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"Design and Development of Extended Release Dosage of an Anticonvulsant Drug Gabapentin Tablet"

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ABSTRACT:
In the study, anticonvulsant drug was selected for designing extended release matrix tablets. Pre-formulation studies were done with GABAPENTIN. Compatibility was done before choosing the excipients for the study with physical observation and FTIR studies. The samples were charged in stability chambers at conditions 30°C/65%RH and 40°C/75%RH for 30 days. All the pre-formulation studies and compatibility studies were found to be satisfactory. So formulation trials were followed with the selected excipients.Blend for ER formulation was prepared by wet granulation method. Hypromellose K4M and Hypromellose K15M were used as release retarding polymers for optimizing the formula.Six trials were taken to optimize the release of GABAPENTIN in ER form to be within specifications. F5 is the optimized formula with 11.66% concentration of HPMC K15M polymer which optimized the drug release profile as per predetermined specificatons. A reproducibility trial F6 was performed to check the reproducibility of process of drug release as per F5.For the ER form, Other excipients include povidone as binder, Lactose monohydrate as diluent, colloidal silicon dioxide as glidant and Magnesium stearate as Lubricant. Instacoatyellow was used as ready mix.
Post-Compression analysis of all formulations like Hardness, Weight variation, Friability and Assay were within the limits for all the formulations. In-vitro dissolution studies were performed by HPLC method revealed that the formulation F5 released the drug as per the specifications. Kinetic Model fitting was done by plotting graphs for Zero-Order kinetics, First-Order kinetics, Higuchi's Kinetic model and Korsemeyer - Peppas kinetic model. The formulation selected was F5 which has shown the release rate of the drug by First order kinetics and follows matrix diffusion controlled mechanism. Accelerated stability studies are being performed.

Keywords: Extended release matrix tablets, anticonvulsant drug, gabapentin, wet granulation method.

I. INTRODUCTION

The ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site(s) of action is attained immediately and is then maintained constant for the desired duration of the treatment. If the provided dose size and frequency of administration are correct, therapeutic steady state plasma concentration of a drug can be achieved promptly and maintained by the respective administration of conventional peroral dosage forms. However there are number of potential limitations associated with this. These limitations are: The concentration of drug in the plasma and hence at the site(s) of action of the drug fluctuates over successive dosing intervals, even when the so-called 'Steady-state condition' is achieved. Hence it is not possible to maintain a therapeutic concentration of drug which remains constant at the site(s) of action for the duration of treatment. The inevitable fluctuations of steady-state concentrations of drug in the plasma and hence at the site(s) of action can lead to a patient being over or under medicated. For drugs with short biological half-lives frequent doses are required to maintain steady state plasma concentrations within the therapeutic range. For such drugs, the maintenance of therapeutic plasma concentrations is particularly susceptible to the consequence of forgotten doses and the overnight no-dose period. Lack of patient compliance, which is more likely in the case of regimens requiring frequent administration of conventional dosage

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forms.These limitations and requirements led pharmaceutical scientists to consider presenting therapeutically active molecules in 'extended release' preparations. Over the years, there has been an enormous amount of work put into designing drug delivery systems that can eliminate or reduce the cyclical plasma concentrations seen after conventional drug delivery systems are administered to a specified dosage. Delayed release products

Delayed release indicates that the drug is not being released immediately following

administration but at a later time.

E.g., Enteric coated tablets, Pulsatile-release capsules.

· Repeat action products

Repeat action indicates that an individual dose is release fairly soon after administration and second or third doses are subsequently released at intermittent intervals.

· Prolonged release products

Prolonged release indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

· Sustained release products

Sustained release indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration and then a gradual release over an extended period.

Extended release products (ER)

Extended release dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours).

Controlled release (CR)

Controlled release dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time.

Modified release products

Modified release dosage forms are defined by the USP in those whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

SUSTAINED RELEASE DOSAGE FORMS

Conventional drug products like tablets and capsules are formulated to release the active drug immediately to obtain rGabapentind and complete systemic absorption of the drug. The conventional dosage form maintains the constant plasma drug concentration for the long period of time by administering in a particular dose and at particular frequency. The frequency of administration or the dosing interval of any drug depends upon its half-life or mean residence time (MRT) and its therapeutic index. In most cases, the dosing interval is much shorter than the half-life of the drug resulting in a number of limitations. These limitations can overcome by formulating into Modified-Release dosage forms. Modified-release products provide either delayed-release or extended-release of the drug.

Advantages of Extended-Release System

Ø Reduction in drug blood level fluctuations
Ø Frequency reduction in dosing
Ø Enhanced patient convenience and compliance
Ø Reduction in adverse side effects
Ø Reduction in overall health care costs

Disadvantages

Ø Loss of flexibility in adjusting the drug dose and/or dosage regimen.
Ø Increased risk of sudden and total drug release or dose dumping due to failure of technology of the dosage unit.

Classification of extended release products

Extended release tablets are often classified according to the mechanism of drug release. The following are the most common means used to achieve a slow, control release of drug from tablets.

· Dissolution control
· Diffusion control
· Dissolution and diffusion control
· Erosion control
· Osmotic pump control & Ion exchange control

Dissolution controlled Release system

Most of the products fall into two categories

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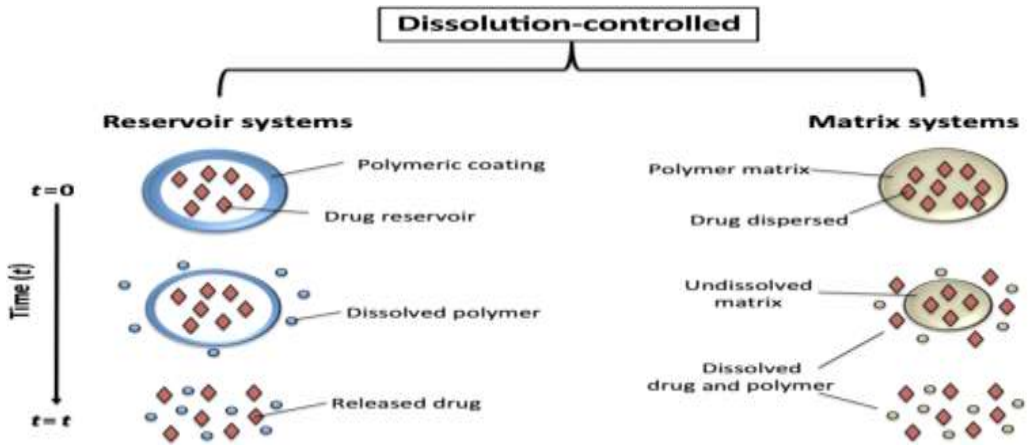
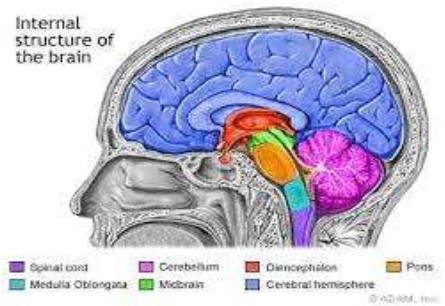


Formulation of extended release system
There are three main classes of delivery system
· Monolithic or matrix systems
· Reservoir or membrane controlled systems
· Osmotic pump systems.
There is a basic principle that governs all these systems. In a solution drug diffusion will occur from a region of high concentration to a region of low concentration. This concentration difference is the driving force of drug diffusion out of the system 8 .
Components of extended release delivery system hese include
· Active drug
· Release controlling agents (matrix formers, membrane formers)
· Matrix or membrane modifier, such as channeling agents for wax matrices and solublisers/and wicking agents for hydrophilic matrices
· Solubiliser, pH modifier and density modifier
· Lubricant and flow aid
· Density modifiers (if any)
EPILEPSY
· Epilepsy is a neurological disorder characterized by unprovoked, recurring seizures that disrupt the nervous system and can cause mental and physical dysfunction.
· The structures of the brain include the spinal cord, the brainstem, consisting of the medulla oblongata, the pons and the midbrain; the cerebellum; the cerebrum (one half, or hemisphere shown); and the diencephalon.



II. MATERIALS AND METHODOLOGY

List of chemicals used with grade and supplier

Materials used Grade Manufacturer Gabapentin IP Gift Sample of Sun Pharma Hypromellose K4m USP/NF Colorcon, Hypromellos K15m ,USP/NF ColorconCarboxy ,Methyl Cellulose, Sodium IP FMC ,Lactose Monohydrate ,USP DMV Fonterra, Povidone USP BASF Ltd, Colloidal Silicon Dioxide, Magnesium Stearate USP Amishi drugs and chemicals.

List of ingredients with their functional category

EXCIPIENTS FUNCTIONAL CATEGORY

Drug Active Ingredient, HPMC K15M/K4M Matrix forming Polymer, Lactose monohydrate Diluent ,Povidone Binder, Colloidal silicon dioxide Glidant, Magnesium Stearate

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Lubricant Purified Water Solvent for granulation List of ingredients with their functional categoryDrug Active Ingredient ,HPMC K15M/K4M Matrix forming Polymer, Lactose monohydrate Diluent Povidone Binder ,Colloidal silicon dioxide Glidant, Magnesium Stearate Lubricant, Purified Water Solvent for granulation.

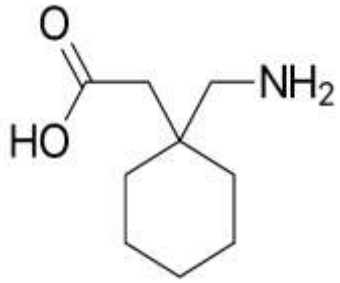
FORMULATION DESIG
Table 5: Formula for extended release tablets

INGREDIENTS QUANTITY USED IN THE FORMULATION

III. EXPERIMENTAL WORK

DRUG PROFILE

Drug Name: Gabapentin



Structure of Gabapentin

Synonyms: Gabapentin, Gabapentina, Gabapentine, Gabapentino,Gabapentinum.
Molecular formula: C 9 H 17 NO 2
IUPAC Name: 2-[1-(Amino methyl) cyclohexyl] acetic acid
Category: Anti-epileptic drug, Anticonvulsants
Brand Names: Gralise, Neurontin
Description: Brown / Yellow powder
Solubility :Soluble in acetic acid, sparingly soluble in chloroform, practically insoluble in water.

Mechanism of action:

The precise mechanism through which Gabapentin exerts its therapeutic effects is unclear.16,17 The primary mode of action appears to be at the auxillary α2δ-1 subunit of voltage-gated calcium channels (though a low affinity for the α2δ-2 subunit has also been reported).10,8,14 The major function of these subunits is to facilitate the movement of pore-forming α1 subunits of calcium channels from the endoplasmic reticulum to the cell membrane of pre-synaptic neurons.

Pharmacokinetics

Absorption

Absorption of Gabapentin is thought to occur solely via facilitated transport by the LAT1 transporter within the intestines. As this process is saturable, the oral bioavailability of Gabapentin is inversely proportional to the administered dose - the oral bioavailability of a 900mg/day regimen is approximately 60%, whereas a 4800mg/day regimen results in only 27% bioavailability.16,18 The Tmax of Gabapentin has been estimated to be 2-3 hours. Food has no appreciable effect on Gabapentin absorption.

DRUG EXCIPIENT COMPATIBILITY STUDY

Gabapentin and excipients were thoroughly mixed in predetermined ratio as per in the given table and passed through the sieve No.40. The blend was filled in 10 ml glass vials and closed with gray rubber stoppers and sealed with aluminum seal and charged in to stress condition at 25ºC/60%RH. Similarly Gabapentin was also kept at above conditions as like the samples. The samples were observed for any physical change in 15th and 30th days.

FORMULATION DESIGN
Formula for extended release tablets
INGREDIENTS QUANTITY USED IN THE FORMULATION
MANUFACTURING PROCEDURE STEP I: DISPENSING OF MATERIALS
All the raw materials are dispensed, packed in an individual clean poly bags and labeled.
STEP II: SIFTING
Gabapentin, HPMC (K4orK15M) and lactose monohydrate sifted through #40 mesh.
STEP III: PREPARATION OF BINDER SOLUTION
Povidone was diluted in sufficient quantity of water.
STEP IV: DRY MIXING:
Materials were loaded in RMG and are mixed for about 15 minutes at slow speed.
STEP V: GRANULATION
Binder solution is added to the dry mix at slow speed. After the addition of the binder, it is mixed for about three minutes at fast speed to form granules.

STEP VI: DRYING
Load blend in rGabapentind dryer at a temperature of 60 0 and air flow about 40. Drying is continued until loss on drying reaches NMT 2%.

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STEP VII: SIZING
Milled in a multimill using 1.5mm screen. Blend was sifted through 20#mesh.
STEP VIII: PRE LUBRICATION
Aerosil, HPMC (K4orK15M) was sifted through 40#mesh and kept aside. Load this in octagonal blender along with the blend.
STEP IX: LUBRICATION
Magnesium stearate was sifted through 60#mesh and added to the above step and mixed
COMPRESSION
Compression was carried out in 8stn. Physical parameters like Weight variation, Hardness, Thickness, are monitored to meet the predefined specifications and noted.
STEP XI: COATING
25 grams of instacoat yellow in 250ml of water kept under mechanical stirring for about 20minutes.Coating is done with temperature of 70 o c with pump rpm of 0-1. Coating is done under F4-F6 trials.
PRECOMPRESSION PARAMETERS
6.3.1 Determination of bulk density and tapped density
A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2 sec intervals.

Bulk
density=W/V 0
Tapped
density=W/V t
Where, W=weight of the
powder, V 0 =initial volume,
V t = tapped volume
Hausner's ratio
Hausner's ratio provides an indication of the flow properties of the powder, which could result from vibration of the feed hopper. A lower value of indicates better flow and vice versa.
Hausner's ratio = Tapped density /Bulk density
Carr's Compressibility Index
Carr's index= (Tapped density- Bulk density/ Tapped density) ×100
ANGLE OF REPOSE
The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose (q) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel Method and is the measure of the flow ability of powder/granules.

6.4 POST COMPRESSION EVALUATION PARAMETERS FOR FORMULATED TABLETS
General Appearance
The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity.
The control of general appearance involves the measurement of size, shape, color, presence or absence of odour, taste etc.
Size and Shape
It can be dimensionally described & controlled. The thickness of a tablet is only a variable.
Tablets thickness can be measured by Digital Vernier calipers. Tablet thickness should be controlled within a 7.5% variation of standard value.
Hardness
Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shake of handling in manufacture, packing and shipping. Hardness generally measures the tablets crushing strength.
Friability
Friability of a tablet can determine in laboratory by Electro lab EF2 Friabilitor. This consist of a plastic chamber that revolves at 25 rpm, dropping the tablets of weight not less than 6.5 g, through a distance of six inches in the Friabilator, which is then operate for 100 revolutions. The tablets are reweighed. Compressed tablets that less than 0.1 to 0.5% of the tablet weight are considered acceptable. The percentage friability was measured using the formula
UNIFORMITY OF DRUG CONTENT: The drug content was performed to check the dose uniformity in the formulation. Randomly ten tablets were weighed and powdered. As following of assay procedure after suitable dilutions, the drug content was determined by HPLC at 215nm.
Procedure for Gabapentin:
Equilibrate the column with the mobile phase until a baseline is obtained. Inject the sample and standard solutions. Record the chromatogram and measure the peak area response of both standard and sample preparations of the Gabapentin.
Calculation for percentage of Gabapentin:

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AT WS 5 100 P 25 AW P
% assay of GABAPENTIN= ------- x ------- x ----- x ------- x ----- x ------- x ------- x 100
Preparation of Calibration Curve in various solvent

Standard Preparation For Gabapentin

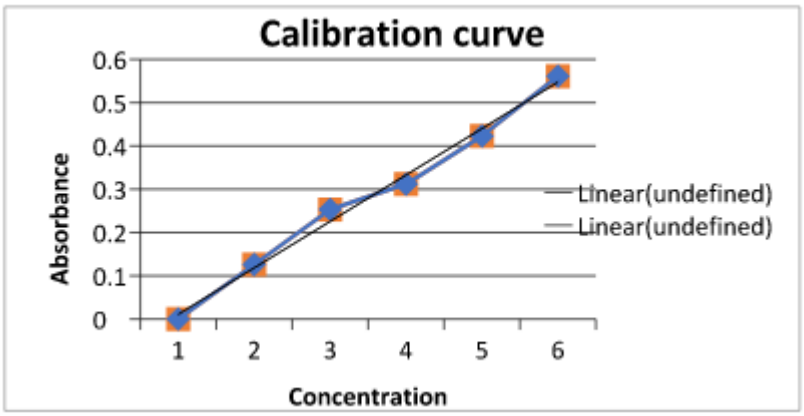
Weigh accurately about 0.1 g of Gabapentin working standard into 50ml volumetric flask, add about 30ml of methanol, sonicate for 15minutes to dissolve with intermittent shaking and dilute to 50ml with methanol, and mix well. Pipette and dilute 5ml of resulting solution into 25ml volumetric flask, and dilute to 25ml with diluent and mix well. Centrifuge a portion of this solution at 3000rpm for 10minutes and use this as standard solution.

Preparation of Calibration Curve in various solvent

Standard Preparation For Gabapentin

Weigh accurately about 0.1 g of Gabapentin working standard into 50ml volumetric flask, add about 30ml of methanol, sonicate for 15minutes to dissolve with intermittent shaking and dilute to 50ml with methanol, and mix well. Pipette and dilute 5ml of resulting solution into 25ml volumetric flask, and dilute to 25ml with diluent and mix well. Centrifuge a portion of this solution at 3000rpm for 10minutes and use this as standard solution.

S. No.	Concentration	Absorbance
1	0	0
2	2	0.126
3	4	0.253
4	6	0.312
5	8	0.423
6	10	0.561



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Calibration curve of Gabapentin Standrad Solution

Specifications for Drug release

Drug	Specification
GABAPENTIN	After 2nd hour, not more than 30% After 6th hour 30% to 60% 12th hour Not less than 85%

IV. RESULTS AND DISCUSSION

STABILITY STUDIES

Introduction:

The ICH Q1A guideline defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the three regions of the EC, Japan, and the United States. It does not seek necessarily to cover the testing for registration in or export to other areas of the world.

Stability testing Protocol

Formulation	Stability condition	Testing frequency	Tests
		3rd month	
	30°C ± 2°C/65%	6thmonth	Appearance,
	RH ± 5% RH	9th month	Physical
Selected		12th month	Parameters, Assay,
Formulation		1st month	Uniformity of
	40°C ± 2°C/75%	2ndmonth	weights, In vitro
	RH ± 5% RH	3rd month	drug release.
		6thmonth	

8.1 Drug Solubility Studies:

Table 16: Drug solubility studies

Quantity of GABAPENTIN- 1	Quantity of solvents	Inference
100 mg	100 ml of Triethylamine	Soluble
100 mg	100 ml of methanol	Sparingly soluble
100 mg	100ml of chloroform	Sparingly soluble
100 mg	100 ml of acetonitrile	Soluble
100 mg	100 ml of acetic acid	Soluble

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8.2 Evaluation of Active pharmaceutical ingredients:

Physical parameters like Angle of repose, Bulk density, Tapped density, Carr's index andHausner's index and Solubility of the Gabapentins were determined and were given here in the table below.

Table 17: Results for Pre-formulation analysis of Gabapentin

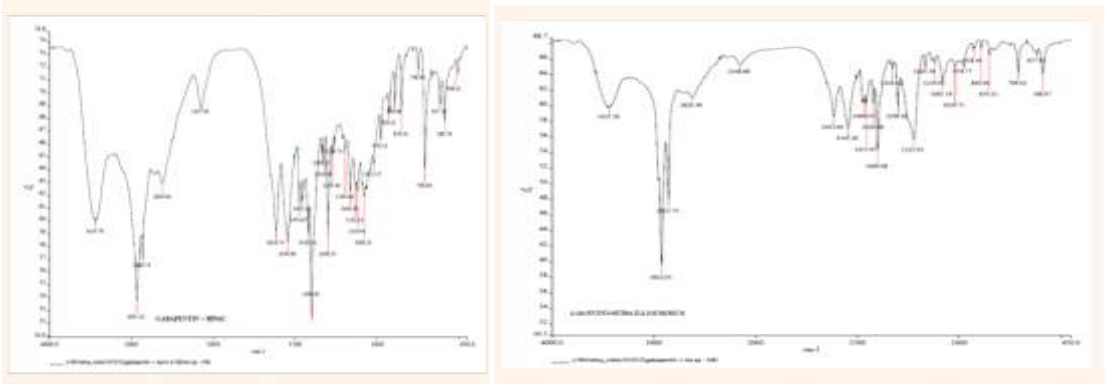
Parameters	**GABAPENTIN**
Solubility	Soluble in acetic acid, sparingly soluble inchloroform and practically insoluble in water.
Angle of repose	25.50
Bulk density	0.48m/cm^3
Tapped density	0.666 gm/cm^3
Carr's index	21.80
Hausner's ratio	1.329
Loss on drying	1.45%
Assay	99.82%

The solubility, Loss on drying, Assay of the drugs are found to be within the specifications. From the Compressibility index, Angle of repose values of Gabapentin, it can be concluded that Gabapentin have poor flow and this can be improved by granulation.

DETERMINATION OF LAMBDA MAX
FTIR STUDY

The samples that were charged in 30^{0}C/65%RH and 40°C/75% RH stability chambers were analysed by IR spectroscopy after 30 days. The graphs of the samples were given below.

FTIR Study of GABAPENTIN+HPMC K4M PREMIUM FTIR study of GABAPENTIN + METHOCEL K15M PREMIUM



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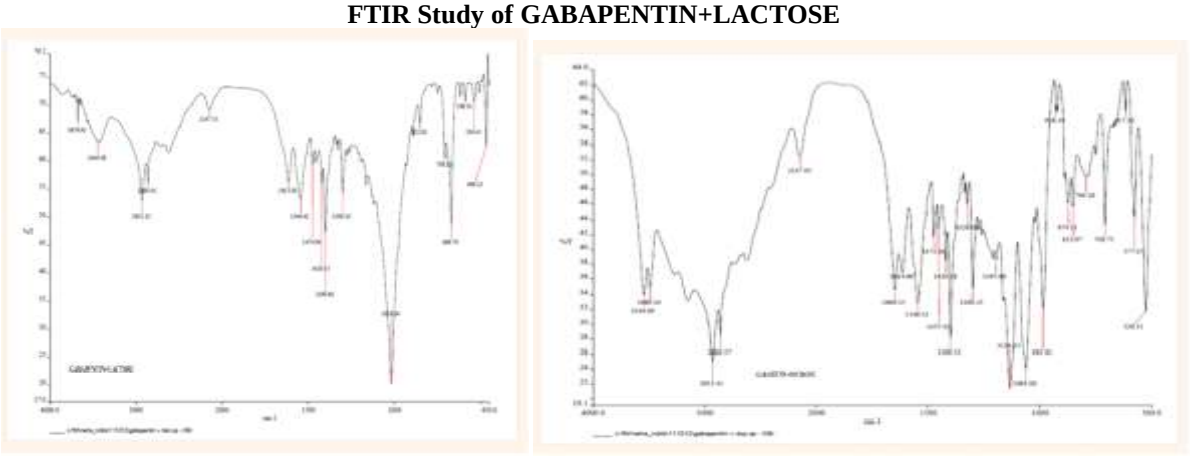
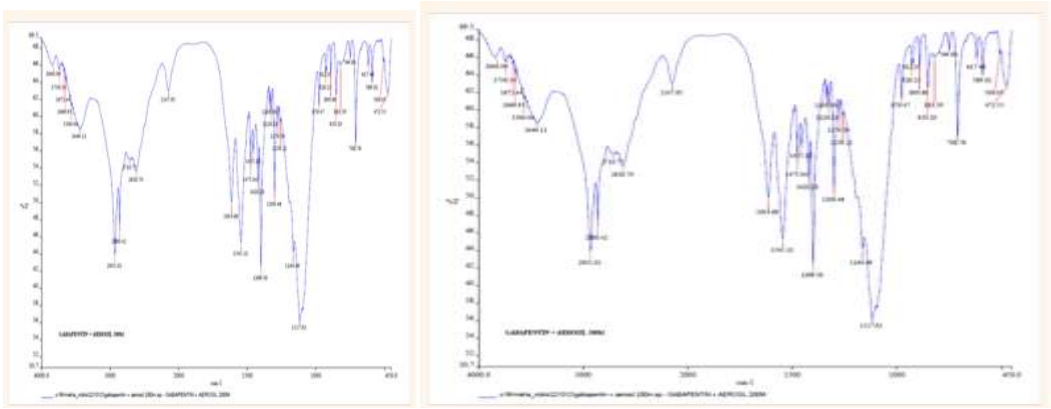
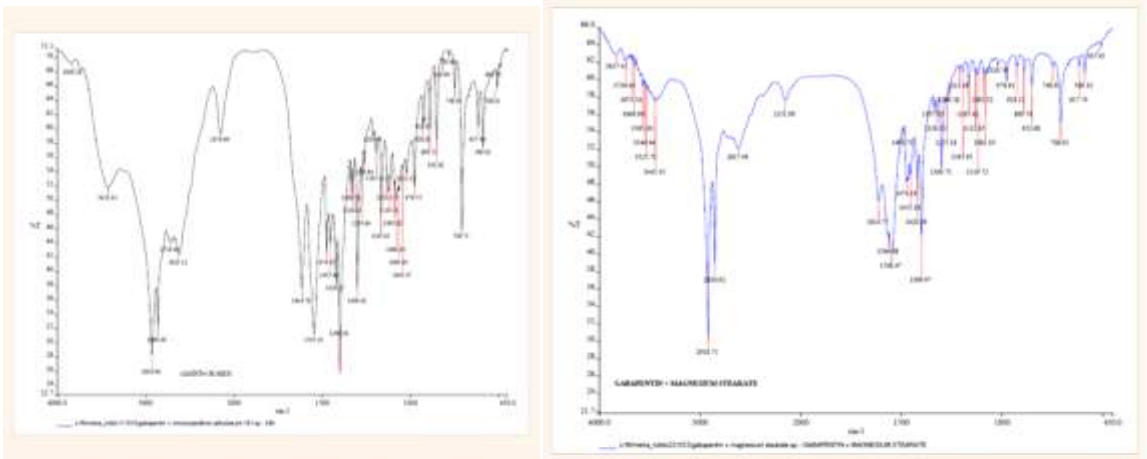
FTIR study of GABAPENTIN + METHOCEL K15M PREMIUM

FTIR Study of GABAPENTIN+LACTOSE





FTIR Study of GABAPENTIN+AEROSIL



FTIR Study of GABAPENTIN+MAGNESIUM STEARATE

FTIR study of GABAPENTIN+CMC sodium

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Table 18: Results of Compatibility studies

Particulars	Ratio	Description	Parameters				Remarks
			30°C/ 65% RH		40°C/ 75% RH		
			15 days	30 days	15 days	30 days	
Gabapentin	-	Yellow Powder	No change	No change	No change	No change	Compatible
Gabapentin: HPMC K15M Premium	1:1	Off white to yellow Powder	No change	No change	No change	No change	Compatible
Gabapentin: HPMC K4M Premium	1:1	Off white to Yellow Powder	No change	No change	No change	No change	Compatible
Gabapentin: Povidone	1:0.5	Off White to yellow Powder	No change	No change	No change	No change	Compatible
Gabapentin: Lactose monohydrate	1:5	Off White to Yellow Powder	No Change	No change	No change	No change	Compatible
Gabapentin: Aerosil	1:0.1	Off White to yellow Powder	No change	No change	No change	No change	Compatible

PRECOMPRESSION EVALUATION

Table 19: Evaluation of micrometrics properties of granules

Formulation Code	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausner's ratio(HR)	Carr's index(CI)	Angle of repose (θ)
FT-1	0.465	0.609	1.373	26.78	32.06

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FT-2	0.448	0.666	1.451	32.05	38.23
FT-3	0.615	0.689	1.14	11.89	45.24
FT-4	0.589	0.660	1.109	10.60	44.98
FT-5	0.548	0.597	1.18	14.61	29.99
FT-6	0.553	0.640	1.169	14.653	32.37

EVALUATION OF PHYSICAL PARAMETERS OF TABLET

Table 20: Evaluation of Post-Compression properties of Core Tablet

TRIALS	**PHYSICAL PARAMETERS**			
	Weight variation (mg)	**Hardness** (N)	**Thickness** (mm)	**Friability** (%)
F1	299 ± 5	120± 10	4.21 ± 0.02	0.197
F2	298 ± 5	130± 10	4.20 ± 0.02	0.099
F3	298 ± 5	140± 10	4.20 ± 0.02	0.162
F4	300 ± 5	140± 10	4.18 ± 0.02	0.97
F5	300 ± 5	150± 10	4.19 ± 0.02	0.08
F6	299 ± 5	150± 10	4.19 ± 0.01	0.09

Evaluation of Post-Compression properties of Coated Tablets

TRIALS	**PHYSICAL PARAMETERS**		
	Weight variation (mg)	**Hardness** (N)	**Thickness** (mm)
F4	302 ± 5	160± 10	4.22 ± 0.02
F5	303 ± 5	170± 10	4.23 ± 0.02
F6	303 ± 5	170± 10	4.23 ± 0.01

DRUG CONTENT UNIFORMITY

Table 22: Evaluation of Drug Content of blend

Drug Content Uniformity	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
GABAPENTIN	101	100	99.6	99	100	99.9

Discussion:
In all trials, uniformity of content was within the limits i.e. equal proportion of drug content ineach tablet.

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ASSAY

Table 23: Evaluation of drug content of ER tablet

Drug Content	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
GABAPENTIN	100.1	99.9	99.9	99.8	100	99.9

8.6 IN-VITRO DISSOLUTION STUDY

DISSOLUTION PROFILE OF F1

Table 24: Dissolution profile of F1

PERCENTAGE DRUG RELEASE(F1)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
		1	**2**	**3**	**4**	**5**	**6**	
1%w/vSLS medium	**2**	22.3	23.4	22.1	13.0	12.5	23.7	20
	6	84.2	82.6	68.2	70.1	70.4	70.6	74
	12	92.5	81.2	66.6	77.2	100.2	74.4	82

Dissolution profile of F3

PERCENTAGE DRUG RELEASE(F3)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
		1	**2**	**3**	**4**	**5**	**6**	
1%w/vSLS medium	**2**	15.5	19	18.2	14.1	15.0	14.8	16
	6	65.0	70.0	75.0	74.5	75.5	70.0	70
	12	95.0	92.6	94.0	94.1	69.4	67.4	85

Discussion

The average drug release was found to be 66% and 70% respectively in F2 and F3 formula by increasing the quantity of HPMC K4M upto 37.5mg/tablet and CMC sodium concentration was reduced from 15mg to 10mg/tablet. So trial F4 was planned by using HPMC of higher viscosityHPMC K15M.

DISSOLUTION PROFILE OF F4

Table 27: Dissolution profile of F4

PERCENTAGE DRUG RELEASE(F4)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
1%w/vSLS medium		**1**	**2**	**3**	**4**	**5**	**6**	
	2	14.0	18.1	13.9	15.1	15.0	15.1	15
	6	31.4	30.6	31.9	27.2	29.0	30.1	30

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	12	79.6	80.6	75.1	75.6	80.9	77.8	78

Discussion:

Under F4 trial, the polymer was changed i.e HPMC K15M which is of high viscosity grade was chosen and CMC sodium was removed. Methocel K15M polymer concentration was about 16.66% (50mg/tablet) which retards the release more. At 6th hour, the average drug release was 30% which is within the lower limit of specification (30-60%). At 12th hour, the average drug release was 78% which was not within the limit (NLT 85%). It means that the drug retards more,so the polymer methocel K15M concentration was reduced in next trial F5

DISSOLUTION PROFILE OF F5

Table 28: Dissolution profile of F5

PERCENTAGE DRUG RELEASE(F5)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
		1	**2**	**3**	**4**	**5**	**6**	
1%w/vSLS medium	**2**	14.0	18.0	15.1	13.9	12.5	12.4	14
	6	39.6	46.1	46.3	39.6	46.0	47.0	44
	12	101	95.0	90.1	87.5	97.5	81	92

DISSOLUTION PROFILE OF F6

Table 29: Dissolution profile of F6

PERCENTAGE DRUG RELEASE(F6)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
		1	**2**	**3**	**4**	**5**	**6**	
1%w/vSLS medium	**2**	11.2	17.8	9.2	6.4	11.7	15.1	12
	6	38.3	57.8	35.7	29.0	41.1	49.9	42
	12	81.5	101.0	81.7	90.5	86.5	97.9	88

Discussion:

The drug release of F6 trial is reproducible as F5 formula. So F5 formula was finalized as finalprototype formula for the extended release formulation.

COMPARITIVE IN-VITRO DISSOLUTION PROFILE FROM F1-F6

Table 30: Comparative In-vitro dissolution profile from F1-F6

TIME(HOURS)	**% CUMULATIVE DRUG RELEASE** **Average % drug release for all trials**	**SPECIFICATIONS**

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	F1	F2	F3	F4	F5	F6	
2hr	21	17	16	15	14	12	NMT 30%
6hr	75	67	70	33	45	43	30-60%
12hr	83	88	84	79	92	87	NLT 85%

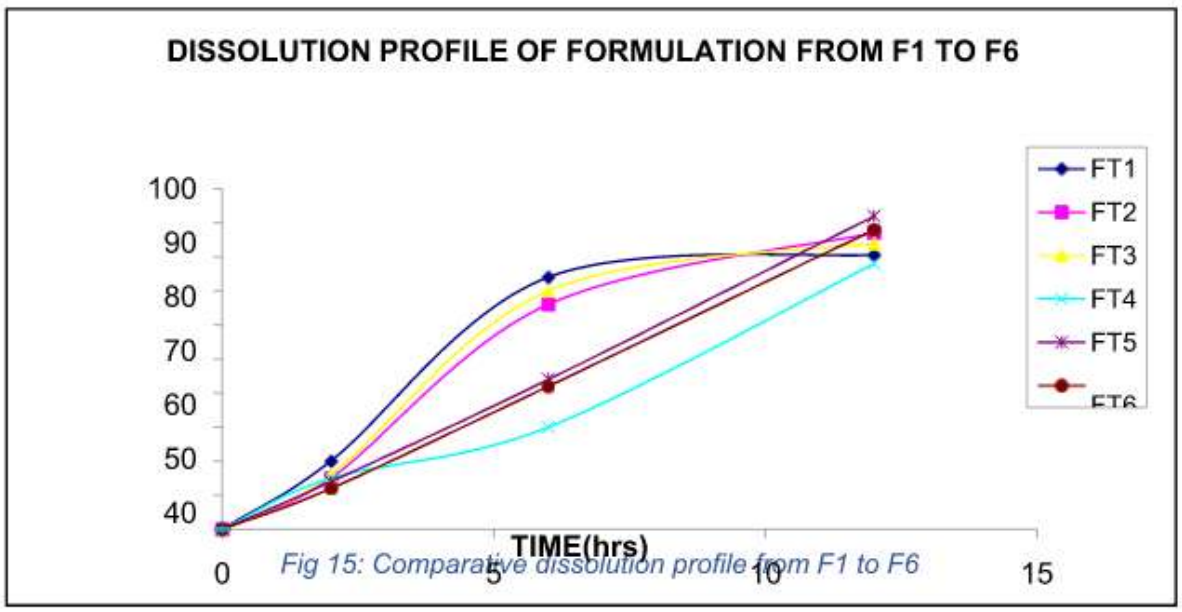

Fig 15: Comparative dissolution profile from F1 to F6

DATA ANALYSIS

Kinetic study:

Formulation-5 was found to be the desired In-vitro dissolution rate, so this formulation wasselected for determining the nature of drug release from dosage form.

Table 31: Different Kinetic models

Time (in hours)	Square root of time	Log Time	% CDR	Log(100 % - CDR)	Log %CDR
2	1.414213562	1.411	14	1.99492	1.146128036
6	2.449489743	2.44	44	1.99280	1.643452676
12	3.464101615	3.46	92	1.99138	1.963787827

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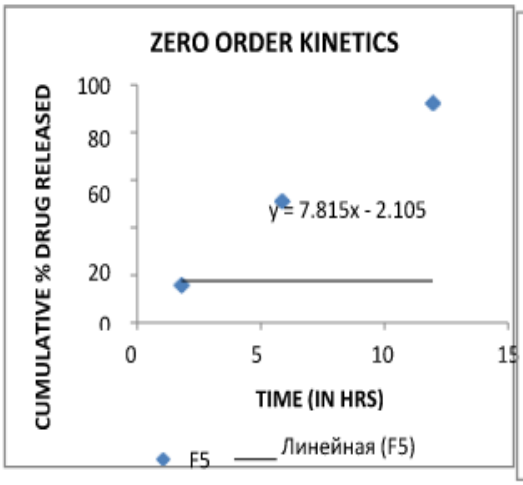
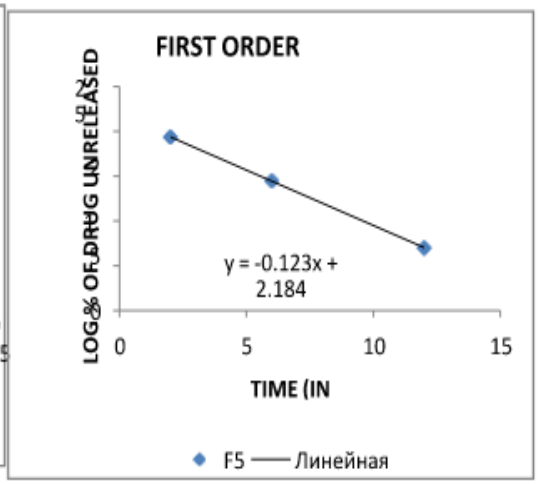
Regression coefficients from all the Kinetic model graphs

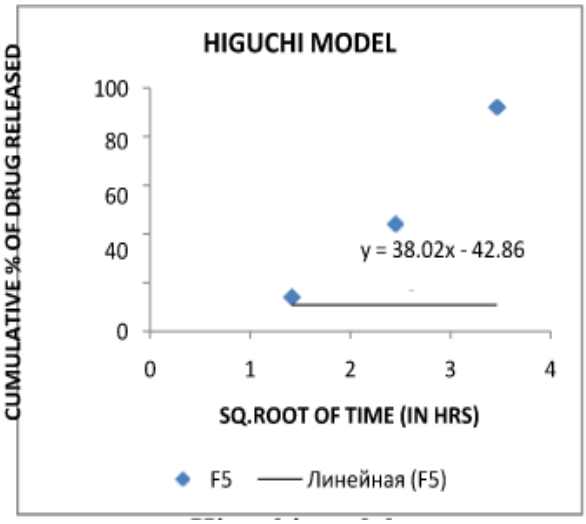
Formulation	Zero-order kinetics	First-order kinetics	Higuchi's kinetics	Korsmeyer-Peppas
F5	0.963	1	0.981	0.986

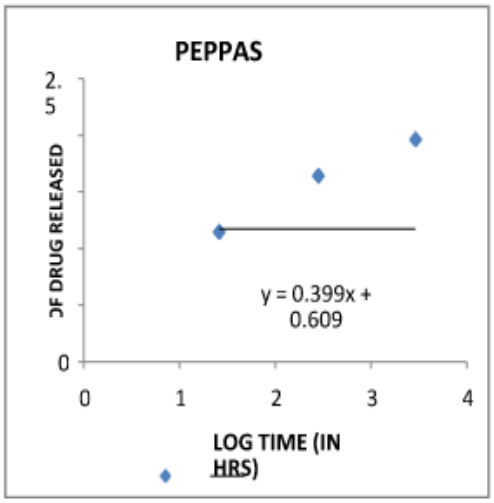
KINETIC MODELS





Zero order kinetics **First order kinetics**





Higuchi model **Peppas model**

DISCUSSION

The curve fitting results of the release rate profile of the designedformulations gave an idea on the mechanism of drug release.

Based on the data analysis, it was found that the drug release follows First order release kinetics, as it showed the highest linearity and concluded that the release mechanism was matrix diffusion contro

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