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FORMULATION AND EVALUATION OF PHENYTOIN SODIUM SUSTAINED RELEASE MATRIX TABLET

Nimmathota Madhavi*[2], Beeravelli Sudhakar[1], P.V.Ravikanth[2], Kodisana Mohan[2] and K.V. Ramana Murthy[1]

[1]*University College of Pharmaceutical Sciences, Andhra University, Vishakhapatnam -530003AndhraPradesh, India.*

[2]*Brown's College of Pharmacy, Ammapalem, Khammam-507305, Andhra Pradesh, India*

*Corresponding Author E-mail: nimmathota.madhavi@gmail.com

ABSTRACT

Epilepsy is a very common disorder, characterized by seizures, which take various forms and result from episodic neuronal discharges, the form of the seizure depending on the part of the brain affected. There is no recognition cause, although it may develop after brain damage, such as trauma, infection or trauma, and other kinds of neurological diseases. The aim of this study is to develop sustained release matrix tablet of phenytoin sodium using eudragit-RL100,eudragit-RS100, HPMC-E15, ethyl cellulose (N-14),Chitosan and HPMC as release controlling factor and to evaluate drug release parameters as per various release kinetic models .The formulated tablets were also characterized by physical and chemical parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model were based on linearity (coefficient of correlation). Based on "n" value (0.168) the drug release was follows Fickian diffusion. Also the drug release mechanism was best explained by Higuchi order (correlation value is o.9063) by using this polymer.

Keywords: phenytoin sodium, sustained release, Eudragit RL100, Eudragit-RS 100, hydrophilic matrix, wet granulation technique.

INTRODUCTION

Phenytoin sodium is an anti epileptic drug. Phenytoin sodium is related to the barbiturates in chemical structure, but has a five-membered ring. The therapeutic concentration is required for therapy with recommended doses of 300mg/day. The therapeutic dose is needed to be maintained for 24 hrs. The conventional doses release the entire drug in just few minutes and the therapeutic concentrations are maintained for a short period of time generating a need for administration of another dose. Therefore a sustained release formulation of phenytoin sodium which would release the drug over a time period of 24 hrs is beneficial.

The concept of sustained release drug delivery has been explored for the delivery of drugs for prolonged period of time for the past few years. Till now there is no sustained release tablet of phenytoin sodium in the market .But phenytoin sodium sustained release capsule (Kapseals) is available. This type of drug delivery has proved to provide a solution to several problems encountered in the repeated administration of such drugs.

Utilizing the concept of incorporating drug in to the polymer matrices and extend the drug release for prolonged period of time, an attempt was made to design and evaluate sustained release matrix tablets of phenytoin sodium. The aim of present study is to prepare hydrophilic matrix sustained release tablets containing phenytoin sodium as a model drug and various polymers as hydrophilic matrix to retard drug release. Another objective of this work is to evaluate drug release data using various kinetic models and to determine the mechanism of drug release.

MATERIALS AND METHODS

Materials

Phenytoin sodium was obtained as a gift sample from (Nakoda Chemicals, Hyderabad) Avicel PH101 (Loba Chemie Pvt. Ltd, Mumbai). HPMC E-15 (Signet Chemical Corporation, Mumbai). Eudragit RS 100 from (Degussa Germany, Mumbai), Eudragit RL 100 (Degussa (Germany), Mumbai) Eudragit RSPO (Degussa Germany, Mumbai), Talc (Qualikems Fine Chemicals Pvt. Ltd, New Delhi).

Preparation of sustained release tablet

Accurately weigh phenytoin sodium and polymers and pass through sieve #40 and blend for 10 mins. Prepare granulating solution by dispersing starch in specified quantity of purified water and stir under a stirrer till a clear solution is formed. Add this binder solution to the previously prepared dry blend of drug and polymer and granulate. . Pass the dried granules through sieve #20.

Add lactose, talc and magnesium stearate which was previously passed through sieve#40 to the dried granules blend. Blend for 5 mins. The granules were sieved by #22 and #40.These granules were compressed into tablets by using 16-station rotary tableting machine, using 7mm flat, round punches. **The composition of the various tablets prepared is given in table no.1**

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Phenytoin sodium	100	100	100	100	100	100	100	100
Avicel PH101	-	-	-	55.15	54.3	54.2	-	-
Ethyl cellulose N-14 (14 cps)	-	-	-	4.25	8.5	7.5	-	-
HPMC	-	-	-	-	-	5.5		-
HPMC-E15	-	-	-		5.3	-	-	-
HPMC- K4M	-	-	-	-	-	-	40	
Chitosan	-	-	-	-	-	-	-	40
Eudragit RSPO	30	-	-	-	-	-	-	-
Eudragit RS100	-		30	8.5	-	-	-	-
Eudragit RL100	-	30	-	-	-	-	-	
Lactose	1.5	2	6.5		-	-	1.6	1.6
Mg.stearate	1.5	1.8	2	1.7	1.7	1.5	1.5	1.5
Talc	0.6	5.5	7		-	-	0.6	0.6
Colloidal silicone dioxide	-			0.4	0.6	0.8	-	-
Starch	5%	5%	5%	-	-	-	-	-
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
SLS	7.5	7.5	6.5	3.25	6.5	7.5	3.25	6.5

Dose Calculations & Construction of Theoretical Release Profile:

The total dose of phenytoin sodium for twice-daily SR formulation was calculated by Michaelis Menton equation using available pharmacokinetic data.

1) Calculation of loading dose (LD):

$LD=V_dxCp/SxF$

LD=49x18/1x0.95

LD= 928.42 mg of Phenytoin sodium.

Oral loading dosing should be given in 3 to 4 divided doses.

2) Calculation of maintenance dose (MD):

MD=Vmax x Css/SxF (Km+Css)

MD=7x15/1x0.95 (5.4+15)
=5.41mg/Kg.

For steady state plasma concentration, total dose per day required is

D=Vm x Css x τ/ (Km+Css) SxF

D=700x15x1/ (6.8+15)1x0.95

D=10500/20.713

D=507.00mg/day.

The dose is given in 2 or 3 divided doses, thus the administered dose is 500mg twice a day.

- F1, F2 and F3 formulations contain processed starch in percentage of 5%.
- F5 and F6 formulations contain colloidal silicon dioxide in the percentage of 0.5-1%.
- F5 and F6 formulations contain Avicel PH101 in the percentage of 53-55%.

EVALUATION OF TABLET

The finished products were evaluated as per the procedures given in USP I which recommends the following tests for sustained release tablets.

- **Weight variation test**
- **Content uniformity**
- **Friability**
- **Hardness**
- ***In vitro* dissolution studies**

Weight variation test:

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Mettler Toledo, Basel, Switzerland). (Then average weight is calculated,) each tablet was weighed individually and weight was noted. The weights of individual tablets were compared with the average weight already calculated. Mean and SD were calculated.

Content uniformity:

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to100 mg was extracted with 100ml pH 6.8 phosphate buffer, and sonicated for 15 minutes. The solution was filtered through a filter paper (0.22µm pore size), properly diluted with pH 6.8 phosphate buffer, and then the drug content was measured as previously mentioned.

Friability:

For each formulation, 6 tablets were weighed. The tablets were placed in a friabilator (Roche friabilator) and subjected to 100 rotations in 4 minutes at 25rpm. The tablets were then deducted and reweighed. The friability was calculated as the percentage weight loss.

Hardness Test:

For each formulation, the hardness of 6 tablets was determined using a hardness tester (Monsanto). Hardness values were reported in kilograms (kg). Mean and SD were calculated.

***In Vitro* Release Studies:**

In vitro release studies of phenytoin sodium sustained release tablets were monitored. The release experiments were performed in a 900-mL dissolution medium of hydrochloric acid pH 1.2 for the first 2 hours and then replaced with the same volume of a phosphate buffer solution pH 6.8 kept at 37ºC ± 0.5ºC and stirred at 100 rpm, using USP-I basket dissolution apparatus I(perfect sink conditions). 5-mL sample was withdrawn through a 0.45-µm filter and replaced with another 5 ml of a suitable fresh dissolution medium at predetermined intervals up to 24 hours. The amount of the drug was determined by UV-spectroscopy at 258nm.

Kinetic data analysis

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics *(4,5)*.

The following plots were made:

- Cumulative % drug release vs. time (Zero-order kinetic model);
- Log cumulative of % drug remaining vs. time (First-order kinetic model);
- Cumulative % drug release vs. square root of time (Higuchi model) ;
- Log cumulative % drug release vs. Log time (Korsmeyer model).

Mechanism of drug release:

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$$M_t / M_\infty = K\, t^n$$

Where M_t / M_∞ is fraction of drug released at time t, K is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms as given in table no.7 for cylindrical shaped matrices.

Result and discussion

Preformulations studies: The pure phenytoin sodium and granules of different formulations were evaluated for angle of repose, bulk density, tap density, Carr's index and sieve analysis. The phenytoin sodium and the formulated granules were characterized with respect to angle of repose. Angle of repose of phenytoin sodium was found to be 33.2°thus indicating that the flow properties were poor (passable). For the granules of all the formulated batches, the angle of repose was found to be in the range of 25° to38°, thus indicating that the flow properties were fair - poor (passable).Therefore it was decided to include 1.0% to 1.2% of talc as a glidant. The phenytoin sodium and the formulated granules were characterized with respect to bulk and tapped density. The Carr's index of phenytoin sodium found to be 11.6.thus indicating that the flow properties were excellent. For the granules of all the formulated batches, the Carr's index was found to be in the range of 5-55, thus indicating that the flow properties were very poor. Therefore it was decided to include 1.0% to 1.2% of Talc as a Glidant. Table no.2

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Concentration	absorbance
0	0
0.02	0.177
0.04	0.340
0.06	0.499
0.08	0.655
0.10	0.820

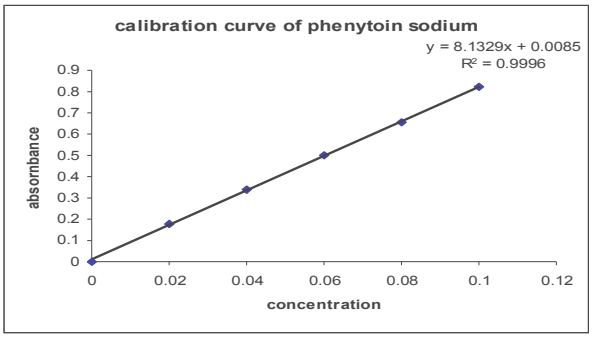

Table no.2: calibration curve of phenytoin sodium

Table no.3: Preformulation studies

Batch no.	Angle of Repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Carr's Index (%)
API	33.2	0.76	0.86	11.6
F1	30.5	0.73	0.85	14.1
F2	32.6	0.513	0.647	20.7
F3	35.7	0.752	0.796	5.52
F4	33.8	0.555	0.673	17.5
F5	38.7	0.597	0.740	19.3
F6	28.6	0.620	0.657	5.63
F7	36.4	0.465	0.712	34.6
F8	25.3	0.333	0.691	55.8

Particle Size Analysis of Phenytoin Sodium

The phenytoin sodium percentage retained was found to be approximately 150µ-200µ. Particles in this size range pose no serious problems like charge development. Therefore it was decided to use the phenytoin sodium as it can be used without any further processing (like milling to decrease the particle size or adsorption or removal of fine to decrease cohesive forces. **Table no.4: Particle Size Analysis of Phenytoin Sodium.**

Sieve number	Microns (µ)	Wt. of sieve (A)	Final weight (B)	% retained (B-A)	Cumulative % weight retained
20	200	368.2	393.4	25.2	25.2
30	212	362.3	372.6	20.3	45.5
40	150	361.3	382.6	21.4	66.9
60	125	355.2	375.6	20.4	87.3
80	90	350.6	357.8	6.6	93.9
100	75	350.6	355.6	5.6	99.5

Physical properties of the Matrix Tablets

All the formulations of tablets were subjected to various evaluation tests, such as friability, hardness, average weight, drug content, and *in vitro* dissolution. In a weight variation test, the average percentage deviation of all tablet formulations was found to be within the limit of IP, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity was found among the different batches of the tablets, and the percentage of drug content was more than 101.22±0.88 (F4).The formulation F4 showed a comparatively high hardness value of 9.53±0.75 kg/sqcm. Tablet hardness is not an absolute indicator of strength. Another measure of tablet strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable.

Table no.5: Physical properties of the Matrix Tablets

Batch	Friability (%)	Hardness (Kg/Sqcm)	Average uniformity of weight (mg)	Drug Content (%)
F1	0.21	8.56±0.31	766.8±2.48	98.25±1.37
F2	0.17	5.34±0.71	765±2.54	95.28±0.80
F3	0.19	7.53±0.25	768.6±2.41	99.12±2.47
F4	0.13	9.53±0.75	770.8±1.64	101.22±0.88
F5	0.22	7.63±0.84	767.6±2.14	100.24±1.25
F6	0.16	7.13±0.25	769.0±2.43	95.35±1.14
F7	0.18	8.24±0.61	770.5±1.80	96.34±2.18

Dissolution profiles

The *in vitro* drug release characteristics were studied (n=3) in 0.01N hydrochloric acid and Phosphate buffer pH 6.8 mediums for a period of 24 hrs using USP-I basket dissolution apparatus. The initial four formulations (F1, F2, F3 and F4) of phenytoin sodium SR tablets were formulated with different types of Eudragit polymers (Eudragit RSPO, Eudragit RS100, and Eudragit RL100). Eudragit RL100 and Eudragit RS100 are insoluble in aqueous media but they are permeable and both have pH-independent release profiles. The permeability of Eudragit RS100 and RL100 in aqueous media is due to the presence of quaternary ammonium groups in their structure; Eudragit RL100 has a greater proportion of these groups and as such is more permeable than Eudragit RS100. The combinations of these polymers in different proportions provide varied sustained release profiles. Therefore the subsequent batches were planned with different concentrations of these polymers. However satisfactory results were not obtained for these polymers and it was decided to proceed with other polymers which would effectively sustained the release of drug. The effect of these polymers on the release of phenytoin sodium is shown in the following table no.6

The F5 batch was formulated with HPMC-E15 and ethyl cellulose (N-14),F6 batch was formulated with HPMC and ethyl cellulose(N-14) . F6 formulation is showing better release from the phenytoin sodium tablet. So F6 formulation is decided as optimized formulation .The effect of these polymers on the release of Phenytoin sodium from the tablets.

The F7 batch was formulated with HPMC-K4M .The F8 batch was formulated with Chitosan. Chitosan is one of the most suitable matrix type of sustained release polymer. The effect of these polymers on the release of phenytoin sodium from the tablets is shown in the following figure no.1

Table no.6: Dissolution profiles of formulations

Batch	Time	30mini	1hr	2hr	4hr	8hr	12hrs	24hrs
F1	0	22.3±2.6	26.1±2.9	35.3±1.8	47.5±2.2	48.2±1.9	48.4±2.4	48.3±2.4
F2	0	27.9±2.1	36.9±1.4	45.9±1.9	48.1±2.2	48.2±1.7	49.7±1.7	49.3±1.7
F3	0	32.7±1.6	35.2±2.1	39.7±2.3	43.9±1.9	45.5±2.1	47.2±2.2	47.3±2.2
F4	0	38.2±2.1	42.3±2.3	45.3±1.6	46.4±2.4	49.7±1.9	50.3±1.8	52.3±1.8
F5	0	26.3±1.8	28.3±2.1	35.5±1.6	38.6±1.4	39.3±1.7	40.7±1.7	40.7±1.7
F6	0	39.5±2.1	42.9±1.8	44.2±2.2	48.6±2.3	55.3±1.9	58.3±1.6	60.4±1.7
F7	0	35.5±2.4	37.9±2.1	40.2±1.8	46.8±1.6	47.1±1.7	49.9±1.9	52.2±1.7
F8	0	30.2±1.8	42.2±2.1	45.6±1.9	49.3±2.4	51.5±2.1	53.6±1.8	55. 8±2.

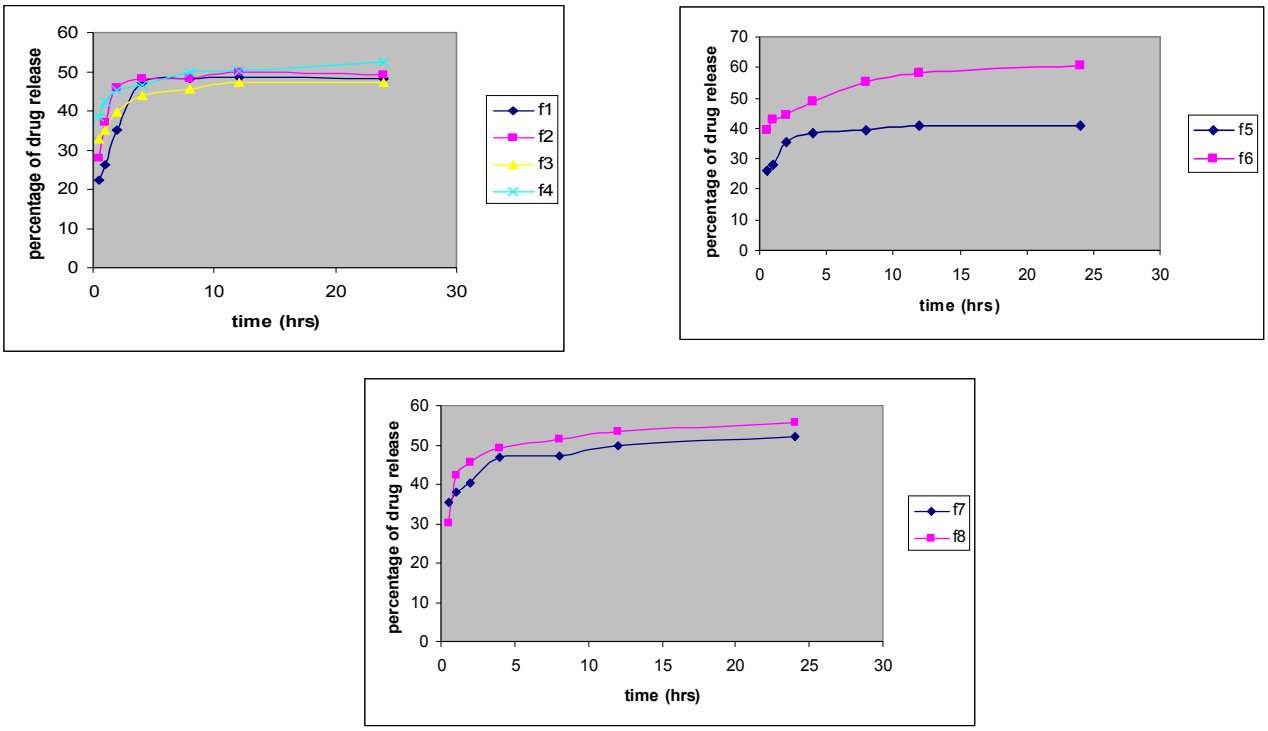

Figure no.1: Percentage release graphs

Release Mechanism

Based on the "n" value of 0.168 obtained for F6 formulation, the drug release was found to follow Fickian diffusion. Also, the drug release mechanism was best explained by Higuchi's equation, as the plots showed the highest correlation 0.9063, r^2 value is 0.821. Drug release kinetics of this formulation corresponds best to Higuchi's model.

Table no.7 release kinetic data

Batch	Zero order		First order		Higuchi		peppas		
	R^2	correlation	R^2	correlation	R^2	Correlation	R^2	n	Correlation
F1	0.520	0.7215	0.570	0.7555	0.768	0.8767	0.771	0.221	0.8782
F2	0.529	0.7277	0.595	0.7720	0.779	0.7828	0.827	0.203	0.9094
F3	0.527	0.7263	0.613	0.7832	0.773	0.8792	0.981	0.151	0.9908
F4	0.451	0.6720	0.537	0.7333	0.701	0.8373	0.965	0.111	0.9826
F5	0.550	0.7419	0.614	0.7839	0.794	0.8913	0.918	0.179	0.9584
F6	0.603	0.7692	0.741	0.8612	0.821	0.9063	0.953	0.168	0.9766
F7	0.543	0.7371	0.644	0.8028	0.780	0.8835	0.971	0.150	0.9856
F8	0.576	0.7590	0.677	0.8230	0.814	0.9026	0.894	0.204	0.9456

R^2 = Regration Coefficient**; n**= Diffusion all exponent

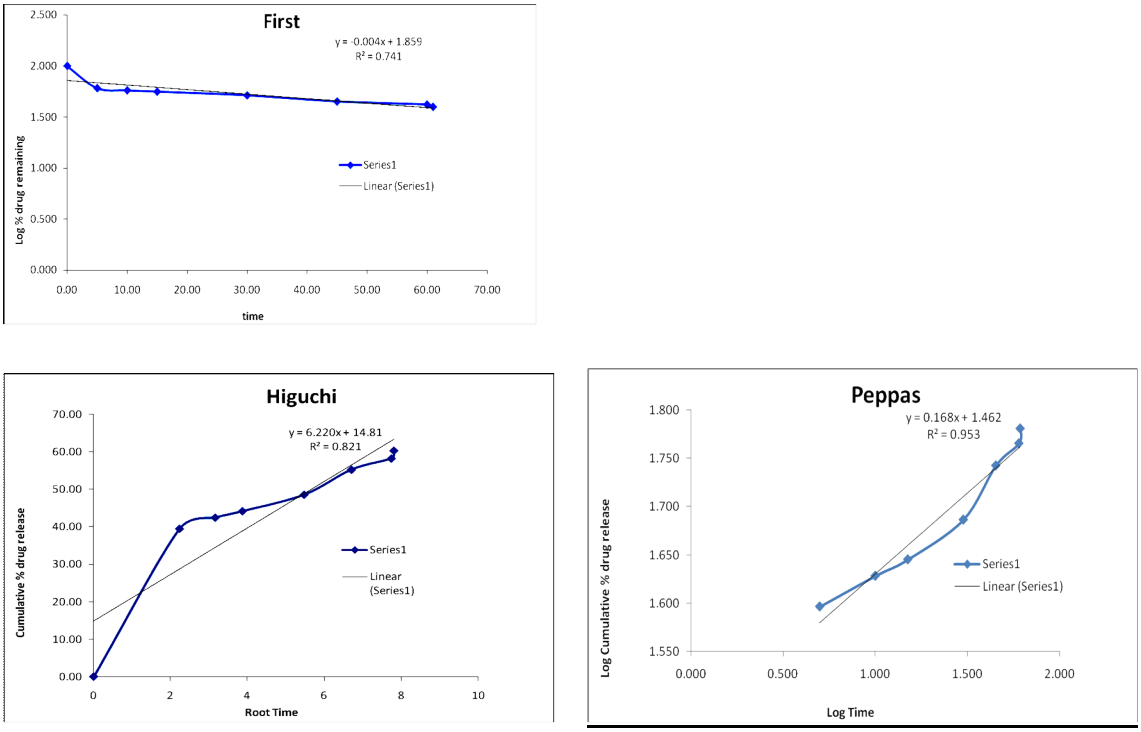

Figure no.2: Release fitting graphs

CONCLUSION

The aim of the present study was to develop a sustained release tablet of phenytoin sodium due to narrow therapeutic window of phenytoin sodium to reduce dosing frequency. An efficient sustained release formulation of phenytoin sodium could not be designed as sustained release tablets, because up to 12 hrs it releases 60% of the drug. So it required some extent of work for desired sustained release. In this study the optimized formulation (F6) was developed by using hydroxy propyl methyl cellulose as a polymer base. Regulated drug release in Higuchi order manner was attained by using this polymer

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