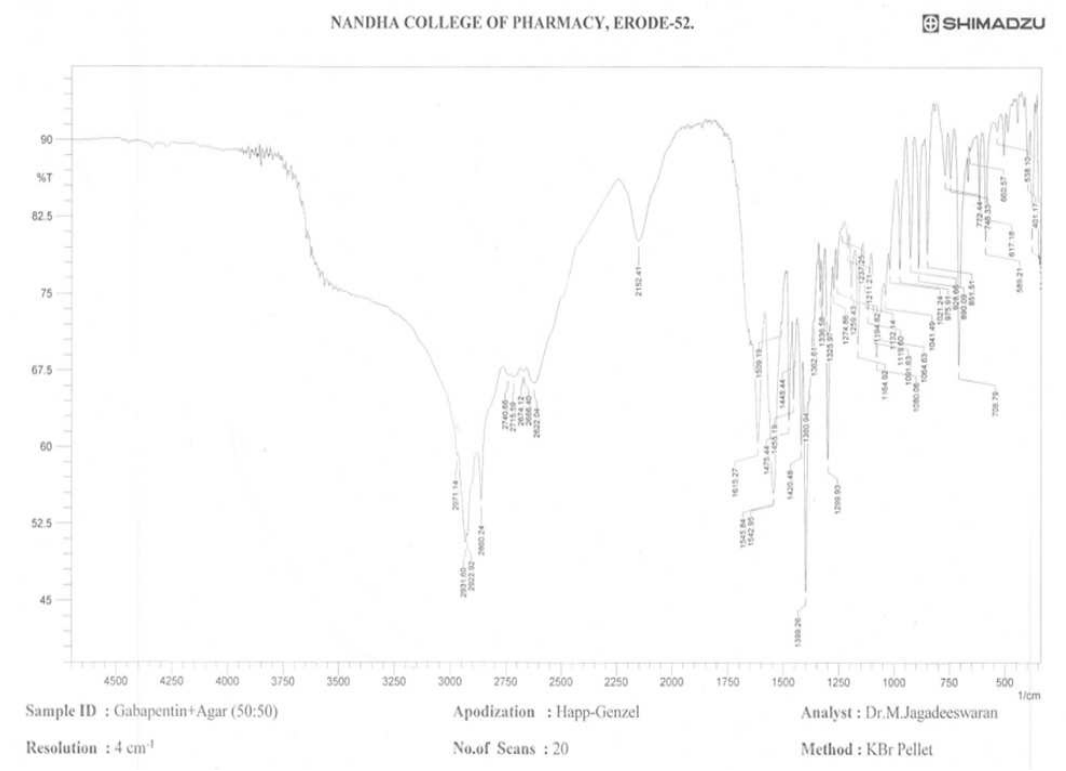


Figure 15: FTIR Spectrum of Guar gum

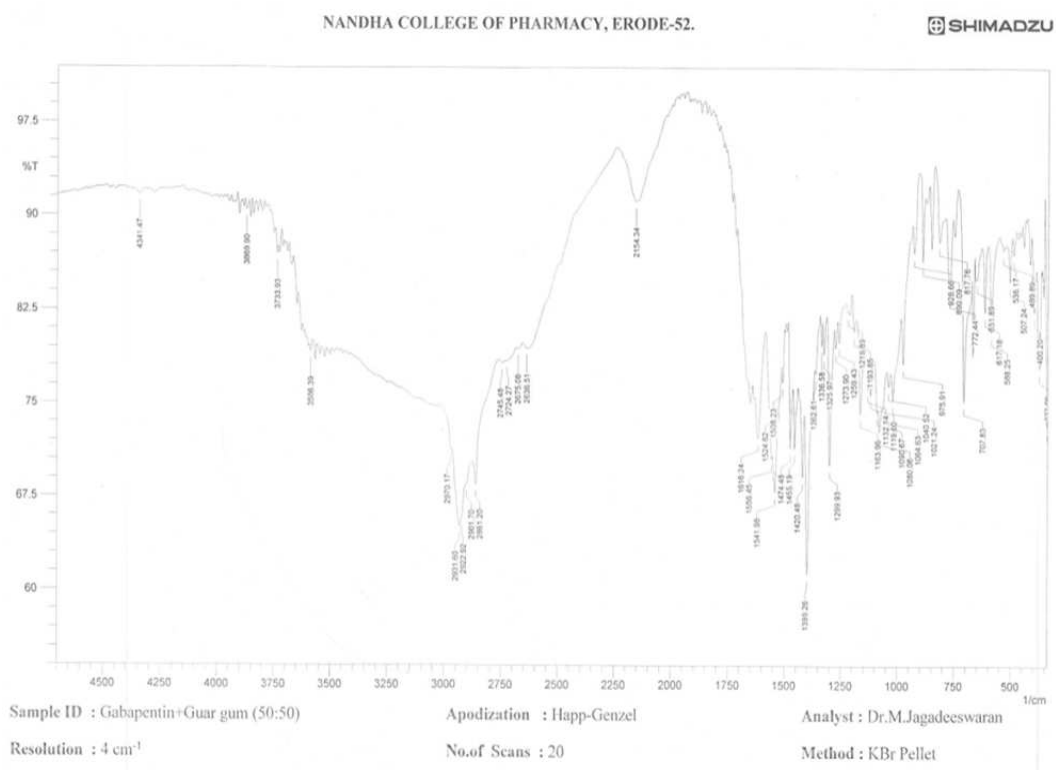


Figure 16: FTIR Spectrum of Xanthan gum

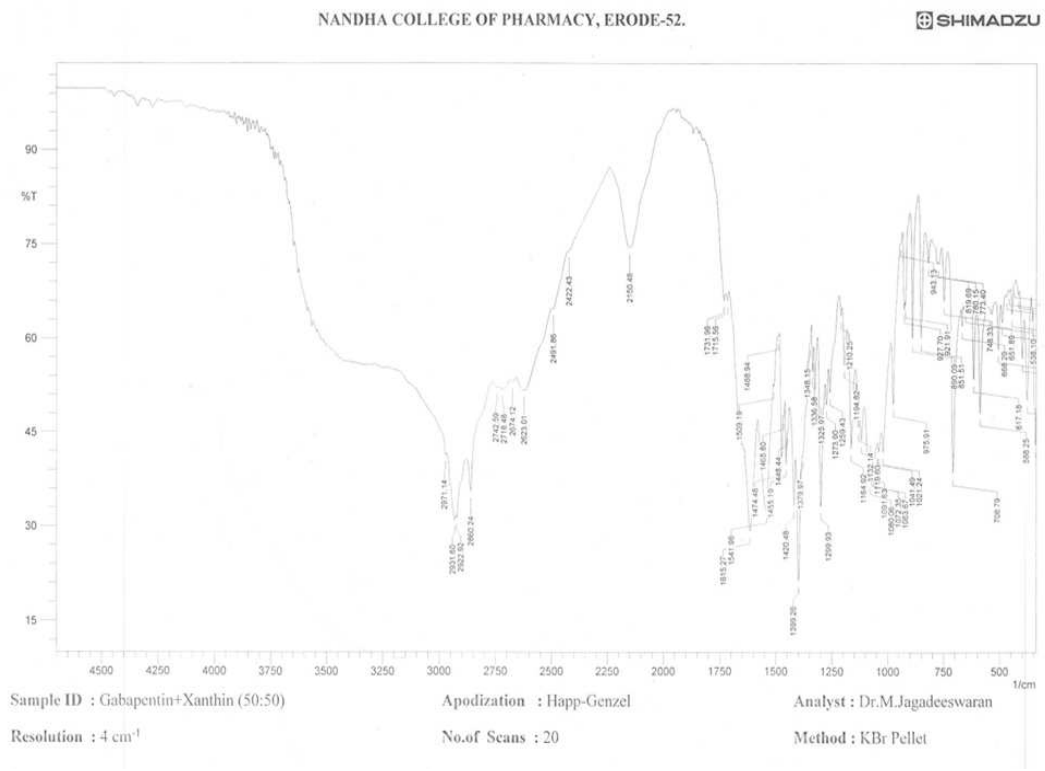


Figure 17:FTIR Spectrum of Gabapentin + Acacia + Agar-Agar

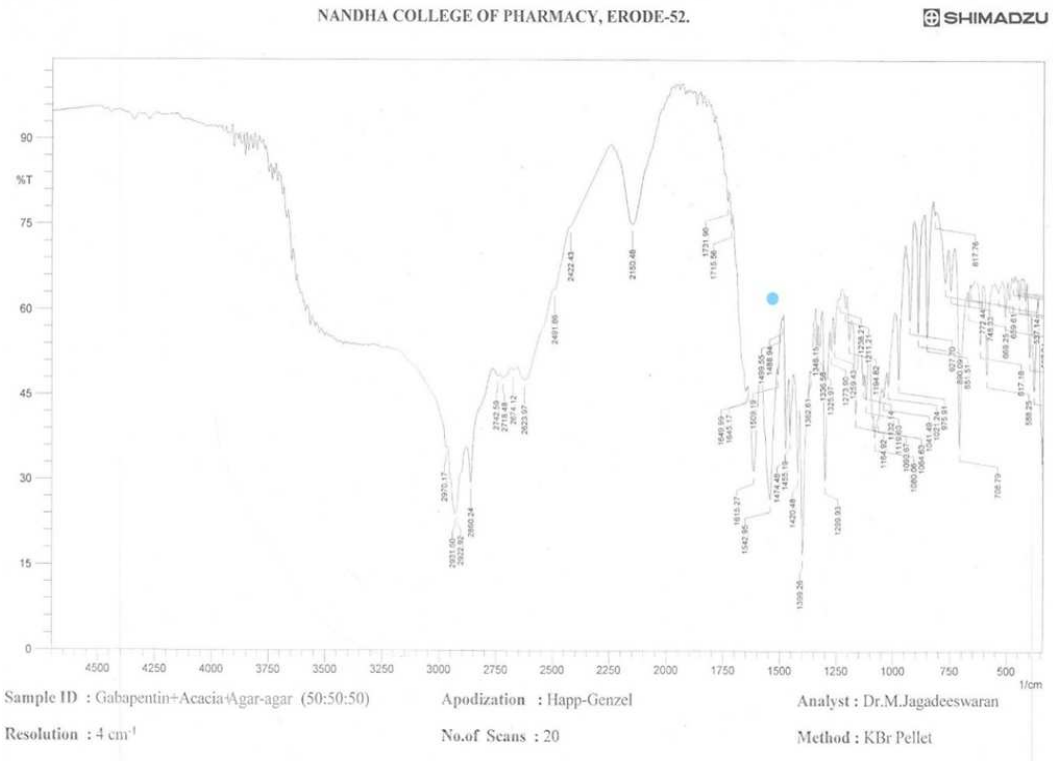
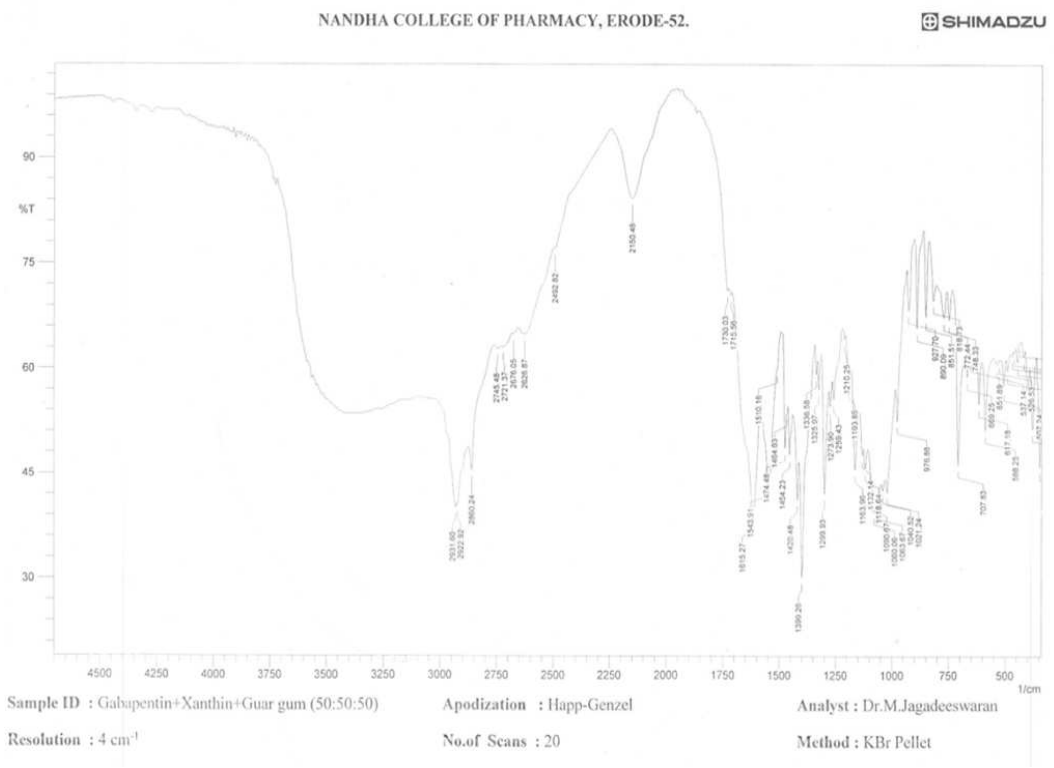


Figure 18: FTIR spectrum of Gabapentin + Guar gum + Xanthan gum



Compatibility studies of drug and polymers were carried out using FTIR spectrometer There was no appearance or disappearance of any characteristic peak, which confirms the absence of chemical interaction between drug and polymer.

7.4. FORMULATION OF GABAPENTIN CONTROLLED RELEASE TABLETS

Acacia, Agar-agar, Xanthan gum, Guar gum polymers were used in different ratios for controlled release systems to find out the effect of different drug polymer ratio and the different batches of tablets were formulated as per procedure given in 6.4.

7.5. EVALUATION OF GABAPENTIN CONTROLLED RELEASE TABLETS

7.5.1. Precompression parameters:[75]

Precompression parameters were evaluated as per the procedure given in 6.5.1 and the results were given in table no.15

Table 15 : Evaluation of precompression parameters of F1-F12 Formulations

Formulation code	Angle of repose (degree±SD)	Bulk Density (gm/ml±SD)	Tapped Density (gm/ml±SD)	Carr's index (%± SD)	Hausner ratio (%± SD)
F1	26.42±0.04	0.311±0.02	0.337±0.02	14.35±0.06	1.03±0.05
F2	27.17±0.01	0.325±0.04	0.359±0.04	15.61±0.07	1.23±0.04
F3	29.01±0.03	0.339±0.06	0.361±0.07	14.64±0.04	1.14±0.02
F4	27.57±0.07	0.307±0.04	0.317±0.06	13.46±0.01	1.13±0.06
F5	26.77±0.09	0.287±0.03	0.321±0.05	12.29±0.05	1.25±0.03
F6	25.61±0.06	0.271±0.01	0.345±0.01	16.35±0.03	1.15±0.01
F7	26.16±0.03	0.297±0.04	0.357±0.03	14.46±0.07	1.20±0.03
F8	29.11±0.09	0.307±0.05	0.366±0.02	13.61±0.04	1.19±0.05
F9	28.05±0.02	0.320±0.06	0.359±0.04	13.85±0.09	1.21±0.00
F10	25.61±0.03	0.271±0.02	0.345±0.01	16.35±0.02	1.15±0.01
F11	29.57±0.07	0.307±0.03	0.317±0.04	15.46±0.01	1.13±0.05
F12	27.17±0.02	0.325±0.04	0.359±0.04	15.61±0.06	1.23±0.04

The powders were evaluated for various flow properties. The powders of all batches showed good flow properties evident from the results shown in table-15. The angle of repose values were ranged from 25.61±0.06to 29.11±0.09. The results were

found to be below 30; hence they have good flow ability. The Carr's index value ranged from 12.29±0.05to 16.35±0.03andHausner's ratio value ranged from 1.03±0.05to 1.25±0.03 hence they have good flow and free flowability.

All the formulations were shown good flow properties which suggested that the blend was suitable for direct compression.

7.5.2: Post compression parameters:[75]

Post compression parameters were evaluated as per the procedure given in 6.5.2 and the results were given in Table no.16.

Table 16 : Evaluation of post compression parameters of F1-F12 Formulations

Formulation code	Weight variation (n=20) (mg ± SD)	Hardness (kg/cm^2±SD)	Friability (%)	Drug content (%± SD)	Thickness (%± SD)
F1	502±0.29	6.6±0.1	0.69	99.13±0.04	5.2±0.007
F2	501±0.67	6.4±0.2	0.67	98.19±0.01	5.3±0.006
F3	498±0.45	7.0±0.3	0.74	99.09±0.12	5.2±0.011
F4	504±0.71	6.7±0.5	0.71	98.19±0.09	5.3±0.008
F5	499±0.15	7.2±0.2	0.65	99.17±0.07	5.2±0.009
F6	501±0.31	6.8±0.4	0.63	98.61±0.03	5.2±0.013
F7	496±0.04	6.5±0.3	0.76	99.13±0.17	5.3±0.004
F8	497±0.71	7.3±0.3	0.70	98.11±0.14	5.2±0.012
F9	503±0.52	7.4±0.5	0.68	98.21±0.05	5.3±0.05
F10	499±0.34	6.5±0.4	0.78	99.13±0.07	5.3±0.008
F11	501±0.71	6.7±0.5	0.73	99.19±0.11	5.3±0.006
F12	502±0.68	6.4±0.2	0.69	98.19±0.02	5.3±0.002

The formulated controlled release tablets were then evaluated for various physical characteristics like thickness, weight variation, hardness, friability, drug content. The weight variation of tablets was uniform in all formulations and ranged from 496±0.04 to 503±0.32.The **%** deviation was coming within 5**%** range.For 500 mg tablet the accepted **%** deviation should be 5**%**.F1to F12 batches came within limit and passed the test.The hardness of the prepared tablets was ranged from 6.4±0.2 to 7.4±0.3. Friability values were ranged from 0.63 to 0.76 which fallen with in the limit of standard (0.1 to 0.9%). Drug content of tablets was ranged from 98.11±0.03 to 99.91±0.14, F11 showed maximum drug contene. Thickness of tablets was uniform and values are ranged from 5.2±0.013to 5.3±0.006.

7.6. In vitro dissolution study of gabapentin controlled release tablets:

Dissolution study was carried out according to the procedure given in 6.6.The results were shown in figure .Data for F1-F12 formulations given in table no 17.

Table 17 *:Invitro*drug release study of gabapentin controlled release formulations F1- F12

TIME	CUMULATIVE PERCENTAGE DRUG RELEASE (%)											
	Fl	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	22.18	20.44	15.32	21.26	20.01	14.36	8.48	7.46	6.82	7.02	6.32	5.32
2	40.32	38.62	33.28	39.98	38.56	33.46	16.42	15.38	14.02	14.96	12.42	11.76
3	60.66	58.16	50.24	59.86	58.28	50.68	30.26	29.2	26.32	28.46	27.64	25.2
4	79.68	77.24	63.48	78.28	77.22	62.94	42.38	39.86	35.8	38.58	38.48	34.84
5	90.14	89.18	78.64	90.26	88.16	78.42	58.24	56.28	52.48	56.62	54.5	50.88
6	99.38	92.46	85.92	99.42	92.48	86.02	69.76	64.46	58.26	64.82	59.28	57.42
7		99.22	92.32		99.84	92.64	75.22	70.52	63.74	70.92	64.72	62.68
8		-	99.04			99.62	88.12	81.72	71.78	82.84	72.94	70.12
9	-	-	-		-		95.42	88.84	79.92	89.1	82.46	78.42
10	-	-	-		-		99.24	94.38	85.82	95.22	89.24	84.86
11								99.48	95.1	99.74	96.32	94.98
12									98.26		99.88	97.86

Average of n value n=3

Figure 19 : *Invitro* drug release of F1 to F3

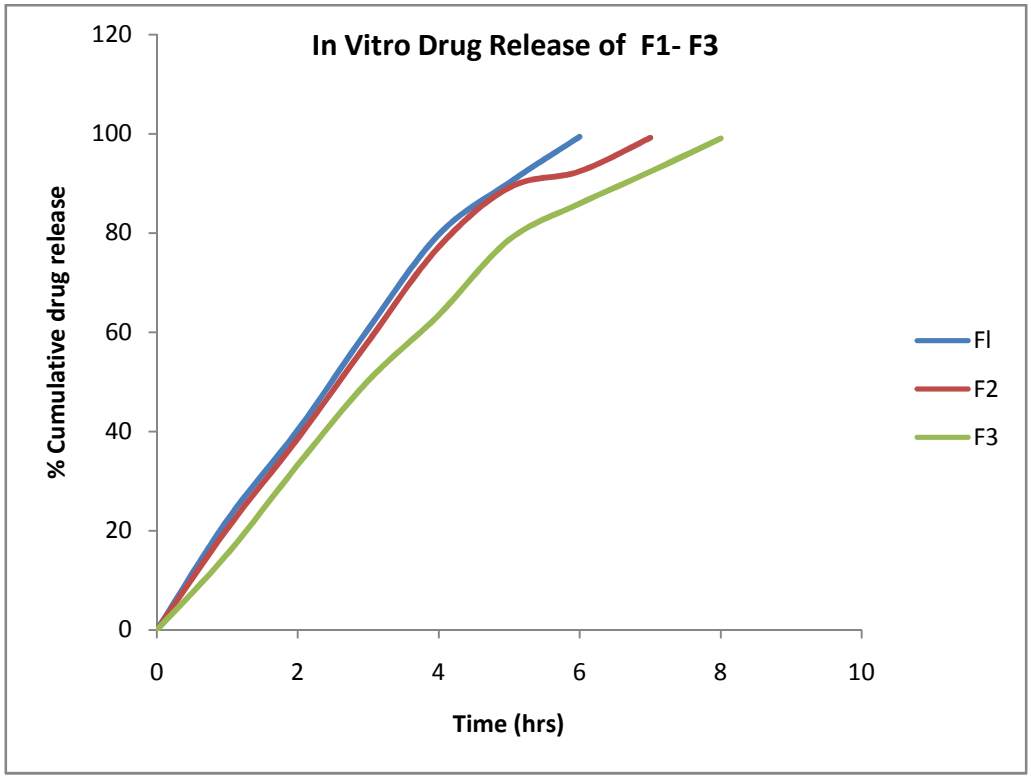


Figure 20 : *In vitro* drug release F4 to F6

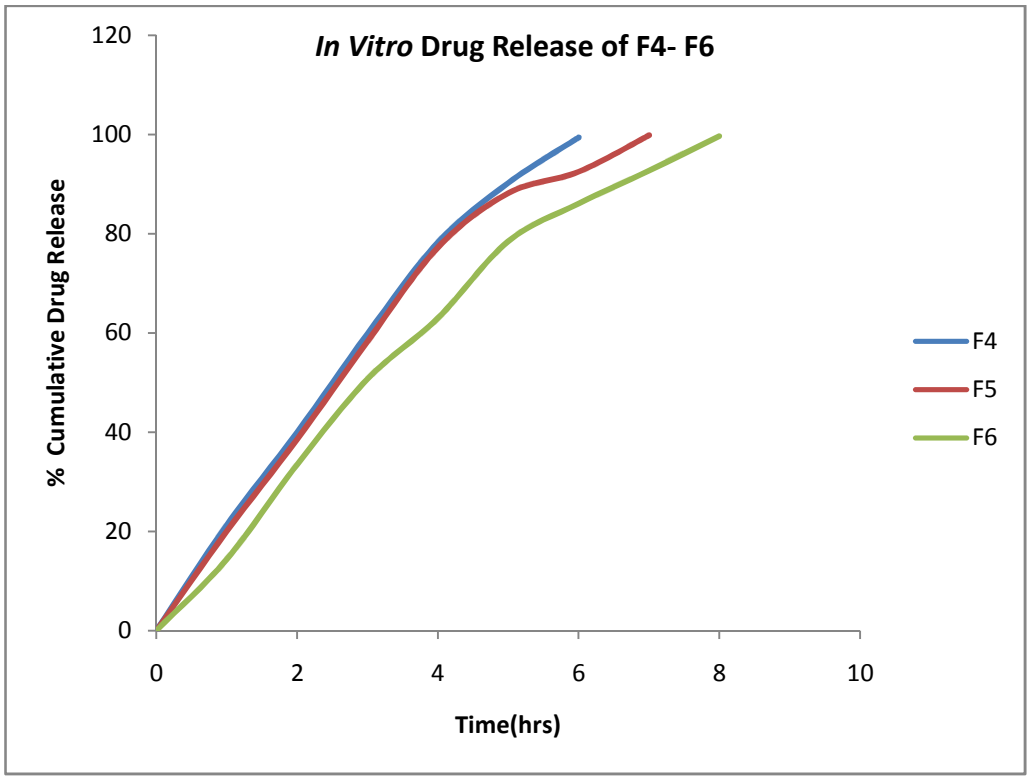


Figure 21 : *In Vitro* drug release of F7 to F9

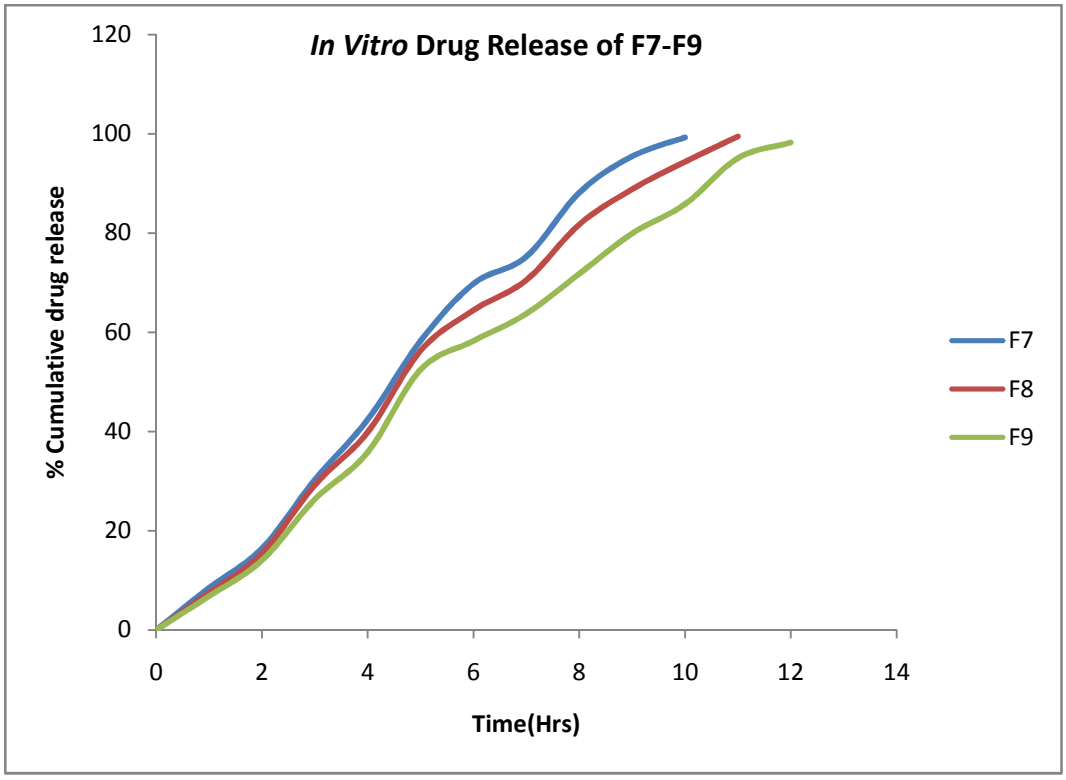
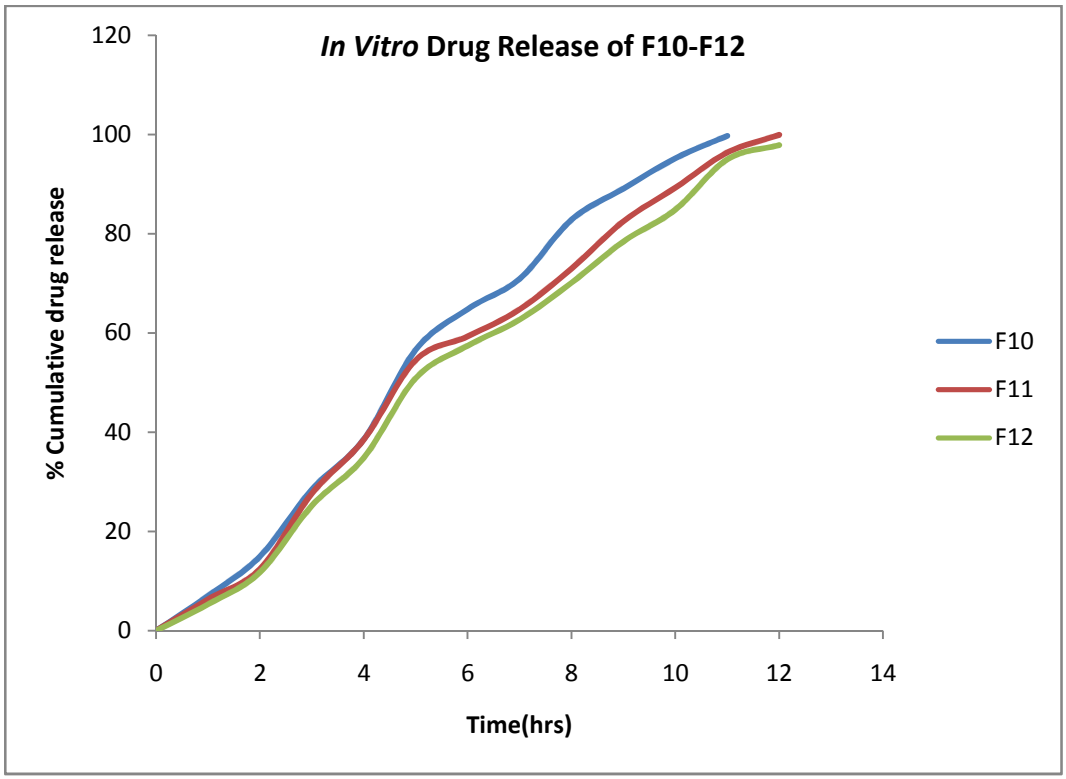


Figure 22 : *In vitro* drug release of F10 to F12



The formulated controlled released tablets were then subjected to *invitro* dissolution test for evaluating drug release from the formulation. The *invitro* dissolution test was carried out in 900 ml of 0.1N Hcl in USP-II paddle type apparatus at 50 rpm and 37±0.5^{o}C for first 2 hrs followed by 900ml of phosphate buffer pH.6.8 upto 12hrs.The results of dissolution study was depend on polymer concentration. Among all 12 formulations Formulation F11 containing Xanthan gum had given drug release 99.88% in 12 hrs. Formulations F1 to F3 and F4 to F6 which contain acacia and agar-agar respectively release the drug within 8 hrs due to the less binding nature and controlled release property. Then the formulations containing guar gum andXanthan gum was given better release profiles when compared with formulations containing Acacia, Agar-agar.Even compared with guar gum xanthan gum showed better release profile. So Formulation F11 which contains xanthan gum was selected as best formulation.

7.7. Drug release kinetics–Model fitting of the dissolution data drug release kinetics

Table 18 : Kinetic study of best formulation

Time (hrs)	Log Time	√Time	Cumulative %drug release	Log cumulative % drug release	Cumulative % Drug remained	Log Cumulative %drug remained
0	0	0	0	0	100	2.000
1	0	1.000	6.32	.8007	93.68	1.971
2	0.3010	1.414	12.42	1.094	87.58	1.942
3	0.477	1.732	27.64	1.433	72.36	1.859
4	0.6020	2	38.48	1.585	61.52	1.789
5	0.698	2.236	54.5	1.736	45.5	1.658
6	0.7781	2.449	59.28	1.772	40.72	1.609
7	.8450	2.645	64.72	1.811	35.28	1.547
8	.9030	2.828	72.94	1.862	27.06	1.432
9	.954	3	82.46	1.916	17.54	1.244
10	1	3.162	89.24	1.950	10.76	1.031
11	1.041	3.316	96.32	1.983	3.68	.5658
12	1.079	3.464	99.88	1.999	.12	-0.920

Figure 23 : Zero order plot

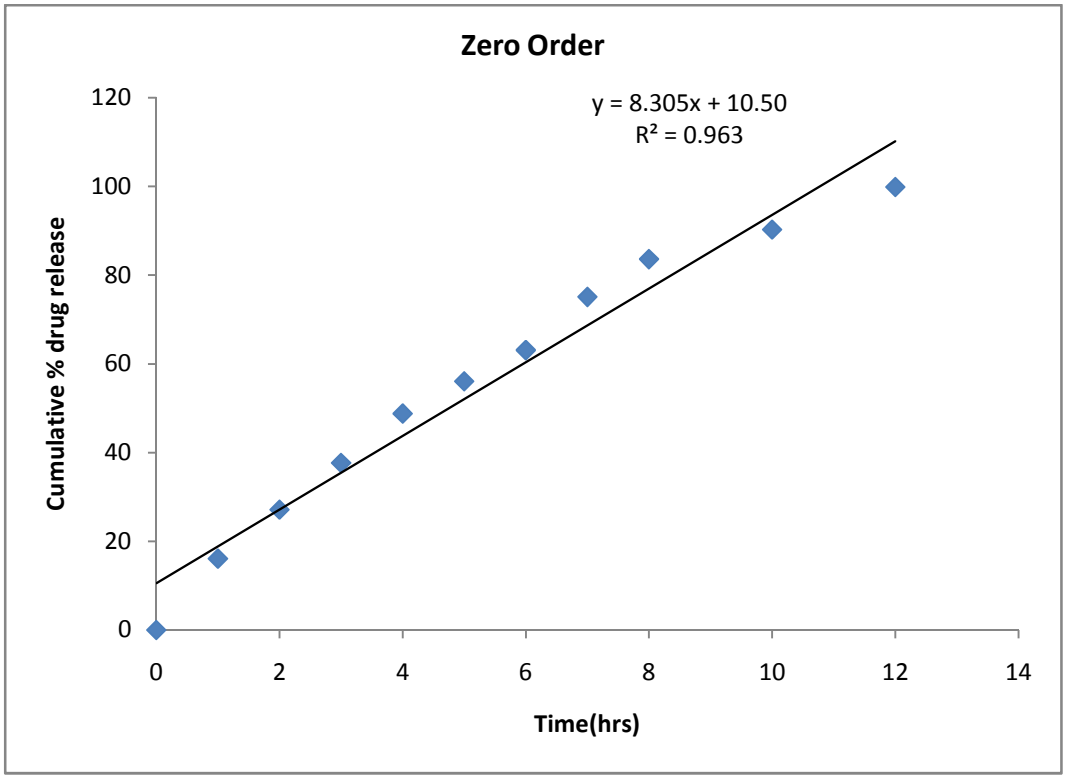


Figure 24 : First order plot

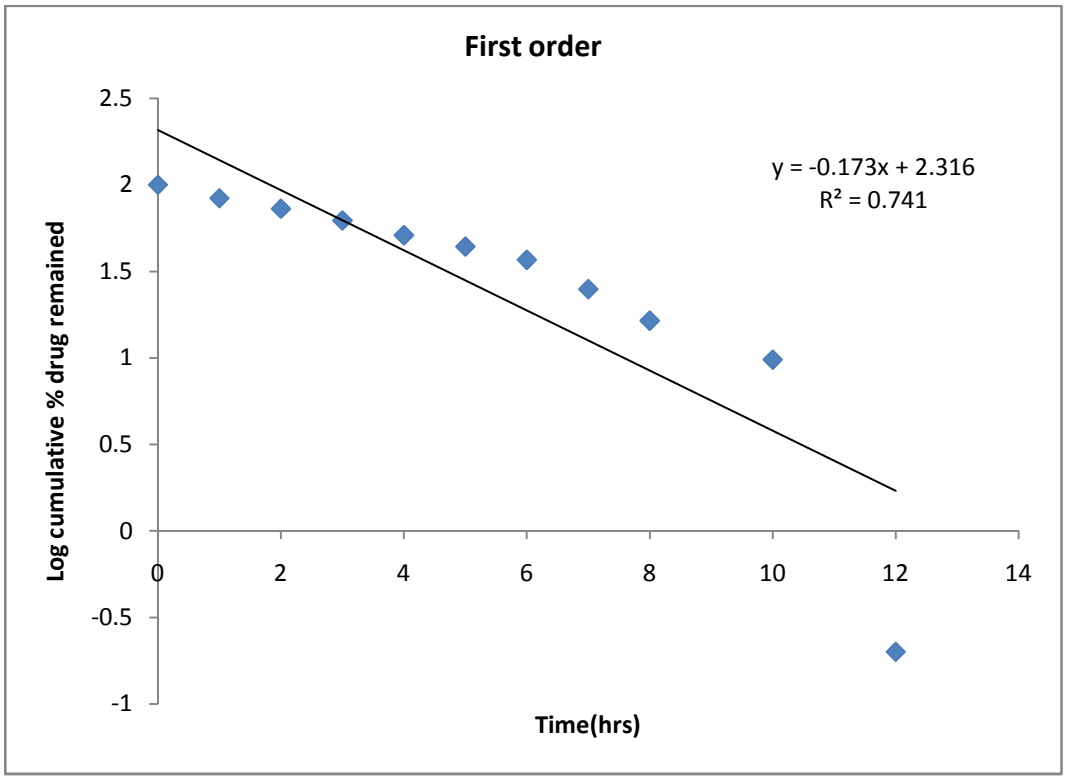


Figure 25 : Higuchi plot

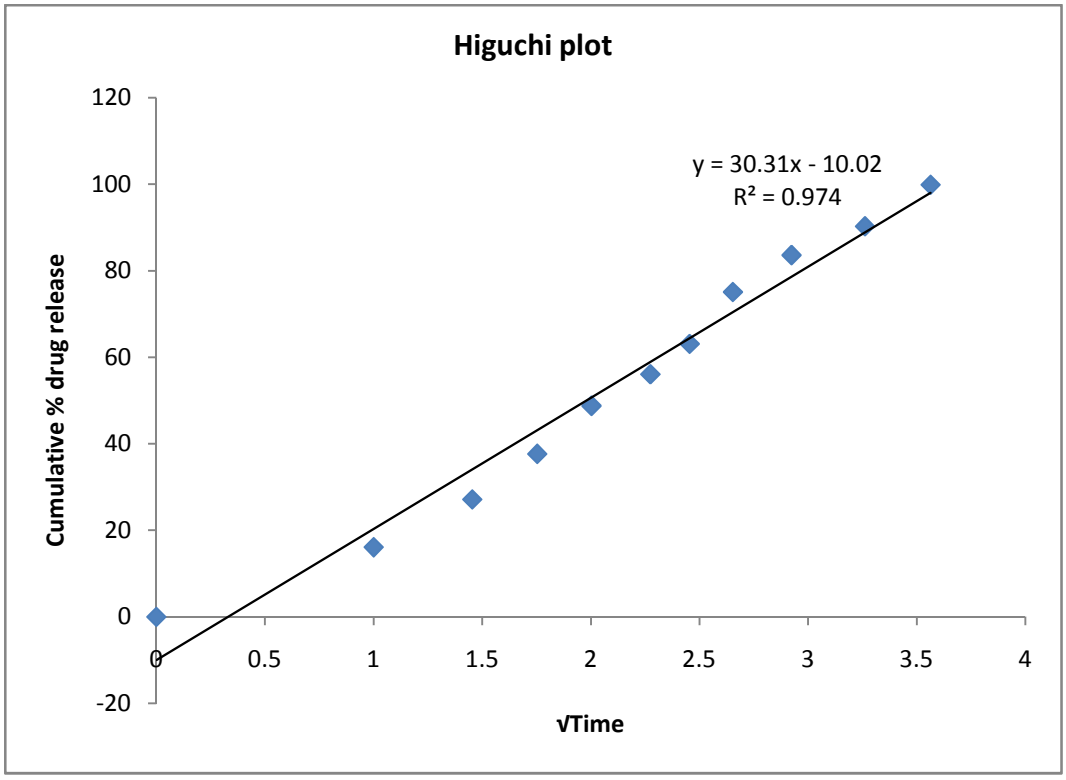


Figure 26 :Korsmeyer- peppas plot

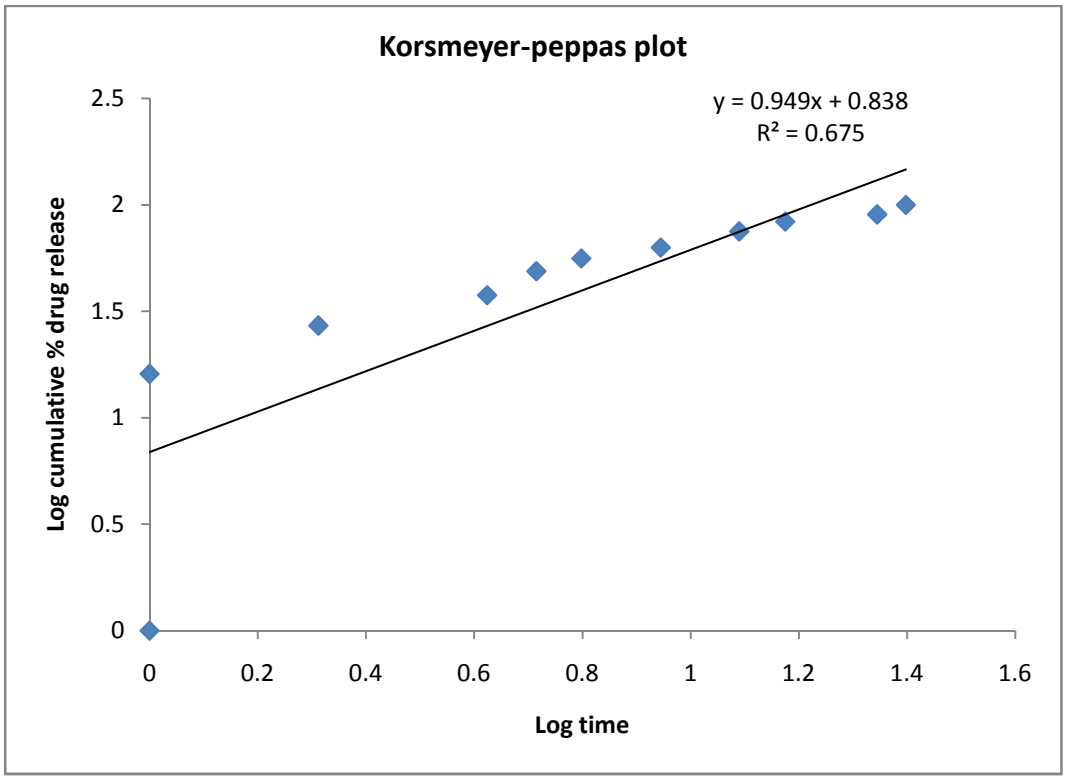


Table 19 :Kinetics of drug release

Formulation	Regression coefficient of zero order	Regression coefficient of first order	Order of release
F11	0.963	0.741	Zero order release

Formulation	Higuchi Model	Korsmeyer –Peppas Model
	R^2	R^2
F11	.974	.675

In order to determine the mechanism of drug release form the formulations, the Invitro dissolution data was fitted to zero order, first order, higuchi plot and korsmeyer-peppas plot was drawn and interpretation of release exponent value (n) was calculated and results are shown in tables & figures. The results of R^2 for zero and first order were obtained as 0.963, 0.741. Based on that confirmed the best formulation followed zero order release.

The drug release was diffusion controlled as the plot of optimized formulation F11 was found 0.974 as regression coefficient in higuchi plot. From korsmeyerpeppas plot the release exponent value n was found as 0.675 and it was confirmed as the release of drug from the formulation was founded as anomalous non-fickian transport of diffusion.

7.8.Stability studies[71]:

Gabapentin formulation F11 was subjected to accelerated stability studies for a period of 3months. The samples were withdrawn after periods of 30days,60 days and 90days and were analyzed for their appearance, hardness, friability, drug content

and *in vitro* drug release.The results revealed that F11 had no significant changes in appearance,drug content, hardness, friability, and *in vitro* releaseThus it could be concluded that the formulation was stable Storage condition at40°C±2°C/ 75%RH±5%:

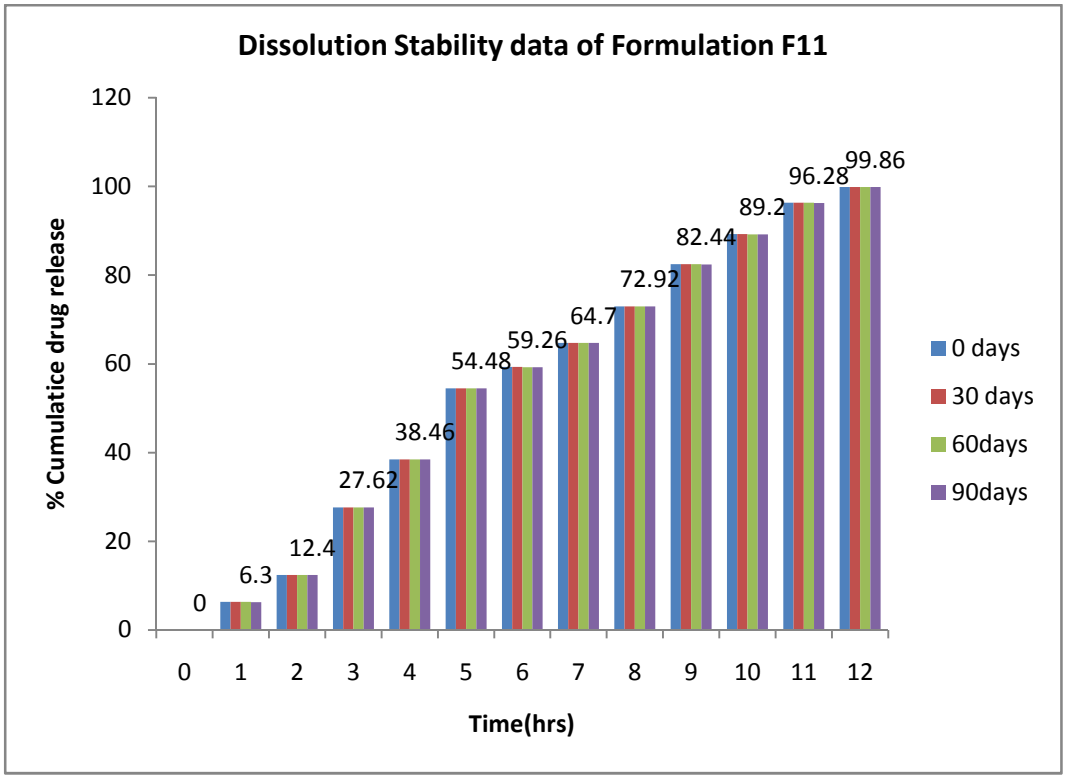
Table 20 : Stability data

TEST	F11	30 days	60 days	90 days
WeightVariation	501±0.71	501±0.55	501±0.22	501±0.12
Hardness	6.7	6.7	6.7	6.7
Friability	.73	0.73	0.73	0.72
Drug content	99.19±0.11	99.19±0.05	99.19±0.04	99.19±0.01

Table 21 : Dissolution data of percent cumulative drug release for formulation F11

Time in hrs	0 days	30 days	60days	90days
0	0	0	0	0
1	6.32	6.32	6.32	6.3
2	12.42	12.42	12.4	12.4
3	27.64	27.64	27.64	27.62
4	38.48	38.48	38.46	38.46
5	54.5	54.5	54.5	54.48
6	59.28	59.28	59.26	59.26
7	64.72	64.72	64.72	64.7
8	72.94	72.94	72.94	72.92
9	82.46	82.46	82.46	82.44
10	89.24	89.24	89.22	89.2
11	96.32	96.32	96.3	96.28
12	99.88	99.88	99.88	99.86

Figure 27 : Dissolution stability data for sample F11



The stability studies for optimized formulation F11 was carried out based accelerated stability conditions and study of various parameters carried out at 0, 30, 60, 90 days of intervals and the results found satisfactorily and that reveals that the selected best formulation was stable under accelerated condition.

8. SUMMARY AND CONCLUSION

The main objective of the present study was to develop controlled-release tablets containing 300 mg of gabapentin for epilepsy therapy by using polymers like acacia, agar-agar, guar gum, xanthan gum. The controlled release of the drug delivery system improves the bioavailability and therapeutic efficiency of the drug.

In the Preformulation FTIR study was carried out for pure drug (Gabapentin), gabapentin, and excipients. It has not shown any interaction. Construction of the calibration curve was done using 0.1N HCl and phosphate buffer p^H 6.8.

The formulations F1 o F12 were prepared by the direct compression method.The angle of repose values for formulations range from 25.61±0.03 to 29.57±0.07. Bulk and tapped densities are used for the measurement of the compressibility index. The bulk and tapped values for formulations range from 0.271±0.01 to 0.339±0.06 and 0.317±0.04 to 0.366±0.02 respectively. The carr's index and Hausner's ratio values for formulations range from 12.29±0.05 to 16.35±0.03 and 1.03±0.05 to 1.25±0.03 respectively. Thus all formulations exhibited good flow characteristics.

The prepared controlled-release tablets were evaluated for various parameters like thickness, weight variation, hardness, friability, and drug content uniformity. The thickness of tablets in all formulations was ranged from 5.2±0.007 to 5.3±0.008. The weight variation of tablets in all formulations were ranged from 496±0.04 to 503±0.32.The hardness and friability of all the formulations F1-F12 were found to be 6.4±0.2 to 7.4±0.5 and 0.63 to 0.78 respectively. The drug content of all the formulations were ranging from 98.11±0.14 to 99.19±0.12.

In vitro drug release study was carried out for formulations F1 to F12 containing different ratios of natural polymers like acacia, agar-agar, guar gum, and xanthan gum. Among 12 formulations F11 was selected as best formulation based on in vitro drug release. The cumulative percentage drug release of F11 was 99.88% after 12hrs.

The kinetic study was carried out for F11 formulation which showed that the drug release follows zero-order kinetics.

The stability studies were carried out for F11 formulation at $40^{o}C \pm 2^{o}C$ / 75% RH± 5% for 3months. Data revealed that there was no considerable difference and the product was stable.

From the above study, it can be concluded that F11 is the best formulation which has shown better drug release **99.88%.** However, further *in vivo* studies can be carried out to support the results.

9. BIBLIOGRAPHY

1. Harish Gopinath, B. Pragati Kumar, S. Duraivel, K. P. Sampath Kumar, D., DebjitBhowmik et.al., Controlled Release Drug Delivery Systems. Nimra College of Pharmacy, Vijayawada, Andhra Pradesh, India: 2012.

2. Doddayya Hiremath., Formulation and Evaluation of controlled release matrix tablets of Ambroxol Hydrochloride. Journal of Pharmacy Research. 2010; 3(8),1810-1813.

3. Brahmankar DM, Jaiswal SB. Biopharmaceutics and Pharmacokinetics: Pharmacokinetics. 2nd ed. VallabhPrakashan, Delhi: 2009; 399-401.

4. John C, Morten C, The Science of Dosage Form Design, Aulton: Modified release peroral dosage forms. 2nd ed. Churchill Livingstone.2002; 290-300.

5. Mamidala R, Ramana V, Lingam M, Gannu R, Rao MY. Review Article Factors Influencing The Design And Performance Of Oral Sustained/Controlled Release Dosage Form. Journal Of Pharmaceutical Science And Nanotechnology. 2009; 2:583.

6. Allen LV, Popvich GN, Ansel HC. Ansel's Pharmaceutical dosage form and drug delivery system. 8th ed. 2004; 260-263.

7. Patrick JS. Martin's Physical Pharmacy and Pharmaceutical Sciences.3rd ed. Varghese Publishing House. Bombay: 1991; 512-519.

8.Pauline M. Doran, in Bioprocess Engineering Principles; Elsevier Science & Technology Books, 1995; ISBN: 0122208552.

9. Lachman L, Liberman HA, KanigJL. The theory and practice of industrial pharmacy. 3rd ed. Bombay: Varghese publishing house 1987.

10. Jain NK. Controlled and novel drug delivery. CBS publisher and distribution.1997; 1-25.

11. Venkataraman DSN, Chester A, KleinerL.An overview of the controlled release system.Handbook of pharmaceutical controlled release technology. Marcel Dekker Inc. 2000; 1-30.

12. Mamidala R, Ramana V, Lingam M, Gannu R, Rao MY. Review article factors influencing the design and performance of oral sustained/controlled release dosage form.Journal of pharmaceutical science and nanotechnology.2009; 2:583.

13. Gupta S, Singh RP, Sharma R, Kalyanwat R, Lokwani P. Osmotic pumps: A review. Journal of comprehensive pharmacy.2011; 6:1-8.

14. Robinson JR, Lee VH. Controlled drug delivery. 2nd ed. Marcel Dekker, 1987; 4-15.

15. Kamboj S, Gupta GD. Matrix Tablets: An important tool for the oral controlled release dosage form. Pharmainfo. Net. 2009; 7:1-9.

16. Bechgaard, H. and Nielsen, G.Controlled-Release Multiple-Units and Single-Unit Doses a Literature Review. Drug Development and Industrial Pharmacy, 1978; 4(1), pp.53-67.

17. Wise DL. Handbook of pharmaceutical controlled release technology. Marcel Dekker Inc. New York: 2002; 432-460.

18. Tripathi KD. Essentials of Medical Pharmacology. 5th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2003.

19. Gibaldi, M. Biopharmaceutics, and Clinical Pharmacokinetics. 3rd Edition, Lea and Febiger, Philadelphia,1984; 45-111.

20. Heilmann K. Therapeutics systems rate controlled drug delivery: Concept and Development. 2nd ed.Stuttgart Georg ThiemeVerlag; 1984.

21.Xu, Q., Ibrahim, S., Higuchi, W., and Li, S., Ion-exchange membrane assisted transdermal iontophoretic delivery of salicylate and acyclovir. International Journal of Pharmaceutics, 2009; 369(1-2), pp.105-113.dx.doi.org/10.1016/s0378-5173(98)00144-6.

22. Mahore JG, Wadher J, Umekar MJ, Bhoyar PK. Ion exchange resins: Pharmaceutical application and recent advancement. Journal of Pharmaceutical. Science Review.Research. 2010; 1(2): 8-13.

23. Javed Ali, RK Khar, AlkaAhuja. Dosage form design. 4th ed. Birla Publication Pvt. Ltd; 2009; 181-194.

24. Cristina M, Aranzazu Z, Jose ML. Review: Critical factors in the release of drugs from sustained release hydrophilic matrices. Journal of Research in Ayurveda and Pharmacy.2011; 21: 1701-08.

25. Herbig SM, Cardial JR, Korsmeyer RW, Smith KL. Asymmetric membrane tablet coating for osmotic drug delivery. J. Control. Release.1995; 35:127-136. dx.doi.org/10.1016/0168-3659 (95)00028-7

26. Gupta RN, Gupta R, Basniwal PK, Rathore GS. Osmotically controlled oral drug delivery systems; AReview. Journal of Pharmaceutical. Science. 2009;1(2): 75-269.

27. Wagner JG. Biopharmaceutics and pharmacokinetics. Org. Intelligence Publisher; 1971; 57-148.

28. Srikanth MV,Sunil SA, Rao NS, Uhumwangho MU, Ramana Murthy KV. Ion exchange resins as controlled drug delivery carriers.Journal of Science Research. 2010; 2(3): 11-597.

29. Ballard BE. Sustained and controlled release drug delivery system. USA: Marcel Dekker Inc. 1978; 76-106.

30. Leppik IE. Contemporary diagnosis and management of the patient with epilepsy, 2nd ed. Newtown, PA. Handbooks in health care. 1996

31. https://www.who.int/news-room/fact-sheets/detail/epilepsy

32. Kornblau DH, Conway Jr EE, Caplen SM. Neurologic Disorders. In: Marx JA, ed. Rosen's Emergency Medicine: Concepts and Clinical Practice. 7th ed. Philadelphia, PA: Mosby Elsevier. 2009; chap 173.

33.French JA, Pedley TA. Clinical practice.Initial management of epilepsy. N Engl J Med. 2008; 359(2):166-76.

34. Krumholz A, Wiebe S, Gronseth G, et al. Practice parameter: evaluating an apparent unprovoked first seizure in adults (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. 2007; 69.

35. Richard E. et.al studied and reported that “New antiepileptic drugs in treating the epilepsies of childhood Current Pediatrics. 2005; 15, 280–286.

36. Leppik IE. Contemporary diagnosis and management of the patient with epilepsy, 2nd ed. Newtown, PA. Handbooks in health care. 1996.

37. Sridharan, R. Epidemiology of epilepsy. Current science. 2002; 82 (6): 664-670.

38. Guberman, AH. &Bruni, J. Essentials of clinical epilepsy. 2nd ed. Butterworth Heinemann, Boston.1999; 3-10.

39. Hauser, WA. &Annegers, JF. In: A Textbook of neurology. Laidlaw, J., richens, A. & Chadwick, D. eds, 4th ed. Edinburgh: Churchill Livingstone.1993; 23-45.

40. Brodie, MJ. & French, JA. Management of epilepsy in adolescents and adults. Lancet 2000; 356: 323-328.

41. Schachter SC. Seizure disorders. Med Clin North Am. March 2009; 93(2).

42. Trescher WH, Lesser RP. The Epilepsies. In: Bradley WG, Daroff RB, Fenichel GM, Jakovic J, eds. Neurology in Clinical Practice. 5th ed. Philadelphia, Pa; Butterworth-Heinemann. 2008; chap 71.

43. Sridharan, R., Radhakrishnan, K., Ashok, PP. &Mousa, ME. Epilepsia 1986; 27:60-65.

44. Walker SP, Permezel M, Berkovic SF. The management of epilepsy in pregnancy.BJOG. 2009; 116(6):758-67.

45. C. L. Harden, J. Hopp, T. Y. Ting, et al. Practice Parameter update: Management issues for women with epilepsy --Focus on pregnancy (an evidence-based review). Neurology 2009; 73;126.

46. Dhana Lakshmi P**.** International Journal of Biopharmaceutics.2012; 3(2):70-77.

47. Swati jagdale, Bhanudas Kuchekar, Pharmaceutical equivalence of Gabapentin tablets with various extra granular binders. Rev Ciênc Farm BásicaApl., 2010;31(1):25-31.

48. Lin, Hong-Liang & Lin, Shan-Yang & Lin, Chih-Cheng & Hsu, Cheng-Hung & Wu, Tieh-Kang & Huang, Yu-Ting, et, al., Mechanical grinding effect on thermodynamics and inclusion efficiency of loratadine-cyclodextrin inclusion complex formation. Carbohydrate Polymers. 2012.87.512517.10.1016/j.

49. Cowles V. E., Gordi T., Hou S. Y.Steady-state pharmacokinetics of gabapentin after administration of a novelgastroretentiveextended-release formulation in postmenopausal women with vasomotor symptoms. 2012. DOI: 10.3389/fphar.2019.00504.

50. Rhee, Y., Park, S., Lee, T., Park, C., Nam, T., Oh, T., Jeon, J., Han, S., Lee, D. and Park, E.et, al., In Vitro/in Vivo relationship of gabapentin from a sustained-release tablet formulation: A pharmacokinetic study in the beagle dog. Archives of Pharmacal Research, 2008; 31(7), pp.911-917.

51.Yari, Abdollah, FatemehPapi, and Said Farhadi. "Voltammetric Determination of Trace Antiepileptic Gabapentin with a Silver-Nanoparticle Modified Multiwalled Carbon Nanotube Paste Electrode." Electroanalysis 23.12 2011; 2949-2954.

52.KuKanich, B., and Cohen, R.,.Pharmacokinetics of oral gabapentin in greyhound dogs.The Veterinary Journal, 2011, 187(1), pp.133-135.

53.Zong, Z., Desai, S., Kaushal, A., Barich, D., Huang, H., Munson, E., Suryanarayanan, R. and Kirsch, L., The Stabilizing Effect of Moisture on the Solid-State Degradation of Gabapentin. AAPS PharmSciTech, 2011;12(3).

54.Achrai, Ben &Libster, Dima&Aserin, Abraham &Garti, Nissim. Solubilization of Gabapentin into H-II Mesophases.The journal of physical chemistry. 2011;B. 115. 825-35. 10.1021/jp108801d.

55.Abood, Ahmed &Rassol, Alaa).Preparation and in-vitro evaluation of floating microspheres of gabapentin.Kufa Journal For Veterinary Medical Sciences, 2011; 77-92.

56.Argoft CE, Clinical development of a once-daily gastrorententive formulation of Gabapentin tablets for the treatment of post-therapeutic neuralgia. 2012 .

57.Pfizer, Bioequivalence study of gabapentin between tablet and liquid formulation and the food effect study of the liquid formulation.2009, NCT00987779.

58.Sandercock, D., Cramer, M., Wu, J., Chiang, Y., Biton, V. and Heritier, M.,Gabapentinet, al., Extended Release for the Treatment of Painful Diabetic Peripheral Neuropathy: Efficacy and tolerability in a double-blind, randomized, controlled clinical trial. Diabetes Care, 2009; 32(2), pp.e20-e20.

59.Mohana, K. and Ramdas Bhandarkar, P.,Oxidation of 2-Phenylethylamine withN-Bromosuccinimide in Acid and Alkaline Media: A Kinetic and Mechanistic Study. Journal of the Chinese Chemical Society, 2007; 54(5), pp.1223-1232.

60. Taksande, Formulation, and pharmacodynamic investigations of lamotrigine microspheres. Asian Journal of Pharmaceutics • Jan-Mar 2017 (Suppl) • 2017;11 (1) | S215.

61. Narasimha s. managoli, Crosslinked chitosan hydrogelmatrix tablets for controlledrelease of gabapentin.FARMACIA -BUCURESTI; 2012; 60; 272-286.

62. Issam B. Rimawi, Ramzi H. Muqedi,Development of Gabapentin Expandable gastroretentive Controlled Drug Delivery System. 2019; 9:11675 | https://doi.org/10.1038/s41598-019-48260-8.

63. DemblaNM, Maniyam AP, Agarwal S, Formulation Development, and Evaluation of Gabapentin Controlled-Release Tablets. Pharmacy & Pharmacology International Journal, 2015; 2(3): 00021. DOI: 10.15406/ppij.2015.02.00021.

64. Samar M. Abouelatta, Ahmed A. Aboelwafa,Gastroretentive raft liquid delivery system as a new approach to release extension for carrier-mediateddrug, Drug Delivery, 2018; 25:1, 1161-1174.

65. MdTausifAlam, NayyarParvez, et. al., (2014) FDA-Approved Natural Polymers for Fast Dissolving Tablets.Article ID 952970, 6 pages.

http://dx.doi.org/10.1155/2014/952970.

66. http://drugbank.ca/drugs/DB00996(APRD00015)

67.Raymond C Rowe, Paul J Sheskey and Marian E Quinn, Handbook of pharmaceutical excipients, 6th edition, Pharmaceutical press; America acolInt J. 2015; 2(3):75–81. DOI: 10.15406/ppij.2015.02.00021.

68. United States Pharmacopoeia. 1995; 23 NF 18, 1-5.

69. United States Pharmacopoeia. 2004; 27 NF 23, 1-5.

70. Wood, J.,Pharmaceutical Dosage Forms: Parenteral Medications, vol. 1. Journal of Pharmaceutical Sciences, 1985; 74(8), p.907

71. Tyle, P., Robinson JR, Controlled drug delivery: Fundamentals and applications. Journal of Pharmaceutical Sciences, 1988; 77(1), p.94.

72. KanigJl, and editor.The theory and practice of industrial pharmacy. 3rd edition 1986; 293-335.

73. Dembla NM, Maniyam AP, Agarwal S. Formulation development and evaluation of gabapentin controlled-release tablets. Pharmacy & Pharmacology International Journal,2015; volume 2 issue 3:75–81. DOI: 10.15406/ppij.2015.02.00021

74. Waldwell, L.J; Gardner. C.R; Cargill, R.C;US Patent 4, 1988; 735,804.

75. Lal, R., Sukbuntherng, J., Luo, W., Tovera, J., Lassauzet, M., and Cundy, K. Population Pharmacokinetics and Pharmacodynamics of Gabapentin After Administration of Gabapentin enacarbil. The Journal of Clinical Pharmacology, 2013; 53(1), pp.29-40.