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Formulation and Evaluation of Phenytion Sustain Release Tablets

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ABSTRACT

The main aim of proposed work was to develop Phenytion matrix tablets, sustained release dosage form, for the treatment of epilepsy. Sustained release formulation is the drug delivery system that is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The matrix tablets were prepared by direct compression method using Hydroxylpropylmethylcellulose (HPMC K4M, K15M, K100M), Polyvinylpyrrolidone (PVP K-30) and microcrystalline cellulose (MCC 101) in varying ratios. Tablets blends were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The compressed tablets were then evaluated for various physical tests like diameter, thickness, uniformity of weight, hardness, friability, and drug content. The granules exhibited satisfactory rheological demeanor. The results of all these tests were found to be satisfactory. The in vitro dissolution study was carried out for 24 hours using paddle method in phosphate buffer (pH 7.4) as dissolution media. Formulation F1 to F7 failed to sustain release and among all the formulations, F8 shows 77% of drug release at the end of 24 hours. This finding reveals that above a particular concentration of MCC 101, HPMC K-100 and PVP K-30 are capable of providing sustained drug release.

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1. INTRODUCTION

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and gradual release of additional amounts of drug to maintain this effect over a predetermined period. Matrix systems are the most popular method among innumerable methods used in the development of sustained release formulations. Hydrophilic polymeric matrix systems are widely used in controlled drug

delivery, since they make it easier to achieve a desirable drug release profile, are cost effective and have broad FDA acceptance.[1,2]

Phenytion (S) - 3 - amino methyl hexanoic acid, is a structural analogues of γ-amino butyric acid (GABA). They constitute an important group of compounds that are used in the treatment of epilepsy and neuropathic pain. It is a white crystalline solid. It is soluble in water and in both basic and acidic aqueous solutions. Phenytion has been studied for use in a variety of disorders, including monotherapy in refractory partial seizures, diabetic neuropathy, surgical dental pain and other pain syndromes, post herpetic neuralgia, and social anxiety disorders. Phenytion's innovator is Pfizer-Global and appears world-wide under the brand name Lyrica. The half-life of Phenytion is also short (5-6.5 hrs) which makes it suitable candidate for sustained release formulation, moreover it reducing side effects, decreasing frequency and improve patient compliance.[3-7] Keeping these factors in view it is aimed to formulate and evaluate sustained release matrix tablets, to provide a controlled and predictable release of Phenytion, which is an oral antiepileptic drug used in the management of epilepsy. For the sustain release layer it was intended to use four different polymers to formulate a polymer matrix systems namely hydroxylpropyl methyl cellulose (HPMC K4M,K15M,K100M), Polyvinylpyrrolidone (PVP K-30) and Microcrystalline cellulose (MCC 101).

2. MATERIALS AND METHODS

2.1 Materials

Phenytion, HPMC K4M HPMC K 15M,HPMC K100M,PVP K30, MCC PH101, Mg.Stearate and aerosil were obtained from Spectrum Pharma lab, Hyderabad. All the other ingredients used were of analytical grade.

2.2 Method of Preparation of Matrix Tablets [8]

All ingredients was collected and weighed accurately. Sifted Phenytion and polymers through sieve no. 60# and then rinsed with remaining excipients. Sifted colloidal silicon dioxide (Aerosil-200) and magnesium stearate separately, through sieve no. 60#.Preblending of all ingredients (except lubricant magnesium stearate) in blended for 15 minutes. Blend then again blended for 5-6 min then added magnesium stearate blended 5 min. Lubricated powder was compressed by rotary machine having circular concave shaped and one side break line on upper punch, with pressure of 7-8 tons. Compressed tablets were examined as per official standards and unofficial tests. Prior to the compression the drug and polymers were evaluated for several tests. The composition of different formulation of Phenytion was given in table.No.1.

Table 1: Formulation composition of phenytion sustained release tablets

INGREDIENTS	F1 l.l.l	F2 l.l.h	F3 l.h.l	F4 l.h.h	F5 h.h.h	F6 h.h.l	F7 h.l.h	F8 h.l.l
H.P.M.C K4M	50 mg	50 mg	50 mg	50 mg	100 mg	100 mg	100 mg	100 mg
H.P.M.C K15M	50 mg	50 mg	100 mg	100 mg	100 mg	100 mg	50 mg	50 mg
H.P.M.C K100M	50 mg	100 mg	50 mg	100 mg	100 mg	50 mg	100 mg	50 mg
M.C.C	280 mg	230 mg	230 mg	180 mg	130 mg	180 mg	180 mg	230 mg
P.V.P	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Mg.sterate	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Aerosil	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Phenytion(drug)	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
Total weight (mg)	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg

2.3 Evaluation of tablet blends [9]

Angle of repose:

The angle of repose of tablet blends was determined by the funnel method. The blends were allowed to flow through the funnel freely onto the surface. The

diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Tan θ = h/r

Where 'h' and 'r' are the height and radius of the powder cone, respectively.

Bulk density:

Apparent bulk density was determined by pouring a weighed quantity of tablet blends into graduated cylinder and measuring the volume and weight.

Bulk Density = Mass of powder / Bulk Volume of the powder

Tapped bulk density:

It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

Tapped density = Weight of powder / Tapped volume of the powder

Carr's index:

Carr's compressibility index CI (Carr, 1965) is defined as follows:

CI = ρt - ρa / ρt = Va – Vt / Vt

Where ρt and ρa – tapped and poured bulk density; And Vt and Va – tapped and poured bulk volume respectively.

Hausner's ratio:

A similar index has been defined by Hausner.

Table 2: Physical characteristics of prepared blends of Phenytion

Parameters	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Angle of repose	29° 24' ± 0.21	30° 18' ± 0.34	28° 34' ± 0.46	32° 21' ±0.39	29° 18' ± 0.24	30° 41' ± 0.55	31° 41' ± 0.45	22° 41' ± 0.55
Bulk density	0.32 ± 0.06	0.31 ± 0.05	0.35 ± 0.03	0.34 ± 0.02	0.34 ± 0.04	0.3 ±0.05	0.32 ±0.03	0.31 ±0.05
Tapped bulk density	0.45	0.44	0.43	0.41	0.42	0.42	0.4	0.41
Compressibility Index	29.06	26.38	19.82	18.57	21.26	26.71	24.71	25.71
Hausner's Ratio	1.21 ± 0.04	1.19 ± 0.01	1.14 ± 0.06	1.17 ± 0.07	1.22 ± 0.05	1.2 ± 0.07	1.18 ± 0.03	1.17 ± 0.07

2.4 Evaluation of Tablets [10]

Thickness

The thicknesses of the tablets were determined using a Vernier caliper, 20 tablets from each batch were used and average values were calculated.

Uniformity of weight

Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. The weights were determined to within ±1mg by using digital balance. Weight control is based on a sample of 20 tablets.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where, I - Initial weight, **F** - Final weight

Weight variation test

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula,

$$\text{Percentage deviation} = [X - X^{*} / X] \times 100$$

X - Actual weight of the tablet

X*- Average weight of the tablet

Estimation of Drug Content

An accurately weighed amount of powdered Phenytion (100 mg) was extracted with water and the solution

was filtered through 0.45 µ membrane filter paper. The absorbance was measured at 275 nm after suitable dilution.

Calculation

The amount of Phenytion present in tablet can be calculated using the formula

$A_t/As \times S_w/100 \times 100$

Where,

A_t = Absorbance of sample preparation

A_s = Absorbance of Standard preparation

S_w = weight at Metformin working standard (mg)

***In vitro* release studies:**

Dissolution test:

In vitro dissolution test was carried out by using USP type II (paddle) apparatus. 1000 mL of acetate buffer pH 7.4 with 1% triton X-100 was used as dissolution medium and the paddle was rotated at 50 rpm at temperature ($37_0C \pm 0.5^0C$). Sampling was done at regular intervals and was replaced by media after each sampling interval. The samples are then analysed spectrophotometrically at λmax 275nm of the drug. (FDA method).

Medium**:**	phosphate buffer pH 7.4
Volume:	900ml
Temperature:	$37^0C \pm 0.5^0C$
Apparatus:	USP type-II (paddle)
RPM:	50 RPM
Time interval:	1 hr up to 24 hrs

Release Kinetics:

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, diffusion and Peppa's- Korsemeyer equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppa's-Korsemeyer equation.

Zero Order Release Kinetics

It defines a linear relationship between the fractions of drug released versus time.

$Q = k_o t$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$\ln (1-Q) = - K_1 t$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$Q=K_2 t^{½}$

Where, K2 is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant.

Power Law:

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppa's and Korsemeyer equation (Power Law).

$M_t/M_\alpha = K.t^n$

Where, M_t is the amount of drug released at time t and M_α is the amount released at time α, thus the M_t/M_α is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent. To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted in Table. A plot between log of M_t/M_α against log of time will be linear if the release obeys Peppa's and Korsemeyer equation and the slope of this plot represents "n" value (diffusion coefficient) which describes mechanism of diffusion.[11]

3. RESULTS AND DISCUSSIONS

3.1 Preformulation studies

Drug excipient compatibility studies were performed by force degradation and Fourier transform infrared spectroscopy. Results obtained from (Figure.No:1&2) showed that drug and excipients were compatible with each other.

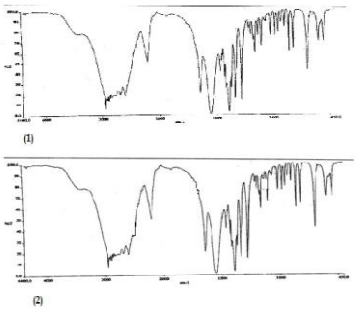

Fig 1: FTIR spectrum of pure drug

Fig 2: FTIR spectrum of optimized formula

3.2 Evaluation of pre-compression parameters

The present investigation was undertaken to design, formulate and evaluate Phenytion matrix tablets for sustained release dosage form. The blends of different formulations were evaluated for angle of repose, bulk density, tapped bulk density, compressibility index and hausner's ratio. The results of bulk density, tapped bulk density, compressibility index and hausner's ratio are mentioned in (Table .No.2). The bulk density of the tablet blend was in the range of 0.30± 0.05 to 0.35± 0.03 g/ml; the tapped density was in the range of 0.41± 0.02 to 0.45± 0.04 g/ml, which indicates that the powder was not bulky. The blend indicated good flow properties for all the formulation with the angle of repose values 22° 41'±0.55 to 32° 21'±0.39 according to fixed funnel and free standing cone method. The results of compressibility index lies between range from 18.57±1.17 to 29.06±1.21, while hausner's ratio lies between 1.14±0.06 and 1.22±0.05 indicating good to excellent flow properties.

3.3 Physicochemical evaluation of Phenytion sustained release tablets

The tablets of different batches formulated were evaluated for test such as hardness, friability, thickness, uniformity of weight and drug content. The results obtained from all formulations were within the range. The weight variation test indicates that all the tablets were uniform with low standard deviation values and hence all formulation passed the test for uniformity of weight. The tablets mean thickness values ranged from 5.8±0.11 mm to 6.2±0.44 mm. The hardness of all the tablets was within the range of 7±0.03 to 7±0.08 kg/cm^2.The loss in friability test was in a range of 0.07 to 0.14%. The percentage drug content for different tablet formulations were discrete from 97.24% to 99.34%, were found to be within range (table.No.3).

Table 3: Physico-chemical characterization of prepared Phenytion sustained release tablets

Parameters	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
Uniformity of weight (mg)	497 ±4	498 ±1	500 ±1	500 ±1	498 ±2	499 ±1	498 ±2	497 ±2
Thickness (mm)	6.8± 0.11	7.1± 0.14	6.8± 0.23	7.2± 0.42	6.9± 0.08	6.8± 0.34	7.2± 0.42	6.9± 0.42
Friability	0.09	0.14	0.08	**0.07**	0.12	0.13	0.04	0.07

(%)Tablet Hardness (Kp)	7±0.05	7±0.03	7±0.04	7±0.01	7±0.02	7±0.03	7±0.04	7±0.01
% Assay	99.11	98.61	97.24	99.18	99.34	97.12	99.21	98.11

3.4 In vitro drug release studies

In vitro dissolution studies (Table.No.4&Figure.No.3) of all the formulations of sustained release tablets of Phenytion were carried out in pH 7.4 phosphate buffers for 24 hours. Only three (F2, F4 ,F5 and F8) tablet formulations showed acceptable properties as shown in (Table.No.4).

Table.No.4. In-vitro drug release studies of prepared Phenytion sustained release tablets

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
2	14.1	4.7	5.7	8	6	6	3	4.5
4	24	5.5	6.26	14	14	11	3.8	4.8
8	56.2	11	23.1	22	22	26	12	6.5
10	90	25	58	43	31	43.2	29.2	24
16	100	59	79.9	57	51.2	77	71.2	45
20	100	78	95	73	72	85	85	68
24	100	87	100	88	85	96	97	75

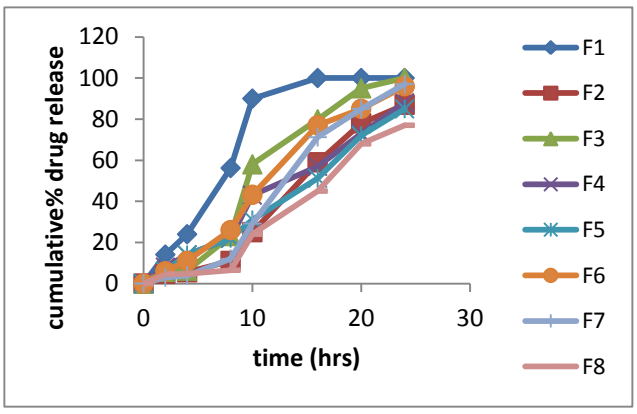

Fig 3: Cumulative percent drug release profile of Phenytion sustained release tablets (F1-F8)

The result of the dissolution study indicating that F1, F3, F6 and F7 released almost drug at the end of 16hrs, here we observed that on decreasing the proportion of HPMC K-100 and on increasing the quantity of MCC 101 and PVPK-30, it retards the drug release from matrix. This might be due to slow hydration of matrix and its property to form a thick gel layer, which retard the drug release from the tablet. It is expected that the developed formulation should have the following theoretical drug release profile, i.e., 100% for 24 hrs. Formulations F1, F3, F6 and F7 failed to meet the needed theoretical drug release profile. Formulation F8 release 77%(not<75%) drug at the end of 24 hrs, for these reasons, it was considered the best formulation among all the six formulations of this series.

3.5 In-Vitro drug release kinetics:

The kinetic data analysis of all the formulations (Table.No.5) reached higher coefficient of determination with the Korsmeyer-Peppas model (R^2 = 0.911 to 0.990) whereas release exponent value (n) ranged from 0.498 to 0.743. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

Table 5: Release kinetic Coefficient of Correlation (R^2) values of tablets

Formulation code	Release model			
	Zero order	First order	Higuchi matrix	Koresmeyer-peppas
F1	0.985	0.953	0.96	0.989
F2	0.911	0.945	964	0.969
F3	0.984	0.953	0.964	0.992
F4	0.94	0.994	0.996	0.975
F5	0.982	0.986	0.996	0.911
F6	0.986	0.997	0.998	0.952
F7	0.973	0.772	0.993	0.991
F8	0.96	0.997	0.993	0.99

4. CONCLUSION

In the above view of findings it can be concluded that the combination of HPMC and PVPK30 are better suited for sustained drug delivery system than polymer alone. A matrix design of this kind can serve as an alternative strategy to modified drug delivery system.

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