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A NOVEL APPROACH OF PHENYTOIN PELLETS FOR MANANGEMENT OF EPILEPSY

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ABSTRACT
Oral route is the oldest and convenient route for the administration of therapeutic agents because of low cost of therapy and ease of administration leads to higher level of patient compliance. Phenytoin is an antiepileptic agent which is regarded as first line, first choice of drug to treat epilepsy during pregnancy. The pellets designed and are prepared by extrusion-spheronization method. The aim of the present research work was to investigate the potential of phenytoin pellets in management of epilepsy. The polymers used in the formulation are Eudragit, hypo methoxy cellulose, xanthan gum. The formulations were evaluated for various physicochemical parameters. The Scanning Electron Microscopy photographs confirmed that the prepared formulations were spherical in nature. The compatibility between drug and polymers in the drug loaded pellets was confirmed by Fourier Transform Infra Red spectroscopy studies. The mean particle size of the drug loaded pellets was in the range 1340-1382µm. The percentage drug content was in the range of 92.88 – 98.12%. In-vitro drug release studies are carried out and the evaluation results obtained showed that the formulation F8 showed a maximum drug release of 96.75 % in 12 hours. Stability studies indicated that pellets are stable.Thus it concludes that sustained drug release of pellets helps in better management of epilepsy.

KEYWORDS: Pellets, Oral drug delivey, Sustained drug release.

INTRODUCTION
The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio recognition, and efficacy Of drug were determined .These new strategies, often called drug delivery systems (DDS).[1] It is necessary to develop suitable drug delivery system for all drugs to allow their effective and safe application to the patient. Indeed, drug delivery systems control the drug release rate and drug absorption and ultimately the therapeutic effects along with side effects of the drug. Ideal drug delivery systems ensure that the active drug is available at the site of action according to the need of patient for an intended duration.[2] Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS. This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver drug directly at specific site. On the other hand, the method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all.[3] From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio recognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS).[3] Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The main aim of preparing sustained release formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decreasing the frequency of dosing, decreasing the required dose employed and providing uniform drug

delivery. Pellets are one of the most popular multi-particulate dosage forms. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipient into small, free-flowing, spherical or semispherical units, referred to as pellets. Pellets range in size, typically, between 0.5 mm and 1.5 mm.[5]

Factors affecting pelletization

- Moisture content
- Rheological characteristics
- Solubility of excipients and Drug in granulating fluid
- Composition of Granulating Fluid
- Physical Properties of Starting Material
- Speed of the Spheronizer
- Drying technique and drying temperature
- Extrusion Screen

MATERIALS AND METHODS

Materials

Antiepilepticdrugie, Phenytoinand PVP fromyarrowchemicals, Mumbai, India. HPMC, Xanthangum, Eudragit, Microcrystallinecellulose, Lactose, Purifiedwaterfrom HIMEDIAlaborator Y, Mumbai, India.

Methods

Organoleptic characteristics[6]

The color, odor, and taste of the drug were characterized and recorded.

Solubility[7]

It determined by dissolving drug substance in water, phosphate buffer pH 7.4 and methanol. The solubility study was conducted by taking excess amount of the drug in 10 ml phosphate buffer pH 7.4. Then the samples were kept in the water bath shaker and agitated for 48 h at 25 ± 0.5°C. The samples were filtered and diluted suitably with phosphate buffer pH 7.4. Solubility was measured by using UV spectrophotometer.

Determination of melting point[8]

Melting point is determined by capillary method. Powder of phenytoin is filled in a glass capillary tube (sealed at one end). Capillary tube and thermometer is placed vertically in a melting point apparatus.

Preparation of phosphate buffer ph 7.4[9]

- 27.218 g of KH2PO4 taken in 1000ml water to prepare 0.2M Pottassium Dihydrogen Phosphate and 0.2 M Sodiumhydroxide is prepared by dissolving 8g Sodiumhydroxide in 1000ml water.
- 250 ml Pottassium DihydrogenPhosphate and 195.5 ml Sodiumhydroxide taken and makeup till 1000ml with distilled water.
- pH adjusted by HCL using pH meter.

Scanning of absorbance maximum (λmax)[10]

The standard solution of phenytoin (100mg/ml) in phosphate buffer pH 7.4 is scanned in the wavelength region of 200-400 nm and the λmax is found.

Preparation of standard graph[11]

Standard stock solution A: (1000µg/ml)

A stock solution prepared by dissolving 100mg of phenytoin in 50 ml methanol and made up to 100ml with phosphate buffer pH 7.4 in a 100 ml volumetric flask.

Stock solution B: (10 µg/ml)

From the standard stock solution A, 1 ml of the stock solution B was further diluted to 100 ml with phosphate buffer pH 7.4 up to the mark of volumetric flask.

Standard calibration curve

Aliquots of 1, 2, 3, 4, 5,6,7,8,9 and 10 ml of stock solution B is pipette out into 10ml volumetric flasks. The volume is made up to the mark with phosphate buffer pH 7.4 to get 1,2,3,4,5,6,7,8,9 and 10µg/ml respectively. The absorbance is measured in the UV-Visible spectrophotometer and graph of concentration versus absorbance is plotted.

Compatibility studies[12]

The drug-polymer and polymer-polymer interactions were studied by Fourier Transform Infrared spectrometer, (Jasco-FTIR-4100). 2% w/w of the sample, with respect to a potassium bromide disc, was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 psi. The sample were scanned over the range 4000-400cm-1. The characteristic peaks were record

Pellet preparation[13,14]

Pellets were prepared by extrusion spheronisation

↓

Accurately weighed amount of phenytoin with different ratios of polymers was transferred to a clean bowl

↓

The whole mixture is mixed thoroughly. The mixture was mixed properly by adding water to form a dough mass.

↓

The wet mass is extruded through a screen extruder equipped with a standard screen having a 0.8 mm diameter aperture, and rollers rotating at 30 rpm.

↓

Spheronization was performed with a rotating plate of regular cross-hatch geometry, at a speed of 800 rpm, for 5 minutes. Pellets were then dried on a tray in a hot oven at 50–60°C for 6 hours. After drying the pellets were kept in desiccator.

Table 1: Formulation table of phenytoin pellets based on percentage.

Ingredients	Formulation								
Phenytoin	100%	100%	100%	100%	100%	100%	100%	100%	100%
HPMC	8%	12%	16%						
Xanthan gum				10%	20%	30%			
Eudragit							8%	12%	16%
MCC	52%	48%	44%	50%	40%	40%	52%	48%	44%
Lactose	35%	35%	35%	35%	35%	35%	35%	35%	35%
Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs
PVP	5%	5%	5%	5%	5%	5%	5%	5%	5%

Evaluation of micrometric properties

Angle of repose (θ)[15]

The angle of repose of pellet was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blends were allowed to flow through the funnel freely on to the surface. From the cone formed on a graph sheet was taken to measure the area of pile (r), thereby evaluating the flowability of the granules. Height of the pile (h) was also measured.

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

Table 2: Effect of Angle of repose (θ) on Flow property.

Angle of repose(θ)	Types of flow
<20	Excellent
20-30	good
30-34	Passable
>35	Very poor
<20	Excellent

Bulk Density and Tapped density[16]

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of accurately weighed powder (bulk) from each formula, and tap density is measured in a tapping machine containing a graduated cylinder that moves up up and down .Powder material is introduced into the cylinder. The tapping begins. The mark of the graduated cylinder was noted. LBD and TBD were calculated using following formula,

LBD = Weight of the powder/volume of the packing

TBL = Weight of the powder/tapped volume of packing.

Hausner's ratio[17,18]

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula,

Hausner's Ratio = Tapped Density / Bulk Density

Carr's compressibility index[19]

The compressibility index of the granules was determined by Carr's compressibility index. (%) Carr's Index can be calculated by using the following formula.

Carr's Index (%) = [(Tapped Density-Bulk Density) x100]/Tapped Density

Table 3: Effect of carr's index (%) on flow property.

Carr's Index (%)	Flow character	Hausner's Ratio
< 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Evaluation of phenytoin pellets

Surface morphology[20]

The surface and shape characteristics of pellets were determined by scanning electron microscopy (S-4800 Hitachi Japan). Photographs were taken and recorded at suitable magnification.

Average particle size[21]

The particle size of drug loaded formulations were measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. The Weswox model having resolution of 10x was used for this purpose. The instrument was calibrated at 1 unit of eyepiece micrometer was equal to 30.07 mm.

Drug content[21,22]

100 mg equivalent granules were accurately transferred into a 100 ml volumetric flask and. the solution was made up to volume with phosphate buffer pH 7.4. The resulted solution was filtered and suitably diluted and the drug content was estimated spectrophotometrically by measuring the absorbance at λ max.

Amount of drug = concentration from the standard graph × DF
1000
Where DF=dilution factor

In-vitro dissolution studies[23]

The in vitro release of the drug from pellets of all formulation batches were performed using USP apparatus Type I (Basket). In this, 100mg drug equivalent pellets were packed in hard gelatin capsules and were subjected to in-vitro dissolution studies. The dissolution medium consisted of 900 ml of phosphate buffer of pH 7.4. Dissolution was performed at 37±0.5°C, with stirring speed of 75 rpm. 5 ml of aliquots were collected at regular time intervals 0.5,1,2,3,4,5,6,12hours and the same amount of fresh dissolution medium was replaced into dissolution vessel to maintain the sink condition throughout the experiment. The collected aliquots were filtered using Whatman filter No. 1, and further diluted suitably to analyze using UV method at λmax.

Comparison of dissolution profile with marketed product[24]

Comparison of dissolution data eptoin tablet I.P.100mg Vs best formulation phosphate buffer pH 7.4.

Kinetic modelling[25]

The sustained release pellets was studied for release kinetics.by using mathematical models such as zero-order, first-order Coefficient of correlation values were calculated for the linear curves obtained by regression analysis of the plots

Stability studies[26]

The optimised formulation is packed in a sachet of aluminium foil lined with polyethylene of thickness and subjected to accelerated stability testing as per ICH guidelines .The samples are placed in Thermolab humidity chambers at condition of 40±2 °C at 75±5% RH at 0,3,6 months

RESULT AND DISCUSSION

The present study was carried out to formulate phenytoin SR pellets. The study involves pre-formulation studies of drug and excipients, formulation and processing development.

Preformulation studies

Table 4: Preformulation studies of phenytoin.

Properties	Results		Reported	
Description	Crystalline powder		Crystalline powder	
Taste	Tasteless		Tasteless	
Odor	Odorless		Odorless	
Color	White		White	
Melting point	296°C		296°C	
Solubility	Water	0.85 mg/ml	Water	0.86mg/ml
	Phosphate buffer	0.90mg/ml	Phosphate buffer	0.93mg/ml
	Ethanol	1.36mg/ml	Ethanol	1.38mg/ml

Organoleptic characteristics

Organoleptic characteristics like general description, taste, odor and colour was determined. It was found that Phenytoin is crystalline powder, almost tasteless, Odorless and almost white colour powder respectively and was found to be within the reported literature limits. The results obtained were shown in table 4.

Melting point

The study was carried out and found that the drug melted at 296°C which is same as the reported value of 296˚C and indicating that the drug is pure. The results obtained were shown in table 4.

Solubility

Phenytoin was found to be soluble in water 0.85 mg/ml, phosphate buffer pH 7.4 0.90gm/ml and ethanol 1.36mg/ml. Solubility in all the solvents was within the reported literature limits. The results obtained were shown in table 4.

Scanning of λmax

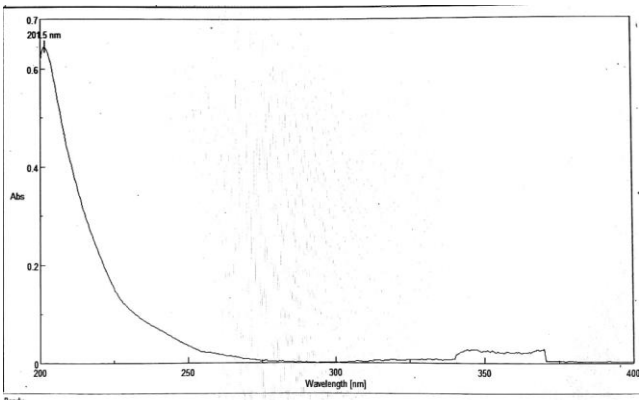

Fig. 1: UV spectra of Phenytoin.

The absorption spectrum of pure phenytoin was scanned between 200-400nm. The λmax of pure phenytoin found to be 201.5nm by using phosphate buffer pH 7.4. The curve obtained were shown in fig. 1.

Standard calibration curve

Table 5: Standard graph of phenytoin.

Sl. No.	Concentration ((µg/ml)	Absorbance
1	1	0.1012±0.01
2	2	0.1915±0.04
3	3	0.2847±0.02
4	4	0.3798±0.01
5	5	0.4855±0.02
6	6	0.5774±0.05
7	7	0.7853±0.03

Data expressed as a mean ±SD, n=3

Standard graph of Phenytoin

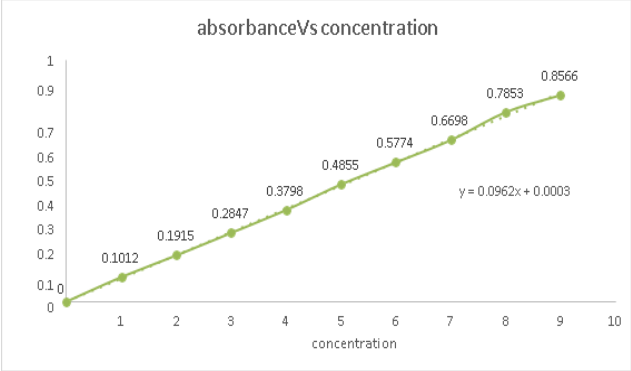

Fig. 2: Standard curve of Phenytoin in 7.4 pH Phosphate buffer.

The absorbance reading of phenytoin standard solution containing 01- 09µg/ml of drug in phosphate buffer pH 7.4 at the maximum wavelength of 201.5nm shown in table 5.

Fig.2 shows the standard calibration curve of Phenytoin in phosphate buffer. Which was found to be linear with values 0.0962 and 0.9994 as slope and regression value respectively.

Drug-Excipients compatibility studies

The possible interaction between the drug and the carrier was studied by Fourier transform infrared spectroscopy.

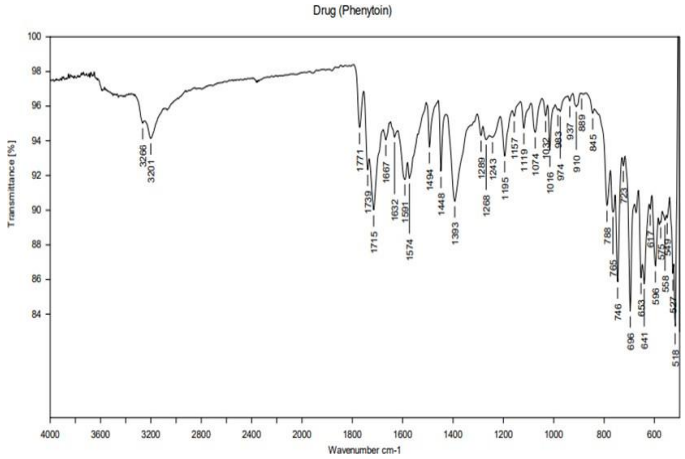

Fig. 3: FTIR spectra of pure drug phenytoin.

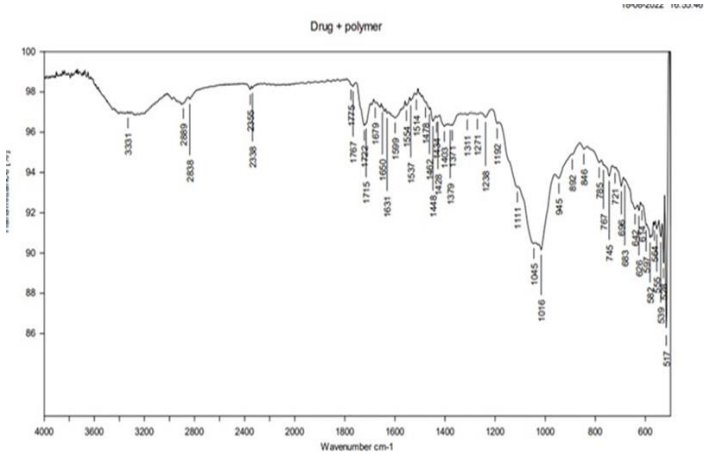

Fig. 4: FTIR spectra of Drug + Polymer.

Table 6: Comparison of FTIR spectra of phenytoin pellets.

SL No	Functional groups	Reported frequency	Observed frequency
		Pure drug (cm-1)	Drug +polimer (cm-1)
1	N-H	3000-2800	3201
2	C-H	1600-1300	1591
3	C=O	1685-1666	1667

The IR spectra of Phenytoin was compared with the standard spectrum of drug + polymer mix and the characteristic peaks associated with specific functional and bonds of the groups molecule and their presence or absence were noted in table 6 and the overlay of pure drug and drug + polymer mix was shown in figure 3& 4.The characteristic absorption peaks of phenytoin were obtained at 3201 cm-1, 1591cm-1, 1667cm-1. The range of peak values were found to be the same indicating that there were no interaction of phenytoin with polymer conforming the stability of drug in the formulation.

Scanning electron microscopy

The surface morphology was studied by Scanning electron microscopy (SEM).

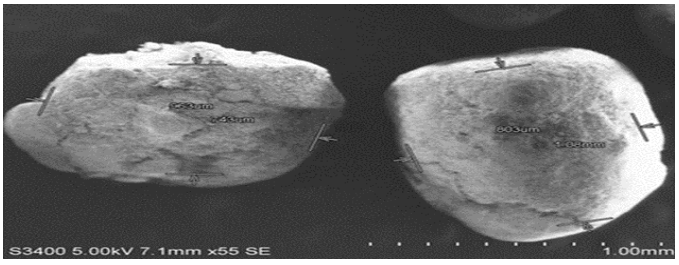

Fig. 5: SEM images of formulation (F8).

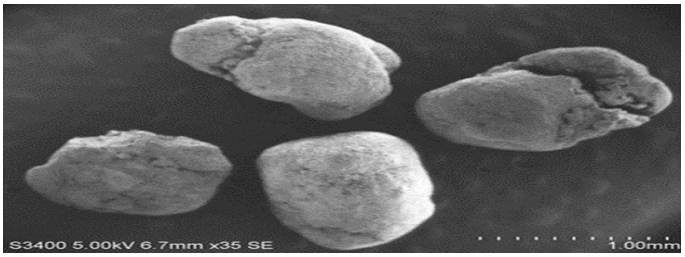

Fig. 6: SEM images of pellets (F8).

The shape and surface morphology of the prepared pellets were observed by scanning electron microscopy The SEM photographs of pellets of formulation F8 are shown in fig. 5 and fig.6. SEM photomicrographs of F8 formulation of pellets were spherical in nature and had a smooth surface. Pellets reveal the uniform distribution of the drug in the pellets.

Evaluation parameter

Micrometric properties

All formulations are subjected to the Micrometric properties like Angle of repose, Bulk density, Tapped density, Hausner's ratio and Carr's index and results are discussed below.

Table 7: Micrometric properties of formulation F1-F9.

Formulation	Angle of repose (θ)	Bulk density (gm/c c)	Tapped density (gm/cc)	Hausner's ratio
F1	22023'±0.12	0.420±0.005	0.470±0.007	1.11±0.005
F2	22017'±0.14	0.437±0.006	0.476±0.004	1.08±0.011
F3	21021'±0.20	0.444±0.006	0.482±0.008	1.08±0.041
F4	21093'±0.12	0.458±0.004	0.485±0.007	1.05±0.097
F5	20091'±0.13	0.469±0.007	4830. ±0.007	1.02±0.025
F6	19028'±0.24	0.486±0.005	0.493±0.008	1.01±0.040
F7	19°17±0.23	0.492±0.002	0.495±0.006	1.02±0.039
F8	18°15±0.21	0.502±0.002	0.498±0.003	1.04±0.036
F9	18°33±0.15	0.504±0.003	0.501±0.005	1.03±0.092

Data expressed as a mean ±SD, n=3

Angle of repose (θ):

The data obtained for angle of repose for all the formulations were tabulated in the table7 Formulation F9 showed least angle of repose value18°33±0.15and F1 showed highest angle of repose value 22023'±0.12. Angle of repose value of all formulations ranges from18°33±0.15 to 22023'±0.12. The values indicated that all the formulations showed acceptable flow properties with low standard deviation value. In the preliminary formulations, all formulations showed good flow properties.

Bulk Density and Tapped density

The bulk density and tapped density values were shown in the table 7 Formulation F1 showed lowest bulk density value 0.420±0.005 gm/cc and formulation F9 showed highest bulk density value0.504±0.003 gm/cc respectively. Bulk density of all seven formulations ranges from 0.420±0.005 to 0.504±0.003gm/cc. Formulations F1 showed lowest tapped density value 0.470±0.007 gm/cc and formulation F9 showed highest tapped density of 0.501±0.005 respectively. Tapped density of all nine formulations ranges from 0.470±0.007to0.501±0.005 gm/cc.

Carr's consolidation index

Results of Carr's consolidation index of all the formulations were shown in the table 7 Formulation F9 showed least Carr's index value 0.92±0.082and F1 showed highest Carr's index value 10.63±0.007 %. The result of the Carr's consolidation index of all the formulations ranges from 0.92±0.082to 10.63±0.007 %. Results clearly showed that the flow ability of all the formulations was good and also the granules had good compressibility.

Evaluation of formulated pellets

All nine formulations were prepared by using Micro crystalline cellulose ,HPMC, Eudragitxanthan gum and PVP by extrusion spheronization method. The prepared pellets were evaluated for Particle size analysis, uniformity of drug content and in-vitro dissolution studies.

Average particle Size and Size distribution

Table 8: Average particle size of pellets.

Formula	Particle size((µm)
F1	1348±0.71
F2	1368±0.55
F3	1346±0.84
F4	1379±0.67
F5	1380±0.51
F6	1382±0.48
F7	1345±0.61
F8	1340±0.58
F9	1348±0.79

Data expressed as a mean ±SD, n=3

Particle size analysis of phenytoin pellets was determined using optical microscope. The pellets of all the formulations were in the size range of 1340±0.58 – 1382±0.48 µm are shown in Table 8. The results showed that as the Micro crystalline cellulose content decreases, the particle size increases.

Drug content

Table 9: Drug content of Phenytoin pellets.

Formulation	Drug content(%)
F1	92.88±0.17
F2	92.97±0.72
F3	94.28±0.12
F4	96.35±0.83
F5	96.98±0.23
F6	96.42±0.36
F7	97.14±0.41
F8	98.12±0.329
F9	97.32±0.46

Data expressed as a mean ±SD, n=3

Table 9 showed the percentage drug content in each formulation. Formulation F1 showed lowest drug content value 92.88±0.17%, F8 showed highest drug content 98.12±0.32%. Percentage drug content of phenytoin in all the formulated pellets were found within the limits. The results indicate uniformity of mixing.

In-vitro dissolution study

Table 10: In-vitro drug release data of formulations (F1-F9).

Time	Percentage Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	6.92±0.12	11.21±0.07	5.63±0.11	7.34±0.12	9.31±0.14	11.14±0.12	13.21±0.51	15.13±0.53	13.8 ± 0.34
1	16.92±0.27	25.33±0.23	13.24±0.23	12.27±0.27	16.91±0.21	20.88±0.23	19.01±0.61	21.70 ± 0.56	18.56 ±0.45
2	29.14±0.28	35.52±0.14	28.24±0.28	26.15±0.28	31.92±0.02	33.61±0.28	32 .56 ±0.82	35.01 ±0.45	27.89 ± 0.56
3	37.52±0.23	48.81±0.23	39.45±0.27	35.45±0.25	46.61±0.25	45.10±0.23	43.34 ± 0.45	50.56 ± 0.56	44.54 ± 0.96
4	46.91±0.18	57.82±0.16	50.61±0.17	46.82±0.15	59.94±0.15	53.56±0.16	50.83 ± 0.54	61.32 ± 0.23	52.32 ± 0.42
5	58.20±0.23	73.31±0.48	63.77±0.43	60.01±0.45	76.89±0.45	65.51±0.23	1.78 ± 0.42	78.3 ± 0.43	64.32 ± 0.25
6	71.22±0.10	78.32±0.23	73.19±0.06	76.88±0.24	82.11±0.24	75.09±0.17	80.01 ± 0.31	83.13 ± 0.73	73.52 ± 0.65
12	82.19±0.25	87.31±0.24	86.11±0.25	88.91±0.24	93.55±0.18	83.01±0.23	90.32 ± 0.45	96.75 ± 0.23	84.26 ± 0.52

Data expressed as a mean ±SD, n=3

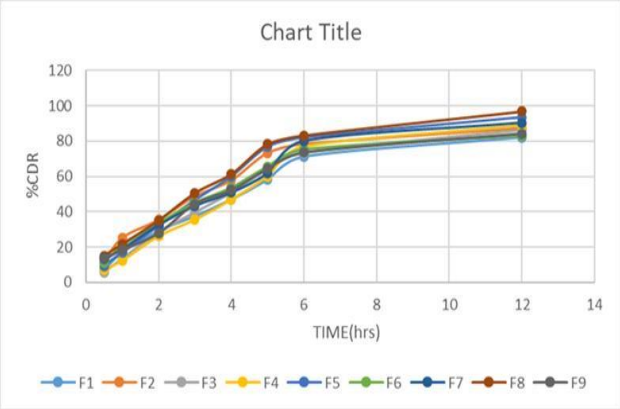

Fig. 7: In-vitro drug dissolution profile of formulation (F1-F9).

In vitro drug release study was performed using USP TYPE I dissolution test apparatus at 75 rpm using phosphate buffer pH 7.4 maintained at 37±0.5ºC as the dissolution medium. In-vitro drug dissolution profile obtained for all formulations (F1 –F9) was shown in table 10 and fig.7.

The cumulative percent drug release after 12 hours were found to be 82.1990.32±0.45%, 96.75±0.23%and 84.26±0.52% formulation F1,F2,F3,F4,F5,F6,F7,F8, and F9 respectively. Each formulation have equal quantity of lactose which will produce more pores with dissolution medium and erode the polymers which cause controlled release .Results revealed formulation F8 shows higher drug release i.e 96.75 ± 0.23% at 12 hours.±0.25%, 87.31±0.24%, 86.11±0.25%, 88.91±0.24%, 93.55±0.18%, 83.01±0.23%.

The drug dissolution is inversely proportional to the concentration of Micro crystalline cellulose. Here F8 formulation exhibited the high percentage drug content and sustained drug release. Therefore pellet formulation F8 in which eudragit and low concentration of MCC is used was selected as the best formulation for stability studies.

Comparison of dissolution data with marketed product

Table 11: Dissolution data of market Sample Vs Best Formulation (F8)in phosphate buffer pH7.4.

Time in hours	Percentage Cumulative Drug Release	
	Eptoin tablet(100mg)	Best formulation F8(100mg)
0.5	8.21±0.12	9.42±0.07
1	12.38±0.21	17.92±0.23
2	29.91±0.27	32.13±0.25
3	43.55±0.25	47.25±0.28
4	61.48±0.45	60.34±0.31
5	76.12±0.24	76.84±0.16

Data expressed as a mean ±SD, n=3

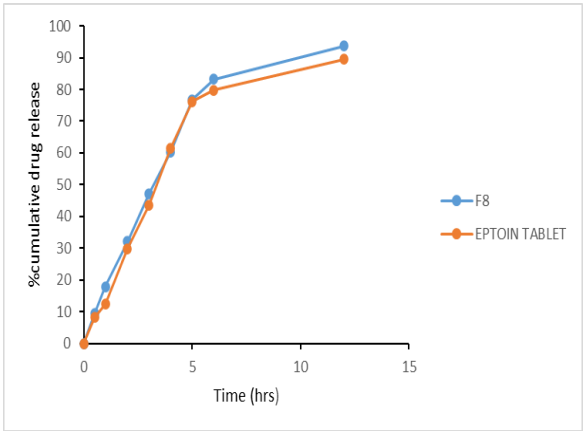

Fig. 8: Comparison of in-vitro release profile of EPTOIN tablet and formulation (F8).

In which formulation (F8) evaluation indicated that the dissolution profile of optimized formulation was comparable to the dissolution profile of marketed sample (eptoin tablet). Formulation F8 shows better release

compared to market product.showed in table 11 and fig.8.

Fig. 9: Best formulation F8.

Fig. 10: Eptointablets.

Releasekinetics

Table 12: Zero order release kinetics.

Time(hrs)	%CDR
0.5	1.117
1	1.33
2	1.544
3	1.703
4	1.78
5	1.893
6	1.77
12	1.98

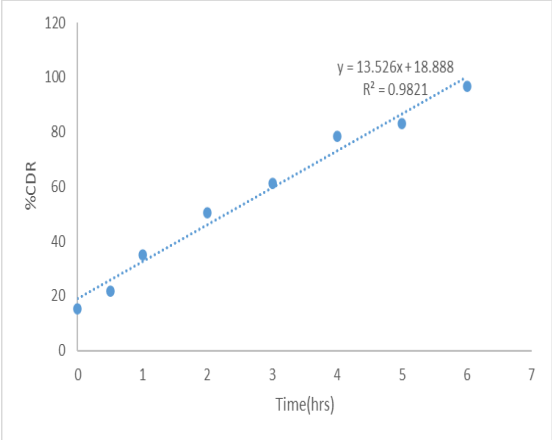

Fig. 11: Zero order release kinetics.

Table 13: First order release kinetics.

Time(hrs)	log%CDR
0.5	15.13
1	21.7
2	35.01
3	50.56
4	61.32
5	78.3
6	83.13
12	96.75

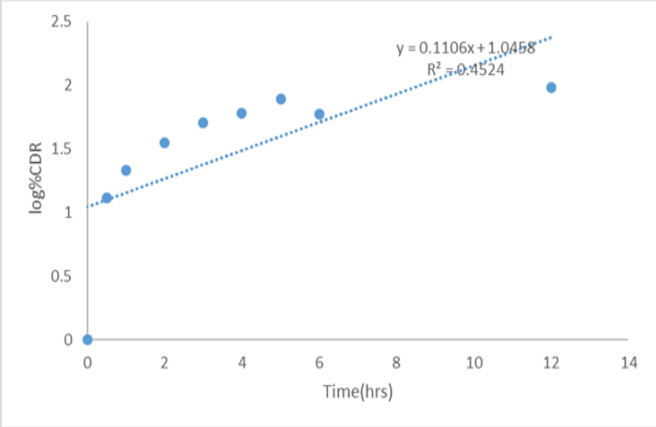

Fig. 12: First order release kinetics.

Table 14: Release kinetics of pellets.

Formulation	First order	Zero order
F1	0.8599	0.9697
F2	0.7989	0.9651
F3	0.7893	0.9570
F4	0.7734	0.9524
F5	0.7653	0.9831
F6	0.7523	0.9426
F7	0.7421	0.9316
F8	0.723	0.911
F9	0.701	0.902

Release kinetics

The In vitro drug release data was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic models in order to determine the mechanism of drug release. When the regression coefficient values of zero order and first order plots were compared, it was observed that 'R2' values of first order plots were in range of 0.701 to 0.8599 and zero order plots were in range of 0.902 to 0.9697 indicating drug release from most of the formulations was found to follows zero order kinetics. Table 14 shows R2 values of all formulations and fig 11&12 were shows the zero order and first order plots.

Stability studies

Table 15: Evaluation of F8 during stability studies.

Evaluation parameter	Time (days) 40±2 °C at75±5% RH.			
	0	30	60	90
% Drug content	98.12±0.329	97.32±0.241	97.22±0.436	96.53±0.452
% CDR	96.75 ± 0.231	95.90±0.432	95.42±0.361	95.09±0.461

Data expressed as a mean ±SD, n=30

The stability studies were carried out for the best formulation F8 at 40±2 °C with 75±5% RH for 90 days. The results indicated that the pellets did not show any physical changes during the study period and the percentage drug content was found of the formulation F8 96.53±0.452 at the end of three months(90days). The %

CDR of formulation F8 found to be 95.09±0.461 at the end of three months. There were no significant differences found in the percentage cumulative drug release after stability study. It is shown in table 15. This indicates that pellets are fairly stable at storage condition.

SUMMARY AND CONCLUSSION

- Preformulation study of phenytoin sodium was carried out.The results of preformulation study was found to be white odourless crystalline ,melting point of 296 and solubility of 0.86mg/ml,0.93mg/ml,1.38mg/ml in water, phosphate buffer pH7.4 and methanol respectively.
- Drug and polymers were subjected for the compatibility study using FTIR spectroscopy. Phenytoin was identified by FTIR spectroscopy (Fig3,4) under Pre formulation study, FTIR between the drug and excipients showed no unaccountable extra peaks, which confirms the absence of chemical interaction between the drug and excipients/polymer. Which suggested that there is no interaction between the drug and polymer.
- Maximum wavelength (λ max) was determined by using UV spectrophotometer by using phosphate buffer pH 7.4 as medium. Maximum absorbance was found at 201.5nm.
- Standard calibration curve was constructed in the concentration range of 0-09 µg/ml using phosphate buffer pH 7.4 as a medium. Which was found to be linear with values
  0.096 and 0.9994 as slope and regression value respectively.
- Nine formulations (F1-F9) of Phenytoin were prepared by using three different polymers
  (HPMC, Eudragit and Xanthan gum), Microcrystalline cellulose, lactose and PVP by using extrusion spheronization technology. The formulated pellets were subjected to various evaluation parameters like particle size analysis, percentage drug content and in-vitro drug release studies. The results of the parameters are tabulated and depicted graphically in the result and discussion section. Based on those results formula F8 in which eudragit used as polymer selected as the best formulation.
- The shape and surface area of pellets was determined by scanning electron microscopy.
  The SEM photographs of pellets of formulation F8 are shown in Fig.5 and Fig.6 SEM photomicrographs of F8 formulation of pellets were spherical in nature and had a smooth surface. Pellets reveal the uniform distribution of the drug in the pellets.
- All nine formulations are subjected to pre formulation tests like bulk density, tapped density, angle of repose and Carr's index. Bulk density of all nine formulations ranges from 0.420±0.005 to 0.486±0.005 gm/cc. Tapped density of all nine formulations ranges from 0.470±0.007 to 0.493±0.008 gm/cc. It is within the acceptable limit. Angle of repose value of all formulations ranges from 19ºC28'±0.24 to 22ºC23'±0.12. The result of the Carr's consolidation index of all the formulations ranges from 1.41±0.066 to 10.63±0.007%. Results clearly showed that the flowability of all the formulations was good.
- The particle size determination of prepared pellet formulations was done by optical microscopy. The pellets of all the formulations were in the size range of 1346 - 1382µm. The results of all the formulations confirmed that as the concentration of the MCC decreases will influence the diameter of the pellets.
- Percentage drug content of phenytoin in all the formulated pellets were found within the range 92.88 to 98.12% indicate uniformity of mixing. Formulation F8 has higher drug content (98.12%) .
- In-vitro drug release study was performed using USP TYPE I dissolution test apparatus at 75 rpm using 7.4 pH phosphate buffer maintained at 37±0.5ºC as the dissolution
  medium for a period of 12 hours were shown in table 11 and fig.8. Here MCC and HPMC used as extrusion aid a used to modify the release of the drug. Therefore, the aim of studying in-vitro release from matrix pellets is to investigate the effect of different concentration of polymer on the drug release patterns. Percentage cumulative drug release at 12 hrs of all formulations ranges from 82.19 % to 96.75%. The best formulation was found to be F8 which showed a cumulative drug release of 96.75% at the end of the study.
- Comparison of dissolution Profile of formulation F8 with marketed product was done.
  The result of formulation (F8) evaluation indicated that the dissolution profile of optimized formulation was comparable to the dissolution profile of marketed sample (Eptoin tablet). It shows better release compared to market product.
- The In-vitro drug release data of the formulations (F1-F9) were subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic in order to determine the mechanism of drug release. It was observed that 'R2' values of first order plots were in range of 0.7523 to 0.8599 and zero order plots were in range of 0.9426 to 0.9831, indicating drug release from most of the formulations was found to follows zero order kinetics.
- Stability studies were carried out for the best formulation F8. The results of drug content and in-vitro drug release studies showed no significant changes indicating the formulation is stable.

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