Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(1), 2655-2660 | ISSN:2251-6727

Effect of Sustain Release Property on the Development of Phenytoin Matrix Tablet by Using Different Polymers

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(Received: 25 January 2024 Revised: 20 February 2024 Accepted: 25 February 2024)

KEYWORDS
Sustain Release, Matrix Tablet, polymer

ABSTRACT

In this work, the release property of a sparingly water-soluble phenytoin medication was controlled by the use of hydroxy propyl methyl cellulose as a hydrophilic, biodegradable, and biocompatible matrix polymer. The various parameters influencing drug release were measured from the hydrophilic matrix tablets. This formulations were manufactured using the direct compression method. The impact of the drug-to-polymer ratio on drug release was investigated, and the formulation was further characterized by physical and chemical characteristics. The findings were within reasonable bounds. Correlate the pre-formulation and post-formulation characteristics with the dissolution profile in the research report. Out of the eight formulations, F8 has the best sustain release characteristics.

INTRODUCTION

There are over 50 million epileptics in the world, and 90 percent of them live in underdeveloped countries. The half-lives of most drugs are shorter than two hours. For a prolonged effect, each dosing unit requires an extremely high concentration of the medication. A sustained-release dosage type is thought to work well with a biological half-life of one to eight hours. The main objective of this research work was to use many types of polymers to construct a novel system that extended the drug's release. Hydroxypropyl methylcellulose [HPMC] K15M, hydroxypropyl methylcellulose K4M, ethyl cellulose [EC], and microcrystalline cellulose [MCC] are examples of hydrophilic polymers and gums that expand and form a gel layer on the system's surface, controlling the drug's release, superior oral carrier materials. These outstanding oral matrix tablet carrier materials are widely accepted, cost-effective, have nontoxic qualities, are easy to handle, and can accommodate a significant proportion of medications. Phenytoin served as a model medication for the treatment of epilepsy. Specifically, the medication distributed in an HPMC-MCC polymeric matrix completely met the predetermined target (F8), releasing around 33.38% of the drug after two hours at stomach pH and rest 65.39% of the drug released in the next three hours in the intestinal fluid.

MATERIALS AND METHODS

Hetero Labs in Hyderabad provided the phenytoin as a free sample. AR Chemicals Limited, Hyderabad, India, supplied all other chemicals.

Preformulation study

The melting point of phenytoin was determined by the capillary method. For the standard curve, Phenytoin

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JCHR (2024) 14(1), 2655-2660 | ISSN:2251-6727

powder 10 mg was dissolved in 10ml of phosphate buffer (pH 1.2 & 7.4) for stock solution preparation. From the stock arrangement (1mg/ml), prepared 10, 20, 30, 40, 50 µg/ml solution and scanned by UV spectrophotometer at 202 nm. Furthermore, the stability of the API polymer mixtures over two months was investigated. Color, order, and texture of such mixtures were changed or not.[3]

Manufacturing of sustain-release phenytoin tablets using the direct compression approach

Various matrix tablets of Phenytoin were set up by direct pressure method utilizing changing extent of polymers. The fixings were gone through a 60-work sifter. The determined measure of the medication, polymer and microcrystalline cellulose were blended all together. Magnesium stearate was included as grease, the fitting measure of the blend was gauged and after that packed utilizing a ten-station rotating press at a consistent pressure power outfitted with a 10-mm level confronted punches at a pressure power required creating tablets of around 5-7 kg/cm2 hardness. Every one of the tablets was put away in sealed shut compartments for further investigation. Preceding pressure, and mix were assessed for their stream and compressibility attributes **(Table 1)**.[4,5]

Table 1. Ingredients used in Phenytoin formulations

Ingredients(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Drug	100	100	100	100	100	100	100	100
Ethyl cellulose	50	100	-	-	-	-	50	-
HPMC k15M	-	-	50	100	-	-	50	50
HPMC k4M	-	-		-	50	100	-	50
Microcrystalline cellulose	95	45	95	45	95	45	95	45
Magnesium Stearate	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2
Total wt	250	250	250	250	250	250	250	250

Evaluation of Tablets

Precompression parameters

The angle of repose, bulk density (BD), tapped density (TD), Hauser's ratio, Carr's index, and scale of flow ability were among the pre-compression features that were identified and data was gathered. A measuring cylinder was filled with a certain amount of powder. To break up agglomerates, powdered was slightly chopped. Tapping was done indefinitely after the initial volume was noticed until no more changes in volume were seen. We computed BD and TD using the following formula.

TBD = weight of the powder/tapped volume of the packing, LBD = weight of the powder/volume of the packing

The funnel method was utilized to calculate the powder's angle of repose. Granules were free to pour onto the surface through the funnel. The greatest angle that may exist between a powder pile's surface and a horizontal plane is known as the angle of repose. The following formula was used to determine the angle of repose and estimate the diameter of the powder cone. Tan θ = h/r where θ is the angle of repose and h and r are the powder cone's height and radius. When the angle of repose is less than 25, it indicates excellent flow qualities; when it is greater than 40, it indicates poor flow properties [7,8] . As shown below, the compressibility index and Hausner ratio can be calculated using measured values for bulk density (bulk) and tapped density (tapped). Carr's Compressibility index was used to calculate the granules' compressibility index.

$$\text{Carr's Index} = \frac{(TD - BD)}{TD} X\ 100$$

Whereas BD: Powder weight divided by packing volume. TD stands for weight of powder divided by packed volume. Post compression parameters

In weight variation evaluation, ten random tablets were selected separately. After that average weight of tablets was calculated by analytical balance. Tablets hardness was determined by utilizing a Monsanto hardness tester

Journal of Chemical Health Risks

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JCHR (2024) 14(1), 2655-2660 | ISSN:2251-6727

(3 random tablets) expressed in kg/cm. 10 accurately weighted tablets were placed in the Roche friability and rotated at a speed of 25 rpm for 4 minutes. The tablets were then dusted and weighed to measure their friability percentage. Thickness was determined by using an vernier calliper.

Table 2. Visual observation of phenytoin tablets

Properties	**Results**
Description	Powder
Taste	Tasteless
Odor	Odorless
Color	Colour h White

Content Uniformity

From each bunch, twenty tablets were powdered and weighed exactly 100 mg of powdered phenytoin. The needed amount of tablet powder was mixed for 15 minutes in 100 ml of 6.8 phosphate support setup. 1 ml of the mixture was pipetted into a 10 ml volumetric cup, which was then filled with pure water.[9]

***In- Vitro* Release Study**

An in-vitro drug release study was carried out at 37 ^{0}C by USP II dissolution apparatus with 900 ml pH 1.2 acidic buffer and pH 7.4 phosphate buffer at 50 rpm for 8 hrs. From that sample was withdrawn at regular intervals through a 0.45 µm filter and the same amount of of pre-warmed fresh buffer was added to maintain the volume constant. The sink condition was maintained for the whole experiment. Finally, absorbance was mastered by UV spectroscopy at 202nm.[10]

RESULTS AND DISCUSSION

Preformulation Study of granules

The optimized formulation F8 in the pre-formulation research was packaged in a PVC blister pack and kept for 45 days at RH 75±5% at three distinct temperatures: 4±2°C, 27±2°C, and 45±2°C. The tablets were assessed for their physical characteristics, drug composition, and drug excipient compatibility at predetermined intervals of time, every 15 days. Stability testing is done to provide a reliable and high-quality product. For three months, each batch of formulation was kept at 37°C, 40±2°C, and 2–8°C in the refrigerator [1]

Precompression parameters

Table 2 describes the visual examination of phenytoin tablets. All formulation granules were subjected to pre-formulation testing, which included, loose bulk density (LBD), angle of repose, compressibility index, drug content, and tapped bulk density (TBD). **Table 3** displays the results. The melting point of phenytoin was determined to be in the 296 0c range, which was within the norm, showing the purity of the medicine sample.

Table 3. Physical properties of granules (Preformulation Study)

Formulation No	**Bulk density**	**Tapped density**	**Compressibility index**	**Hausner ratio**	**Angle of repose(0)**
F1	0.426±0.023	0.531±0.0.054	19.77	1.24	30^0±0.128
F2	0.419±0.035	0.521±0.068	19.57	1.24	28^0±0.153
F3	0.424±0.041	0.530±0.027	20.00	1.25	27^0±0.105
F4	0.422±0.036	0.528±0.042	20.07	1.25	29^0±0.112
F5	0.418±0.062	0.524±0.043	20.22	1.25	30^0±0.132
F6	0.429±0.024	0.540±0.052	20.55	1.25	31^0±0.143
F7	0.428±0.041	0.539±0.026	20.59	1.25	27^0±0.126
F8	0.423±0.072	0.529±0.063	20.03	1.26	30^0±0.135

Post compression parameters

Table 4 summarizes and expresses the post compression parameters. A specific amount of mechanical strength is required for pharmaceutical tablets to endure the shocks of handling during manufacture, packaging, shipping, and dispensing. Friability is a measure of a tablet's ability to endure both shock and vibration. The physicochemical properties of the granules can influence several aspects of tablet quality, including compressibility, dosing accuracy,

Journal of Chemical Health Risks

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JCHR (2024) 14(1), 2655-2660 | ISSN:2251-6727

porosity, hardness, friability, capping propensity, disintegration, dissolving rate, and, ultimately, drug bioavailability in the body. The pharmacopoeial limit for friability is kept less than 1% so to avoid the above problems. Thickness of the tablets was uniform for all the formulations.[5]

Table 4. Physical properties of tablets (Postformulation Study)

Formulation No	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	200±0.43	4.86±0.48	5.22±0.85	0.45±0.004	91.85±0.43
F2	199±0.21	4.78±0.17	5.19±0.64	0.51±0.006	97.20±0.47
F3	200±0.47	4.59±0.50	5.25±0.75	0.48±0.006	96.22±0.36
F4	201±0.53	4.78±0.49	5.21±0.61	0.46±0.005	91.88±0.27
F5	200±0.36	4.56±0.53	5.19±0.79	0.43±0.006	93.89±0.57
F6	201±0.41	4.86±0.31	5.17±0.56	0.50±0.003	89.55±0.38
F7	200±0.36	4.75±0.26	5.20±0.61	0.51±0.005	92.55±0.37
F8	199±0.55	4.88±0.46	5.28±0.54	0.49±0.007	98.92±0.44

In-Vitro drug release study

In-vitro dissolution of all eight formulations were analyzed and among all the eight formulations F8 formulation showed the best dissolution property shown maximum drug release of 98.69% after 8 hours, 33.38% released drug after 2 h at gastric pH, and overcoming 65.31% released drug within the rest of time in intestinal fluid. This delayed release might have resulted for ratio and polymer used that give a proper sustain effect. The F8 batch was created with an HPMC-MCC polymeric matrix, which is one of the best matrices for a sustained release system.[11] **Fig 1** represents the effect of various polymers on the release of phenytoin from tablets.

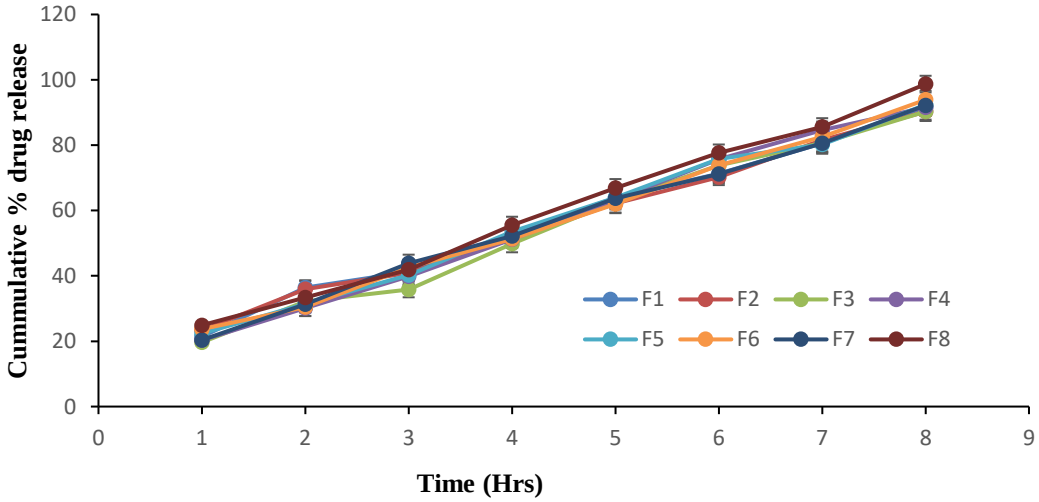

Fig 1: In-vitro drug release study of Phenytoin tablet [1st 2 hr in simulated gastric fluid (pH 1.2 & rest portion in simulated intestinal fluid (pH7.4)]

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Stability Study

Test parameters for the stability sample analysis should be specified in the stability test. a stability test that, after the storage is chosen, keeps an eye on the identity, capacity, purity, and performance. Thus, standard tests performed on test materials include the presentation, processing, material degradation, dissolution, humidity, and microbiological testing. Changes relevant to international research include extending the period of accelerated testing from 6 to 12 months and adding a 3-month 50°C/75% RH test. Furthermore, the interaction of three climatic variables—temperature, humidity, and light—indicates a more drastic impact on pharmaceuticals than what was shown when temperature and humidity levels were taken alone.

CONCLUSION

The goal of the current project was to create and assess phenytoin sodium sustained release matrix tablets employing a variety of polymers, including ethyl cellulose, microcrystalline cellulose, and HPMC k15M and k4M. Before being punched into tablets during the pre-formulation stages, powders were evaluated for Hausner proportion, bulk thickness, tapped thickness, and compressibility file. The tablets' physical attributes were evaluated, with a focus on giving F8 a decent level of hardness. While the drug-to-polymer ratio of 1:1 in HPMC k15 and HPMC k4M allowed for the greatest control of phenytoin release for up to 8 hours. The best dissolving performance was demonstrated by the F8 drug release formulation used in vitro. The drug was released from F8 at 98.69% after 8 hours and passed the stability study. The stability study also confirms that the drug was stable in all polymer ratio.

ACKNOWLEDGEMENT

The authors would like to thank Centurion University of Technology and Management in Odisha, India, for supporting this research.

CONFLICT OF INTEREST

There is no conflict of interest.

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