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Preparation and *In-vitro* Evaluation of Sustained Release Phenytoin Sodium Matrix Tablets Prepared by Co-Evaporation Method Using Different Polymers

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Abstract: Sustained-release matrix tablets of Phenytoin sodium was developed and evaluated. Tablets were prepared by co-evaporation method using hydroxy propyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and polyvinylpyrrolidon-K90 (PVP-K90), the hydrophilic polymers as release sustaining materials. Formulations were designed using drug to polymers ratio 1:1, 1:1.5, 1:2 with the aim to develop twice daily sustained release matrix tablets. Physical characterization of both granules and tablets were evaluated. USP dissolution apparatus I was used for the *In-vitro* drug release study of the tablets. Drug release data was evaluated using various models like Zero-order, First-order, Higuchi model, Korsmeyer model and Hixson-Crowell model. The resulting matrix tablets prepared with all the polymers used in drug to polymer ratio fulfilled all the official requirements for a tablet dosage form except dissolution, while HPMC with drug to polymer ratio 1:2 extend the release of the drug up to 12 hours.

Key words: Hydrophilic Polymers (HPMC, CMC And PVP) · Sustained Release · Co-Evaporation Method · Phenytoin Sodium Tablets

INTRODUCTION

Phenytoin is commonly administered as antiepileptic medication to critically ill patients for seizure prophylaxis and treatment it exhibits non-linear pharmacokinetics characteristics and requires frequently plasma monitoring and dose adjustment. It possesses a relatively narrow therapeutic range (10-20 mcg/ml) with signs and symptoms of central nervous system toxicity more likely at concentrations greater than 20 mcg/ml. The metabolism of phenytoin is through capacity limited processes. Small changes in the amount of phenytoin administered or absorbed from the gastrointestinal tract may result in disproportionate changes in the plasma concentration [1]. Due to its weakly acidic nature (pKa 8.31) and poor aqueous solubility (100 mcg/ml) phenytoin often shows erratic absorption following oral administration, for this reason certain hydrophilic polymers and gums are used to overcome this problem. These polymers and gums on contact with aqueous medium swell and form a gel layer on the surface of the system from that they controlled the release of the drug. As such, hydrophilic matrices dominate today's market of oral controlled release products [2-4]. Hydroxypropyl methylcellulose (HPMC) is the most commonly used hydrophilic polymer. The hydrophilic polymers and gums like hydroxypropyl methylcellulose (HPMC), carboxy methyl cellulose(CMC), polyvinylpyrolidone(PVP), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), xanthan gum (XG) and guar gum (GG), have been extensively used in the formulation of sustained release systems [2,3,5,6]. The broad acceptance, cost effectiveness, nontoxic properties, ease of handling, ease of compression, ability to accommodate a large percent of drug, negligible in?uence of the processing variables on drug release rates and relatively simple tablet manufacturing technology make these excellent carrier materials for oral matrix tablets [2-4]. The present study was aimed to investigate the sustaining effect of various polymers like (HPMC, CMC and PVP) using Phenytoin sodium as a model drug.

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Table 1: Composition of 100 mg Phenytoin sodium Matrices tablets formulations.

	Formulations								
Ingredients	H1	H2	H3	C1	C2	C3	P1	P2	P3
HPMC (mg)	100	150	200	-	-	-	-	-	-
CMC (mg)	-	-	-	100	150	200	-	-	-
PVP K90 (mg)	-	-	-	-	-	-	100	150	200
Lactose (mg)	115.25	65.25	15.25	115.25	65.25	15.25	115.25	65.25	15.25

H=Hydroxypropylmethylcellulose K100M, C= Carboxymethylcellulose, P = Polyvinylpyrrolidone -K90, 1, 2 and 3 indicates drug to polymer ratio 1, 1.5 and 2, respectively. Magnesium stearate 1.0% and Talcum 2.0% was used as a lubricant in all formulations.

MATERIALS AND METHODS

Phenytoin sodium powder (Herman Finochem Ltd. Aurangabad India) was a kind gift from Siza International Phartmaceuticals Pvt. Ltd. Lahore, Pakistan, Polyvinylpyrrolidone (PVP-K90) (BASF, Ludwigshafan, Germany), hydroxyl propyl methyl cellulose (Methocel, HPMC K-100M (The Dow Chemical, USA), carboxymethyl cellulose (Daiul Chemical, Japan), lactose (Lactose New Zealand Company, New Zealand), starch (Rafhan Maize Products Pvt. Ltd, Faisalabad, Pakistan), talcum and magnesium stearate (Katayama Chemical Co. Osaka, Japan) were kind gifts from Medicraft Phartmaceuticals Pvt. Ltd. Peshawar, Pakistan, distilled water used in the formulations and in the analysis was prepared using a Millipore ultra water system (Milford, USA), Phenytoin commercial tablets Dihydan® (French Pharma, Karachi Pakistan) were purchased from the local market.

Instrumentation: Oscillating granulator (F. D & C Karachi, Pakistan), Rotary evaporator, ZP19 Rotary Tablet Press (STC, Shanghi, China), Tablet Hardness Tester (Pharma tester, Germany), Dissolution test Apparatus, Fribilator (Erweka, Germany), UV/Visible spectrophotometer (Model No: CT 06484-4794. U.S.A. Perkin Elmer) were used in this study.

Preparation of Co-Evaporation: Drug was dissolved in isopropyl alcohol using EZ Stir as the formulations of which shown in Table 1. The Polymers were dissolved in distilled water which produced a clear solution. Then the drug solution was added in the form of thin stream to the polymers solution with continuous stirring using the same stirrer. The entire solvent was completely evaporated under reduced pressure, at 40°C using Rotavapor (Heidolph, Germany) with solvent recovery. The recovered solvent was used for next batch. The solid dispersion so obtained was dried at 60 °C in oven for 24 hours [7]. The dried material obtained was passed through mesh #. 12, then talc and magnesium stearate were added as glident and lubricant respectively, lactose was added as diluent and mixed in lab scale mixer for 5 minutes. Microcapsules were evaluated for different physical properties like angle of repose, lose bulk density, taped bulk density, compressibility Index and content of active ingredients.

Preparation of Tablets from Co-Evaporates: After lubrication the co-evaporates were directly compressed into tablets based on theoretical weight depending on the assay of the microcapsules using 10.0 mm beveled edge punches on Rotary tablet compression machine ZP 19 (STC, Shanghai, China). The compressed tablets were evaluated for various physical parameters like friability, hardness, thickness, weight variation and assayed for the active ingredients. The *in vitro* study for each formulation was determined using USP apparatus I. Tablets were also assayed for the active ingredients.

Characterization

Granule Characterization: Angle of repose, bulk density, compressibility index and drug contents were determined as per protocol [8-11].

Tablet Characterization: Tablets were characterized and evaluated for thickness, hardness, weight variation, friability and drug content [11].

In vitro drug release using the USP 32 dissolution apparatus-I specifications were applied [11].

In order to investigate the mechanism of drug release from dosage form, the data was analysed using, Zero order, First order, Higuchi, Hixon-Crowell and Korsmeyer-peppas.

RESULTS AND DISCUSSION

The granules of all the formulations were subjected for physical characterization i.e. angle of repose, loose bulk density (LBD), tapped bulk density (TBD), compressibility index and drug content before compression the results are shown in Table 2. Physicochemical properties of the granules may affect

Table 2: Physical properties of the granules.

Properties	Formulations								
	H1ce	H2ce	H3ce	C1ce	C2ce	C3ce	P1ce	P2ce	P3ce
Angle of repose	26.28 ± 0.08	26.99 ± 0.05	27.52 ± 0.02	25.47 ± 0.04	26.65 ± 0.03	26.91 ± 0.07	25.11 ± 0.03	25.98 ± 0.02	26.92 ± 0.03
Loose bulk density(LBD) (g/ml)	0.313 ± 0.03	0.321 ± 0.04	0.334 ± 0.02	0.299 ± 0.01	0.313 ± 0.04	0.318 ± 0.02	0.298 ± 0.04	0.306 ± 0.03	0.315 ± 0.04
Taped bulk density(TBD) (g/ml)	0.362 ± 0.05	0.375 ± 0.05	0.384 ± 0.01	0.350 ± 0.04	0.355 ± 0.02	0.361 ± 0.07	0.341 ± 0.04	0.354 ± 0.05	0.365 ± 0.05
Compressibility Index (%)	15.41 ± 0.03	15. 81 ± 0.02	17.00 ± 0.05	16.33 ± 0.04	16.98 ± 0.02	17.99 ± 0.02	16.55 ± 0.04	16.81 ± 0.01	17.79 ± 0.01
Drug content (%) of granules	98.68 ± 0.03	98.54 ± 0.05	98.82 ± 0.02	98.45 ± 0.05	98.64 ± 0.03	98.58 ± 0.02	98.56 ± 0.05	98.62 ± 0.02	98.75 ± 0.05

Table 3: Physical properties of the tablets.

Properties	Formulations									
	H1ce	H2ce	H3ce	C1ce	C2ce	C3ce	P1ce	P2ce	P3ce	Reference tablet
Hardness (N)	70.80 ± 3.72	71.90 ± 3.21	73.25 ± 2.55	67.95 ± 4.85	69.55 ± 3.59	71.75 ± 2.48	67.10 ± 4.11	68.45 ± 4.35	71.10 ± 2.44	85.05±3.76
Friability (%)	0.69 ± 0.03	0.63 ± 0.01	0.54 ± 0.05	0.63 ± 0.01	0.59 ± 0.04	0.43 ± 0.01	0.73 ± 0.01	0.66 ± 0.02	0.54 ± 0.01	0.46 ± 0.01
Thickness (mm)	4.59 ± 0.02	4.57± 0.02	4.53 ± 0.02	4.60 ± 0.015	4.56 ± 0.02	4.60 ± 0.015	4.61 ± 0.02	4.63 ± 0.02	4.60 ± 0.02	4.62 ± 1.36
Weight (mg)	326.50 ± 2.18	326.45 ±2.32	326.15 ± 2.85	325.80 ± 2.56	325.85 ± 2.18	325.90 ± 2.17	325.05 ± 1.73	326.20 ± 2.68	326.60 ±2.45	233.9± 1.82
Drug content (%)	98.42 ± 0.05	98.48 ± 0.02	98.52 ± 0.05	98.56 ± 0.05	98.75 ± 0.02	98.64 ± 0.05	98.56 ± 0.05	98.62 ± 0.02	98.75 ± 0.05	98.46 ±0.0

many qualities feature of the tablets, such as compressibility, dose accuracy, porosity, hardness, friability, capping tendency, disintegration, dissolution rate and eventually the bioavailability of the drug in the body. For this reason the evaluation of the granules is very significant before the compression into tablets. The angle of repose and Compressibility Index for the formulations was determined and their results revealed that the granules of all formulations showing excellent flow and compression characteristics. The results of LBD and TBD also showing that the granules prepared were of uniform size and spherical shaped also confirmed the suitable behavior for the flow of the granules. The result for drug content also indicates that the drug was uniformly distributed. From the data obtained for all the parameters it was observed that the granules have good physicochemical properties for the preparation of matrix tablets [12].

For the pharmaceutical tablets certain amount of mechanical strength is necessary to withstand the shocks of handling during its manufacturing, packaging, shipping and dispensing. The tablet may also be able to withstand for a reasonable amount of abuse imparted by the patient. The tablet hardness must also be kept in mind from the early stages for the development of a formulation because it can have a significant role on such quality tablet parameters like disintegration and dissolution properties, which in turn affect the bioavailability of the drug. Statistically the difference in hardness of the test formulations highly significant from the reference tablets significant $P < 0.005$. In addition to hardness another parameter of tablet`s strength is friability. Friability is the measure of tablet`s ability to withstand both shock and abrasion during the handling of manufacturing, packaging, shipping and consumer use. Tablet that tends to powder, chip and fragment when handled lack elegance and hence consumer acceptance. Therefore the pharmacopoeial limit for friability is kept less than 1% so to avoid the above problems and the results obtained for both HPMC and CMC group of formulations was found in the above limit and was statistically significant $P < 0.005$ while for formulations of PVP group it was found in the limit but statistically was non-significant from the reference tablets $P > 0.05$. Thickness of the tablets was uniform for all the formulations and statistically was non-significant from the thickness of the reference tablets $P > 0.05$, while the weight variation test that was observed in official limit of pharmacopoeia statistically was found significant $P < 0.005$. All the tablets parameters were in the specified range regarding to the weight uniformity test and drug content [12, 13]. This shows that the matrix tablets from all the formulations have good physicochemical properties [14, 15].

Drug Release Study: The drug dissolution profile for all polymers (HPMC, CMC and PVP-K90 groups) of formulations of Phenytoin sodium sustained release matrix tablets were shown in Figures 1-3, respectively. Tablets of formulations H1ce, H2ce and H3ce released 46.86 %, 41.66 % and 36.66 % of Phenytoin sodium at the end of 3 hours; and 95.65 %, 90.23 % and 59.43 % of drug at the end of 6 hours, respectively, formulation H3ce prolong the release of the drug and release more than 95 % of the drug at the end of 12 hours (Figure 1). The tablets of formulations C1ce, C2ce and C3ce prolong the release up to four, six and eight hours, respectively as depicted in Figure 2, while the tablets of formulation P1ce, P2ce and P3ce i.e. drug to polymers ratios (1:1, 1:1.5 and 1:2 extend the release of the drug up to three, four and six hours, respectively as indicated in Figure 3.

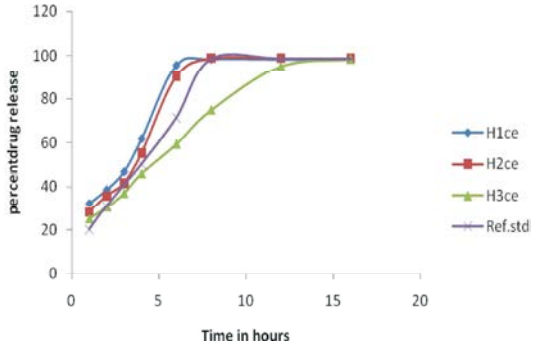

Fig. 1: Cumulative (mean ± SD) % of phenytoin sodium released from SR matrix tablets using different amount of HPMC K100 M (n = 3)

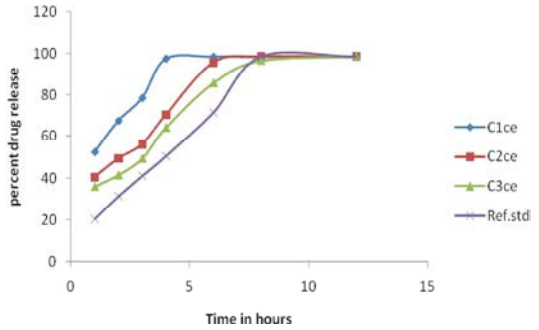

Fig. 2: Cumulative (mean ± SD) % of phenytoin sodium released from SR matrix tablets using different amount of CMC (n = 3)

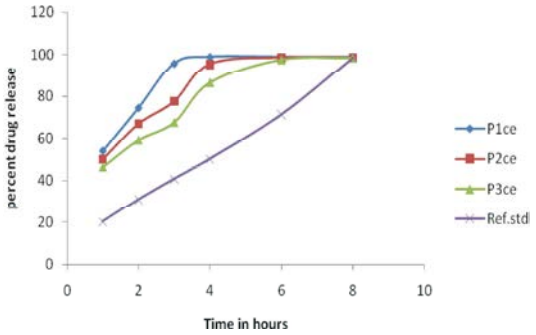

Fig. 3: Cumulative (mean ± SD) % of phenytoin sodium released from SR matrix tablets using different amount of PVP-K90 (n = 3)

As it was observed that with the increase in polymer ratio in the formulations the rate of release was decreased as the release of drug not only depends upon the nature of matrix but also depends upon the drug polymer ratio means that by increasing the drug: polymer ratio ultimately reduces the release rate [16]. This was due to the increase in polymer concentration which in turn increases the viscosity of the system so for a drug it will be difficult that release by diffusion or erosion. Same observations are reported by Ebube and Jones [17]. The dissolution rate of drugs present in heterogeneous formulation can also be extensively affected by physical properties of granules [18].

According to the literature the viscosity of CMC and HPMC are similar, but CMC have faster release rate than HPMC, this may be due to the disintegrating and swell able characteristic of CMC. Wetting on granulation, particle size and hardness can also affect the release rate of drug from the dosage forms which are the important processing factors [19].

The comparison of HPMC and CMC in matrix tablets containing the same amount of polymers showed the rapid release of drug from CMC compared with HPMC, however, the release governed by polymer relaxation and erosion. The high release rate was due to the high solubility of CMC compared with HPMC in dissolution method. This characteristic of the polymer results in a quick gel erosion rate and a high erosion degree of the overall system [20]. While PVP is a water soluble polymer and upon contact with water instead of swelling it become disintegrated and was unable to sustain the drug from the matrix tablets. Although PVP- K90 is a good binder and is used in different types of pharmaceutical tablets formulations but not a good sustaining polymer because it fail to form a gel like structure which is essential for sustaining the drug from the matrix tablets as was observed from the results obtained.

The theoretical release profile is essential for the evaluation of drug release in predetermined manner from the dosage form. The results obtained from all batches of all groups of formulations were not according to the theoretical release pattern, once a day sustained-release Phenytoin sodium formulation of USP specification [11].

Drug Release Kinetics: The cumulative amount of drug released from the matrix tablets of all the formulations at different time intervals was treated using various models as shown in Table 4. The cumulative % of drug released from the formulations was plotted against time on a log-log scale and analyzed for linearity using least squares method. The correlation coefficients were calculated and used to find the fitness of the data.

When the data of these formulations was treated according to these models it was observed that among the HPMC group of formulations H1ce has high linearity with the first order kinetics, the values of $r^2 = 0.9959$, while formulation H2ce and H3ce followed zero order kinetics

Table 4: *In vitro* release kinetics (analyzed by regression coefficient method) of Phenytoin sodium from different batches of HPMC, CMC and PVP-K90 matrix tablets.

Formulation	Zero order r^2	First order r^2	Higuchi r^2	Hixson Crowell r^2	Korsmeyer r^2	Korsmeyer N	Release mechanism
H1ce	0.9622	0.9959	0.8935	0.8731	0.8970	0.5887	non-Fickian
H2ce	0.9627	0.9611	0.9336	0.9441	0.9314	0.6455	non-Fickian
H3ce	0.9934	0.9435	0.9804	0.9732	0.9718	0.5633	non-Fickian
C1ce	0.9902	0.9920	0.9257	0.8967	0.9739	0.4273	Fickian
C2ce	0.9851	0.9958	0.9388	0.9118	0.9309	0.4661	non-Fickian
C3ce	0.9812	0.9632	0.9630	0.9697	0.9428	0.5137	non-Fickian
P1ce	0.9998	0.9953	0.9921	0.9600	0.9934	0.5137	non-Fickian
P2ce	0.9915	0.9838	0.9933	0.9296	0.9844	0.4444	Fickian
P3ce	0.9953	0.9726	0.9901	0.9699	0.9837	0.3926	Fickian

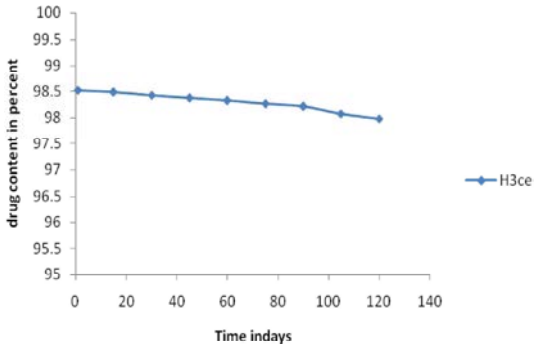

Fig. 4: Effect (mean ± SD) of storage temperatures on the assay of phenytoin sodium from HPMC (H3) matrix tablets (n=3)

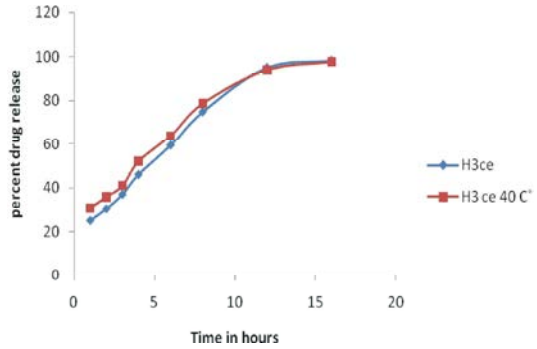

Fig. 5: Effect (mean ± SD) of storage temperatures on the release of phenytoin sodium from HPMC (H3) matrix tablets (n=3)

r^2= 0.9627, 0.9934, respectively, as given in Table 4. The exponential values of (n) for all the formulations using korsmeyer model were found in the range of 0.5633 and 0.6455 indicate that the release mechanism from these formulations followed non- Fickian diffusion means that the release from the tablets followed by both diffusion and erosion process.

Similarly when the % release data of Phenytoin sodium released from CMC matrix tablets at various time intervals was analyzed it was observed that among the formulations C1ce and C2ce followed first order kinetics, the values of r^2 for these formulations are 0.9920 and 0.9958, respectively, while formulation C3ce follow zero order kinetics the value of r^2 = 0.9812 as given in Table 4. The exponential values of (n) for all the formulation C1ce was 0.4273 indicating that this formulation followed Fickian diffusion while, formulations C2ce and C3ce having exponential values 0.4661 and 0.5137 indicate that the release mechanism from these two formulations followed non- Fickian diffusion. When the data of the *in vitro* drug release profile for the formulations of PVP -K 90 group was treated with various models from the results it was observed that among the formulations P1ce and P3ce follow zero order kinetics, the values of r^2 = 0.9998 and 0.9953, respectively, while formulation P2ce follow Higuchi model the values of r^2 = 0.9933.

Stability Studies: As among the three polymers only the HPMC group of formulation was able to sustained the release up to 12 hours with drug to plymer ratio 1:2. Therefore for the purpose of stability studies from the HPMC group of formulation three batches of the successful formulation were selected and stored at the temperature of 40°C and 75 % relative humidity in order to determine the changes in physiochemical characteristics of the formulation. It was observed that there was no change in the organoleptic characteristics, hardness and drug content. The drug content of the tablet was 98.52 % before the storage and it 97.98 % after the storage for 4 months as shown in Figure 4. Dissolution studies also showed no significant change after this period of time. Figure 5 suggesting that the drug was stable in the HPMC matrix tablets apparently and the drug release from these matrices did not change after storage for this period of

time this was according to the literature [21] this suggested that the HPMC matrix formulations have the capability to provide a minimum two years of shelf life.

CONCLUSION

The present work was designed to prepare and evaluate the sustained release matrix tablet of Phenytoin sodium using different polymers like HPMC, CMC and PVP K90. HPMC based matrix tablets with the drug to polymer ratio of 1:2 was able to sustained the release of the Phenytoin up to 12 hours, while CMC and PVP-K90 with drug to polymer 1:2 ratio was able to control the drug release up to 8 and 6 hours respectively. The stability study also confirms that the drug was stable in HPMC based matrix tablets. So HPMC was selected the best polymer to formulate the sustained release formulation of Phenytoin for 12 hours.

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