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

Baviskarparvin[1], Jeevan Patel*[2], Ramakant Sharma, Shabnam khan[2], and Dr.Rakesh Patel[3]

1.PG Scholar, School of Pharmacy, Dr. A.P. J. Abdul Kalam University, Indore.
2.Assistant Professor, School of Pharmacy, Dr. A.P. J. Abdul Kalam University, Indore.
3.Professor and Principal, School of Pharmacy, Dr. A.P. J. Abdul Kalam University, Indore.

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ABSTRACT

The aim of the study is to design and develop extended release matrix tablets of anticonvulsant drugs. Hypromellose, water swellable polymer was selected for the extended release of Gabapentin.

The formulation was optimized to obtain the release of GABAPENTIN for a sustained period of 12 hours. In the initial trials, Hypromellose K4M of low viscosity grade was used, then Hypromellose K15M of high viscosity grade was selected to check the feasibility of the polymer to sustain the release of GABAPENTIN. With HPMC K4M the drug release was not controlled to the desired limit of 30-60% at 6th hour. So, a still high viscous polymer Hypromellose K15M was used in the formulations F-4 to F-6. The incorporation of the Polymer intra- granularly at concentration 11.66% gave an optimum release profile within specifications.

From graphs plotted for various Kinetic models, it can be concluded that the F5 follows First-order kinetics as the plots of that model had shown higher regression value. F5 formula extended the release and follows matrix diffusion controlled mechanism.

KEYWORDS

Extended Release Dosage,Anticonvulsant Drug, matrix diffusion controlled mechanism,Gabapentin Tablet

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 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 regimen.

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Rationale for extended release dosage forms

- Many drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results.

Multiple daily dosing often is inconvenient for patient and can result in missed doses, made up doses and patient non-compliance with therapeutic regimen.

- Extended release tablets and capsules are commonly taken only once or twice daily compared with counterpart conventional forms that may need to be taken three or four times daily to achieve the same therapeutic effect.
- Extended release products provide an immediate release of the drug that promptly produces the desired therapeutic effect, which is then followed by the gradual and continual release of additional amount of drug to maintain this effect over a predetermined period of time.
- The sustained plasma drug levels provided by extended release drug products often times eliminate the need for right dosing that provides benefit not only to the patient but to the caregiver as well.

1.3.2 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

II. MATERIALS AND METHODS

3. MATERIALSANDMETHODOLOGY

Table1:Listof chemicalsusedwithgradeand supplier

S.No.	Materialsused	Grade	Manufacturer
1	Gabapentin	IP	SunPharma
2	HypromelloseK4m	USP/NF	Colorcon
3	Hypromellos K15m	USP/NF	Colorcon
4	CarboxyMethyl CelluloseSodium	IP	FMC
5	Lactose Monohydrate	USP	DMVFonterra
6	Povidone	USP	BASFLtd
7	ColloidalSilicon Dioxide	USP	Evonik
8	Magnesium Stearate	USP	Amishidrugsandchemicals
9	InstacoatYellow	USP	Colorcon

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Table2:Listofingredientswiththeirfunctionalcategory

S.NO	EXCIPIENTS	FUNCTIONAL CATEGORY
1	Drug	ActiveIngredient
2	HPMCK15M/K4M	MatrixformingPolymer
3	Lactosemonohydrate	Diluent
4	Povidone	Binder
5	Colloidalsilicon dioxide	Glidant
6	MagnesiumStearate	Lubricant
7	PurifiedWater	Solventforgranulation

Table 3.:Listof Equipments and Instrumentsused

Sr.no	Instrument	Manufacturer
1	AnalyticalBalance	SartoriusBT224S
2	TopLoadingBalance	SartoriusCPA8201
3	TappedDensityTester	ElectrolabETD-1020
4	VibratorSifter	Gansonsengg.pvt.ltdGMP-LABSrno.236
5	Octagonalblender	Gansonengg.pvt.ltd.GMP,STD
6	TabletCompression machine16station	CADMACH,Ahemdhabad.
7	DigitalVerniercaliper	Mituyutoyo
8	IRMoistureanalyser/Balance(LOD)	SartoriusMA150
9	Tablethardness tester8M	Dr.Schleunigerpharmatron8M
10	FriabilatorUSP	ElectrolabEF-2

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 985-995 www.ijprajournal.com ISSN: 2249-7781

11	High Performance LiquidChromatography	SHIMADZULC2010CHT
12	DissolutionTestapparatus	LABINDIADISSO8000
13	Fourier Transform InfraredSpectrophotometer(FT-IR)	SHIMADZU,IRPRESTIGE-21
14	Ultravoilet-visibleSpectrophotometer	SHIMADZUUV-1700Pharmaspec.
15	RGabapentindMixerGranulator	SainathBoilers

FORMULATIONDESIGN

Table5:Formulaforextendedreleasetablets

INGREDIENTS	**QUANTITYUSEDINTHEFORMULATION (mgpertablet)**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
GABAPENTIN	600	600	600	600	600	600
HPMCK15M	-	-		50	35	35
HPMCK4M	30	35	37.5		-	-
CMCSodium	15	10	10	-	-	-
Lactosemonohydrate	80	80	80	80	80	80
Povidone (PVPK30)	5	5	5	5	5	5

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 985-995 www.ijprajournal.com ISSN: 2249-7781

Colloidal Silicondioxide	1	1	1	1	1	1
HPMCK15M HPMCK4M	- 15	- 15	- 15	15 -	15 -	15 -
Magnesiumstearate	2.5	2.5	2.5	2.5	2.5	2.5
PurifiedWater	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Totalweight	300	300	300	300	300	300

1 MANUFACTURING PROCEDURESTEPI: DISPENSINGOF MATERIALS

Alltheraw materials aredispensed, packed inan individual clean polybags andlabeled.

STEPII: SIFTING

Gabapentin,HPMC (K4orK15M)andlactosemonohydratesiftedthrough# 40mesh.

STEPIII:PREPARATIONOFBINDERSOLUTION

Povidonewasdiluted insufficientquantityofwater.

STEPIV:DRY MIXING:

Materialswereloadedin RMGandaremixedforabout15minutes atslowspeed.

STEPV:GRANULATION

Binder solution is added to the dry mix at slow speed. After the addition of thebinder,itis mixedforaboutthreeminutesat fastspeed toform granules.

6.1 DRUGEXCIPIENTCOMPATIBILITYSTUDY

Gabapentin and excipients were thoroughly mixed in predetermined ratio as per in the given table andpassed through the sieve No.40. The blend was filled in 10 ml glass vials and closed with grayrubberstoppersandsealedwithaluminumsealand chargedintostressconditionat25ºC/60%RH. Similarly Gabapentin was also kept at above conditions as like the samples. The sampleswereobservedforanyphysicalchangein15th and30th days.

Table4:Composition ofGabapentinwithdifferentexcipientsusedforcompatibilitystudy

SERIALNO.	**COMPOSITIONDETAILS**	**RATIO**
1	OnlyGabapentin	1
2	Gabapentin+HPMCK4MPremium	1:1
3	Gabapentin +HPMCK15Mpremium	1:0.5
4	Gabapentin +CMCsodium	1:1
5	Gabapentin +povidone	1:0.5

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 985-995 www.ijprajournal.com ISSN: 2249-7781

6	Gabapentin +colloidalsilicondioxide	1:0.1
7	Gabapentin +magnesiumstearate	1:0.25
8	Gabapentin +lactosemonohydrate	1:5

FTIR spectra were recorded in solid state as potassium bromide (KBr) dispersion onan FTIR spectrometer-430 (Shimadzu 8400S, Tokyo, Japan) in a scan range of 400-500cm^{-1},andresolutionof4cm^{-1}.

c. Thermalanalysis(DSC)

The thermal profiles of doxofylline and soluplusnanomicelles were recorded on aDifferential Scanning Calorimeter (DSC1, Mettler Toledo®, Zurich, Switzerland) at aheating rateof10°Cmin^{-1}from30-350°Cundernitrogenpurgeof50mLmin^{-1}.

d. X-raydiffractionanalysis(XRD)

The X-ray diffractogram of Doxofylline loaded Soluplus nano micelles were recordedonanX-raydiffractometer(Bruker® AXSD8advance,Karlsruhe,Germany).

e. Scanningelectronmicroscopy(SEM)

Filtering electron microscopy (SEM, JSM-6390®, Jeol Datum Ltd., Tokyo, Japan)wasutilizedtoanalyzethemorphologyofDoxofylline-LoadedSoluplusNano micelles.Testswerefaltercoveredwithaslenderlayer(400Å)ofgold.Photomicrographswere caughtat20kVwithanamplificationof1000x.

f. AndersencascadeimpactionStudies

Streamlinedmoleculesizeisacriticalboundaryforallbreathedinitems,straightforwardly affecting territorial testimony in the lungs and respiratory parcel. Itsestimation is consequently basic during the item improvement cycle and for qualitycontrol. Different estimating procedures are accessible, yet course impaction is thestrategydeterminedforadministrativeendorsement,andthusthemostbroadly

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III. RESULTSANDDISCUSSION

8.1 Preformulationstudies

a) Meltingpointdetermination

International Journal of Pharmaceutical Research and Applications
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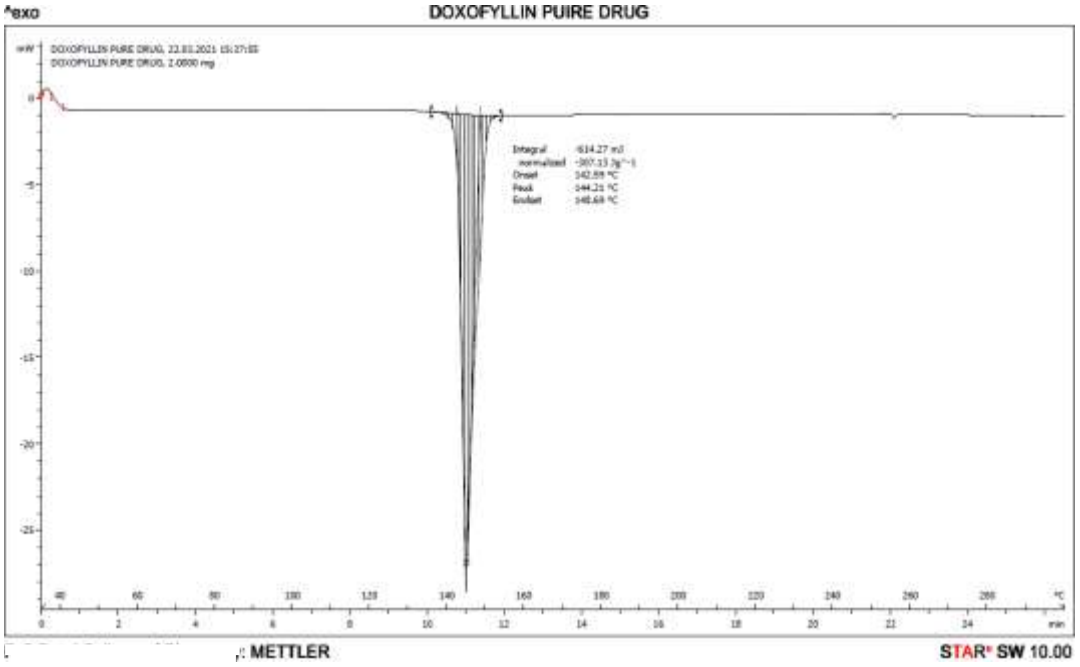
Fig.8.1DSC ofDoxofylline



Thethermal eventofDoxofyllineoccursintherangeof144-148°C,whichrepresentsthevanishingofwaterandresultingweightreduction.Theweightreduction as a result of

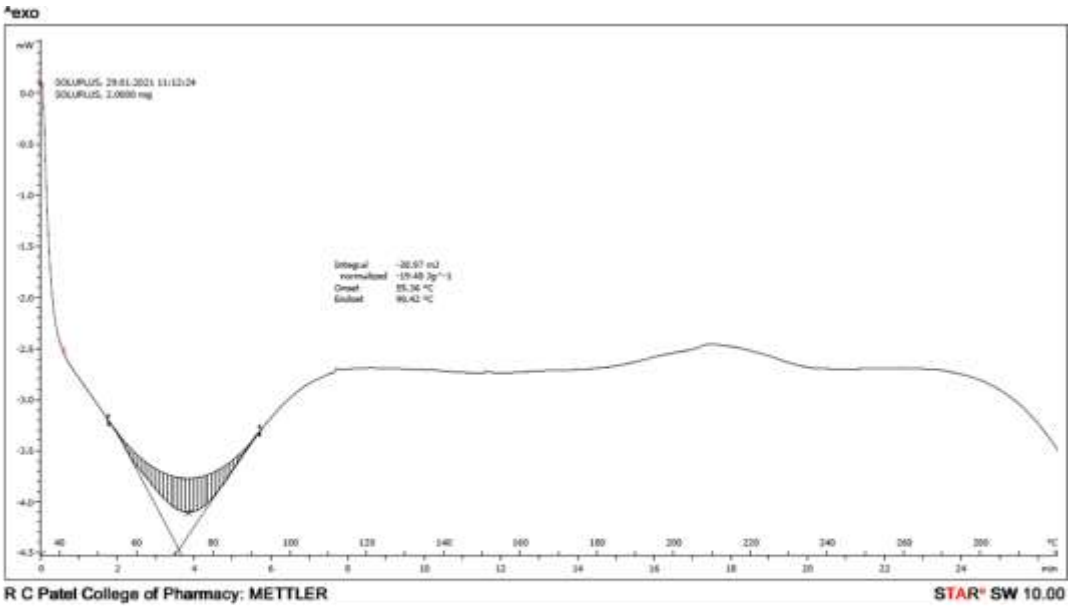


Fig. 8.2DSCofSoluplus

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 985-995 www.ijprajournal.com ISSN: 2249-7781

Thethermal event of Soluplus occurs in the range of 55-90°C , which represents thevanishing of water and ensuing weight reduction. The weight reduction as a result ofdissipationofwaterappearstorelyuponthequantityofchargedestinationspresentonthepolymerchains.The completethermaldecompositionofSoluplus,isaccomplishedattemperaturesabove90°C.(Britto&CampnanaFilho,2004).DifferentialScanningColorimetryisperformedbyStarsoftwareonDifferentialScanningCalorimeter(Mettler).Exprimentwasperformedontemperaturerange200-400. Meltingpointwasobtainedon55-90^{o}C.

a) UV-visiblespectroscopy

Standard aqueous solution of bulk doxofyllinewas scanned between 200-400 nmagainstblank aqueous solution and the wavelength of maximum absorbance wasobserved to be 274 nm **(Figure 8.3**

Figure 8.3:UV-Visible spectrum of doxofylline [Solvent: Methanol,scanningrange: [200-400nm].

b) Fourier-transforminfraredspectroscopy(FTIR)

TheFTIRspectrumofbulkDoxofyllineshowedsharpcharacteristicpeaksaspresentedin **Figure8.4**.The observed peaks arelistedin **Table1**.The obtainedpeaksareinfullsupportofthegivenchemicalstructureofthedrug.

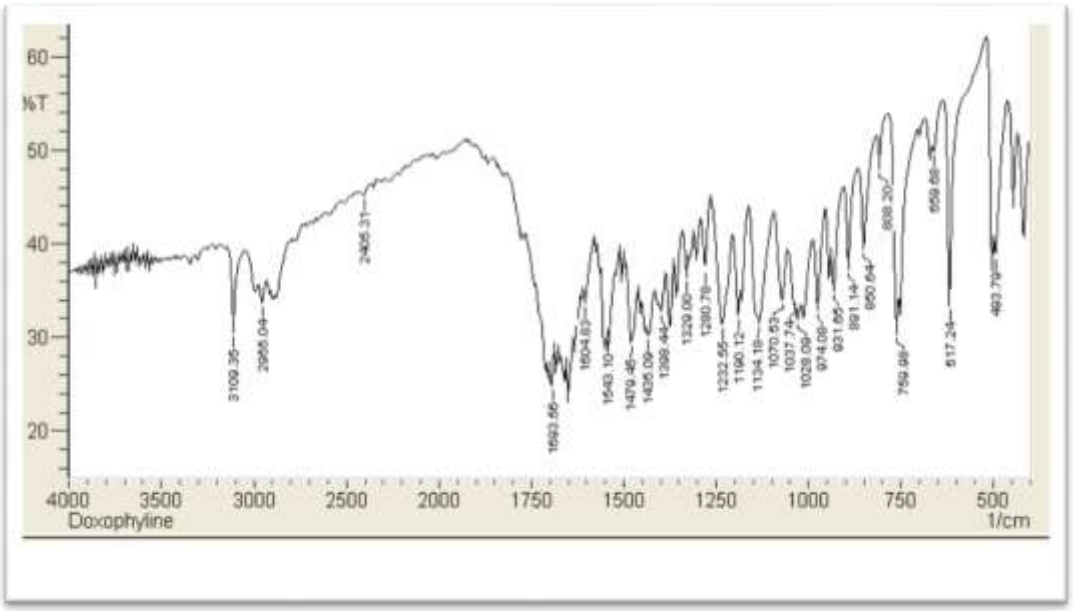
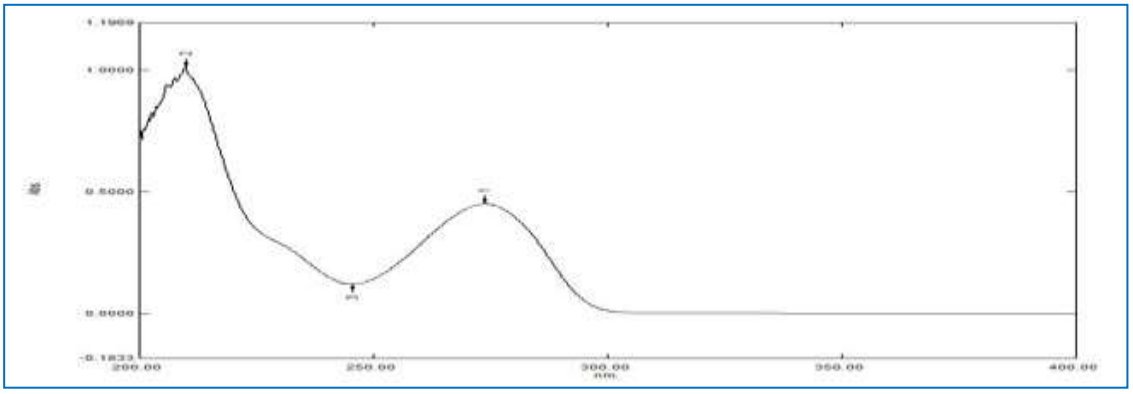


Figure8.4:FTIRspectrumofbulkDoxofylline



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Volume 8, Issue 1 Jan-Feb 2023, pp: 985-995 www.ijprajournal.com ISSN: 2249-7781

IV. SUMMARY

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 theexcipientsfor the study withphysicalobservationandFTIRstudies.The sampleswerecharged in stability chambers at conditions 30°C/65%RH and 40°C/75%RH for 30 days. Allthepre-formulationstudiesandcompatibilitystudieswerefoundtobesatisfactory.Soformulationtrials were followed with theselected excipients.

Blendfor ERformulationwaspreparedby wetgranulationmethod.HypromelloseK4M and Hypromellose K15M were used as release retarding polymers for optimizing theformula. SixtrialsweretakentooptimizethereleaseofGABAPENTINinERformtobewithinspecifications. F5 is the optimized formula with 11.66% concentration of HPMC K15Mpolymer which optimized the drug release profile as per predeterminedspecificatons. Areproducibility trial F6 was performed to check the reproducibility of process of drug releaseas perF5.

For the ER form,Other excipients includepovidone as binder,Lactose monohydrateas diluent, colloidal silicon dioxide as glidant and Magnesium stearate as Lubricant. Instacoatyellowwas used asreadymix.

Post-CompressionanalysisofallformulationslikeHardness ,Weightvariation,Friability andAssay were within thelimitsfor all theformulations.In-vitro dissolutionstudies were performed by HPLC method revealed that the formulation F5 released the drugas per the specifications. Kinetic Model fitting was done by plotting graphs for Zero-Orderkinetics, First-Order kinetics, Higuchi's Kinetic model and Korsemeyer - Peppas kineticmodel. The formulation selected was F5 which has shown the release rate of the drug by Firstorderkineticsandfollowsmatrixdiffusioncontrolledmechanism.AcceleratedstabilitystudiesarebeingperformedIn.

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LISTOFABBREVIATIONS

API	ActivePharmaceuticalIngredient
HPMC	HydroxypropylMethylcellulose
CMCSodium	Carboxymethyl CelluloseSodium
IRGraph	Infra-RedGraph
ppm	Partspermillion
RMG	RGabapentindMixerGranulator
USP	UnitedStatesPharmacoepia
%RH	PercentageRelative Humidity
%RSD	PercentageRelativeStandardDeviation
ICH	InternationalConferenceforHarmonization
RPM	Revolutionsperminute
nm	Nanometers
µg	Microgram
mg	Milligram
gm	Gram
µm	Micrometer
cm	Centimetre
hrs.	Hours
Fig.	Figure
%	Percentage
pH	Hydrogenionconcentration
E R	ExtendedRelease
°C	Degreecentigrade
FT-IR	FourierTransform InfraredSpectroscopy
UV	Ultravioletspectroscopy
R^2	Regression coefficientT½
Eliminationhalflife	
n	Slopeconstant
HPLC	HighPerformanceLiquidChromatograph