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Sustained Release Carbamezapine Matrix Tablets Prepared by Solvent-Evaporation Technique Using Different Polymers

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Abstract: Various formulations of sustained-release matrix tablets of carbamazepine was prepared and evaluated. Tablets were prepared by solvent evaporation method using hydroxy propyl methyl cellulose (HPMC), carboxy methyl cellulose (CMC) and polyvinylpyrrolidon-K90 (PVP-K90), the hydrophilic polymers are used as release sustaining materials. Formulations were designed using drug to polymers ratio 1:1, 1:1.5, 1:2 with a view to develop twice daily sustained release dosage form. Physical properties of co-evaporates and tablets were evaluated. *In vitro* drug release of the tablets was studied using USP dissolution apparatus I. Drug release data obtained was evaluated by applying various mathematical orders and models to know the release pattern and mechanism of drug release from the matrix tablets. 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 · Solvent-Evaporatin Method · Carbamazepine Tablets

INTRODUCTION

Epilepsy is characterized by sudden and transitory abnormal phenomenon, which may cause alterations of consciousness, motor, sensory, autonomic or psychic events that can be convulsive or non convulsive [1]. About 50 million people worldwide are suffering from epilepsy, 90% of which belongs to underdeveloped countries [2].

Carbamazepine (a benzodiazepine derivative) is the drug of choice for epilepsy, which is used alone or in combination with other medications to control certain types of seizures. It is also used to treat trigeminal neuralgia. To reduce the dose frequency of chronic carbamazepine therapy and to decrease variability in plasma concentration, various extended release formulations have been developed [3].

The hydrophilic matrix polymers and gums on contact with aqueous medium swell and form a gel layer on the surface of the system from that controlled the release of the drug. As such, hydrophilic matrices dominate today's market of oral controlled release products [4-5]. Hydroxy propyl methylcellulose (HPMC) is the most commonly used hydrophilic polymer. The hydrophilic polymers and gums like hydroxypropyl methylcellulose (HPMC), carbox ymethyl cellulose (CMC), poly vinyl pyrolidone (PVP), hydroxy propyl cellulose (HPC), hydroxy ethyl cellulose (HEC), xanthan gum (XG) and guar gum (GG), have been extensively used in the formulation of sustained release systems [6-7]. The broad acceptance, cost effectiveness, nontoxic properties, ease of handling, ease of compression, ability to accommodate a large percent of drug, negligible influence of the processing variables on drug release rates and relatively simple tablet manufacturing technology make these excellent carrier materials for oral matrix tablets [8]. The present study was aimed to investigate the sustaining effect of various polymers like (HPMC,CMC and PVP) using Carbamazepine as a model drug.

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MATERIALS AND METHODS

Carbamazepine powder (Rensin Chemicals Ltd., Nanjing, China,) was a kind gift from Usawa Phartmaceuticals Pvt. Ltd., Resalpure, Pakistan, Poly vinyl pyrolidone (PVP-K90) (BASF, Ludwigshafan,Germany), hydroxy 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 sterate (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), Carbamazepine commercial tablets tablet Epitab XR® (Werrick Pvt. Ltd. Islamabad, 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) was used in this study.

Preparation of Co-Evaporates: Drug was dissolved in an organic solvent isopropyl alcohol using EZ Stirrer according to the formulations as shown in Table 1. The Polymers were dissolved in distilled water which produced clear slurry. 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 Rotary evaporator (Heidolph, Germany) and the solvent was recovered. The recovered solvent was used for next batch. The solid dispersion so obtained was dried at 60°C in oven for 24 hours [9]. The dried material obtained was passed through mesh #. 12, then talc and magnesium sterate were added as glident and lubricant respectively, lactose was added as diluent and mixed in lab scale mixer for 5 minutes. The co-evaporates 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 co-evaporates using 12.0 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 [10-11].

Tablet Characterization: Tablets were characterized and evaluated for thickness, hardness, weight variation, friability and drug content [12].

In vitro drug release using the USP 32 dissolution apparatus-I specifications [12] were applied.

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

Table 1: Composition of 200 mg Carbamazepine Matrices tablets formulations.

	Formulations								
Ingredients	H1ce	H2ce	H3 ce	C1ce	C2ce	C3ce	P1ce	P2ce	P3ce
HPMC (mg)	200	300	400	-	-	-	-	-	-
CMC (mg)	-	-	-	200	300	400	-	-	-
PVP K90 (mg)	-	-	-	-	-	-	200	300	400
Lactose (mg)	230.5	130.5	30.5	230.5	130.5	30.5	230.5	130.5	30.5

H=Hydroxy propyl methylcellulose K100M, C= Carboxy methyl cellulose, P = Poly vinyl pyrolidone -K90, 1, 2 and 3 indicates drug to polymer ratio 1, 1.5 and 2, respectively. Magnesium sterate 1.0% and Talcum 2.0% was used as a lubricant in all formulations, while ce stands for co-evaporates.

RESULTS AND DISCUSSION

The co-evaporates 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.

The process of co-evaporates play an important role in the formulation of the sustained release dosage form as it affect the release of the drug from matrix tablets. Various physical parameters of co-evaporates or granules can significantly affect the release rate of dissolution of drugs from the dosage form [13, 14]. For all these reasons the evaluation of co-evaporates are very essential before compression into tablets. As it was observed from the results obtained by performing various tests that the values for all the parameters like angle of repose, compressibility index, loose bulk density and taped bulk density were increased with the increase in concentration of the polymers. This may be due to the binding forces that increase with the increase in concentration of the polymer and causes the production of dense, spherical and small size co-evaporates. Therefore from the results obtained from various tests that all the parameters were in the official range, so, it reflected that co-evaporates having excellent flow characteristics, compressibility and drug content [15].

The tablets were also evaluated for various physicochemical properties; the results for the parameters are shown in the Table 2. A direct relationship between the concentration of polymers and the hardness of the tablets was seen in all the formulations, that with the increase in concentration of polymers the hardness of the tablets was increased Table 2, that cause to increase the release rate of the drug. Statistically the hardness of the test formulation for HPMC group was not significant $P > 0.05$, while for the CMC and PVP-K90 groups of formulations it was found to be highly significant $P > 0.005$. The % friability of tablets was found to be less than 1 % for all the formulations showing that it was in the official range and statistically was to be significant for the formulation H1ce, H2ce, C1ce, C2ce and PVP-K90 group of formulations $P > 0.005$, while for formulation H3ce and C3ce it was not significant $P > 0.05$ from the reference formulation. Tablets of all the batches showed even thickness and statistically it was found to be not significant with $P > 0.05$. The Pharmacopoeial limit for tablets having weight more than 250 mg, ± 5% deviation from the mean weight is acceptable. The test for weight variation indicated that all the tablets were in the range of pharmacopoeia. As the results revealed, that the average weight deviation percentage of 20 tablets selected from each batch was less than ± 5% and all the formulations fulfill the requirement and also statistically was observed significant from the reference formulation $P > 0.005$. The % of drug content was also found in the acceptable range of pharmacopoeia showing good uniformity of drug content in all the formulations. From the result it was observed that all the matrix tablet formulations revealed acceptable pharmacotechnical characteristics i.e. weight variation, hardness, friability and drug content [16, 17].

Drug Release Study: The drug dissolution profile for all polymers (HPMC, CMC and PVP-K90 groups) of formulations of carbamazepine sustained release matrix tablets were shown in Figure 1-3 respectively. Tablets of formulations H1ce, H2ce and H3ce released 55.37 %, 46.07 % and 40.12 % of carbamazepine at the end of 3 hours, 87.05 %, 78.20 % and 62.58 % of drug at the end of 6 hours, respectively, 98.80 %, 98.69 % and 78.04 % at the end of 8 hours, respectively, while the formulation H3ce extend the release of the drug up to 12 hours that it release 97.70 % of the drug at the end of 12 hours.

Table 2: Physical properties of granules and Matrix Tablets prepared by Wet-Granulation Method using CMC, HPMC and PVP K 90.

Formulations	Angle of Repose	Lose bulk density (g/ml)	Taped bulk density (g/ml)	Compressibility Index (%)	Drug Content of granules (%)	Thickness (mm) Mean± SD	Weight(mg) Mean ±SD	Friability (%)	Hardness (N) Mean ±SD	Drug content of tablets (%) Mean ± SD
H1ce	24.36±0.04	0.313±0.04	0.362±0.03	15.76 ± 0.04	98.61±0.03	5.20± 0.04	650.60±3.03	0.68± 0.02	71.55±4.16	99.76 ± 0.05
H2ce	24.97±0.03	0.322±0.03	0.374±0.03	16.59 ± 0.04	98.94±0.05	5.20± 0.04	650.65±3.00	0.62± 0.01	72.65±4.03	98.56 ± 0.06
H3ce	25.26±0.04	0.333±0.03	0.382±0.05	16.64 ± 0.04	98.22±0.02	5.20± 0.04	650.80±2.84	0.52 ± 0.08	74.35±3.04	97.89 ± 0.05
C1ce	24.19 ± 0.04	0.292 ± 0.02	0.346 ± 0.05	15.65 ± 0.04	98.56 ± 0.05	5.20 ± 0.04	650.70 ± 2.97	0.62 ± 0.02	68.70 ± 4.35	98.88 ± 0.04
C2ce	26.93± 0.05	0.306 ± 0.04	0.354 ± 0.03	16.23 ± 0.02	98.24 ± 0.03	5.19 ± 0.04	650.60 ± 2.07	0.58 ± 0.03	70.35 ± 4.34	98.94 ± 0.04
C3ce	27.63 ± 0.04	0.316 ± 0.02	0.362 ± 0.04	17.54 ± 0.03	98.21 ± 0.02	5.20 ± 0.04	650.60 ± 2.07	0.42 ± 0.02	72.70 ± 3.16	98.67 ± 0.03
P1ce	25.19 ± 0.05	0.292 ± 0.04	0.339 ± 0.03	15.55 ± 0.04	98.56 ± 0.05	5.20 ± 0.05	650.70 ± 2.73	0.72 ± 0.02	67.20 ± 4.00	98.57± 0.04
P2ce	26.93± 0.05	0.301 ± 0.02	0.352 ± 0.05	15.73 ± 0.02	98.34 ± 0.03	5.20 ± 0.05	651.05 ± 2.96	0.66 ± 0.02	68.55 ± 4.24	99.68± 0.04
P3ce	28.56 ± 0.03	0.312 ± 0.02	0.362 ± 0.04	16.44 ± 0.03	98.91 ± 0.02	5.21 ± 0.05	650.80 ± 2.84	0.57 ± 0.02	71.20 ± 2.52	98.56± 0.03

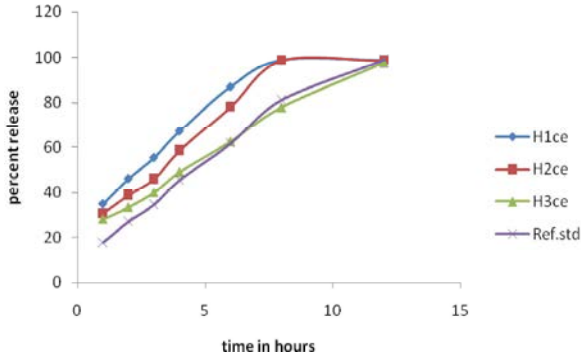

Fig. 1: Cumulative (mean ± SD) % of carbamazepine released from SR matrix tablets using different amount of HPMC K100 M (n = 3)

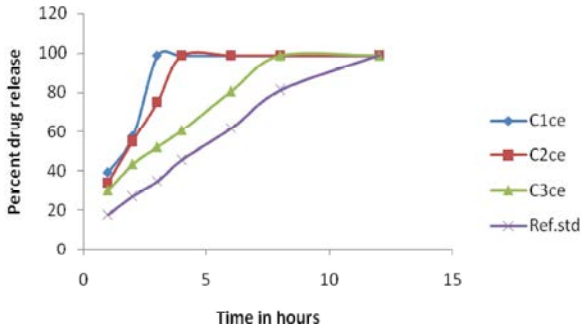

Fig. 2: Cumulative (mean ± SD) % of carbamazepine released from SR matrix tablets using different amount of CMC (n = 3)

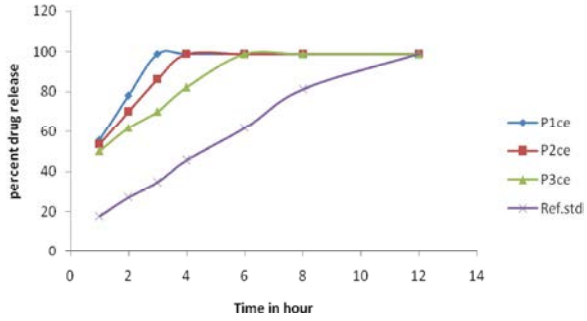

Fig. 3: Cumulative (mean ± SD) % of Carbamazepine released from SR matrix tablets using different amount of PVP- K90 (n = 3)

In case of CMC group of the tablets of formulations C1ce i.e. drug to polymers ratios (1:1) extend the release of the drug up to three hours, while formulations C2ce drug to polymers ratios (1:1.5) up to four hours and the formulations C3ce drug to polymers ratios (1:2) prolonged the release up to eight hours. While the PVP group of formulations P1ce i.e. drug to polymers ratios (1:1) prolonged the release of the drug up to three hours, while formulations P2ce drug to polymers ratios (1:1.5) up to four hours and the formulations P3ce drug to polymers ratios (1:2) up to six hours.

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 carbamazepine formulation of USP specification [12]. As it was evident from the study that as the concentration of the polymers was increase in the formulations the rate of release was become decreased, it was may be due to the poor solubility of carbamazepine in dissolution medium and may also be increase in the viscosity of the gel layer. However the overall release of carbamazepine was decreased.

Although CMC and HPMC have the same viscosity values but the release rate of CMC was high than HPMC, the reason for this may be due to the high solubility of CMC and the polymer characteristic gives to the matrix a quick gel erosion rate which could be due to the disintegrating property along with swellability. However, processing factors including wetting on granulation, particle size and hardness also affect the release rate of drug from tablets [18-19]. Beside of this PVP is a water soluble polymer and on exposure to water it become disintegrated and unable to form a gel like structure which is necessary for sustaining the drug from the matrix tablets. This fast release of drug from dosage was also investigated in the previous literature [18-19] PVP- K90 is a good binder and employed in various types of tablets formulations but not a good sustaining polymer for the matrix tablet. The release rate of a drug from the matrix tablet formulation having hydrophilic polymers usually involves factors of diffusion, which is associated to carry the drug from the matrix into the dissolution medium depending on the concentration. As gradient varies, the drug is released and the distance for diffusion of drug becomes increases [18].

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 3.

By putting the data of HPMC group of formulation to these models the kinetic data reflected that release profile of formulation H1ce showed r^2 value of 0.9947 for Hixson Crowell model revealed that it follows this model but as there was no significant differences in the r^2 value for zero order kinetics and Hixson Crowell model as shown in Table 3, so it may be concluded that

Table 3: *In-vitro* release kinetics (analyzed by regression coefficient method) of Carbamazepine from different batches of HPMC, CMC and PVP-K90 matrix tablets.

	Zero order	First order	Higuchi	Hixson Crowell	Korsmeyer		
Formulation	r^2	r^2	r^2	r^2	r^2	N	Release mechanism
H1ce	0.9865	0.9605	0.9736	0.9947	0.9946	0.5701	non-Fickian
H2ce	0.9930	0.9845	0.9569	0.8801	0.9601	0.5559	non-Fickian
H3ce	0.9924	0.9465	0.9810	0.9618	0.9688	0.5250	non-Fickian
C1ce	0.8932	0.8998	0.9100	0.8566	0.9419	0.7289	non-Fickian
C2ce	0.9988	0.9813	0.9843	0.8979	0.9958	0.7559	non-Fickian
C3ce	0.9975	0.9511	0.9871	0.9238	0.9922	0.5653	non-Fickian
P1ce	0.9996	0.9749	0.9969	0.9406	0.9999	0.9370	non-Fickian
P2ce	0.9679	0.9596	0.9741	0.9519	0.9665	0.7584	non-Fickian
P3ce	0.9544	0.8974	0.9794	0.9838	0.9814	0.6490	non-Fickian

this formulation follow zero order kinetic. Similarly formulations H2ce and H3ce having high regression co efficient values r^2 = 0.9930 and 0.9924 for zero order equation respectively, indicating that release of drug follows zero order kinetic. Furthermore Korsmeyer equation resulted into the value of n range from 0.5250-0.5701 for all the formulations, which is greater than 0.45, showing that the drug release non-Fickian called anomalous pattern of drug release. When n is approximate to 0.5, a Fickian/diffusion controlled release is implied, where 0.5<n. It was observed during the dissolution studies that the matrix tablets undergo swelling and erosion which indicated that polymer relaxation had a great role in the release mechanism of drug. However, it may be concluded that the effect of diffusion on drug release was greater than the effect of polymer relaxation as the values of n were nearer to 0.5 [20, 21].

While in case of CMC group of formulations it was observed that formulation C1ce has high value of r^2 =0.9100 for Higuchi model showing that it followed this model, while formulations C2ce and C3ce having high regression co efficient values r^2 = 0.9988 and 0.9975 for zero order kinetic, respectively, indicating that release of drug from these formulations follows zero order kinetic. By applying Korsmeyer equation the result obtained revealed that the value of n range from 0.5653-0.7559, for all formulations, which is greater than 0.45, showing that the drug release was, followed Non- Fickian mechanism so called anomalous release.

Similarly the dissolution release rate kinetic data for the formulations containing PVP-K90 as sustaining agent for various models is shown in Table 3. Drug release data of matrix tablets of formulation P1ce showed good fit into the zero order equation (r^2 = 0.9996) while P2ce showed high linearity with Higuchi equation (r^2 = 0.9741).

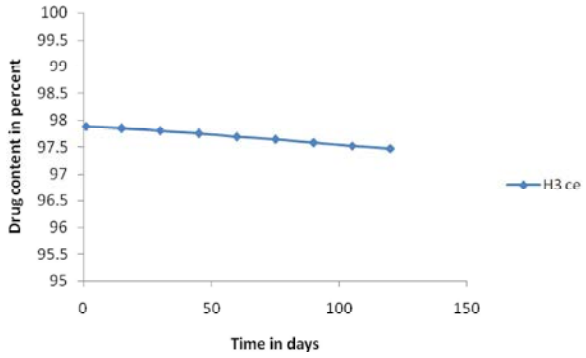

Fig. 4: Effect (mean ± SD) of storage temperatures on the assay of carbamazepine from HPMC (H3ce) matrix tablets (n=3)

However, this models fail to explain the mechanism of drug release by means of swelling (upon hydration) along with slowly erosion of the tablets, while formulation P3ce indicate that it follow Hixson Crowell model (r^2 = 0.9838) but as this model is applicable only to uniform particles and is based upon the assumption that the release of the drug can occurs only in the vertical direction relative to the surface of the matrix tablets. Therefore in case of PVP-K90 the applicability of this model is impossible because of high solubility of this polymer in water due to which it cannot maintain its shape. Thereof to know the exact mechanism the data was treated according to the Korsmeyer equation and then from the (n) values the mechanism can be determined, as the n values for all formulations ranged from 0.6490 to 0.9370, showing that the release from all these formulations were non-Fickian.

Stability Studies: The optimized formulation (H3ce) was subjected to accelerated stability studies in order to verify the changes in physiochemical properties of

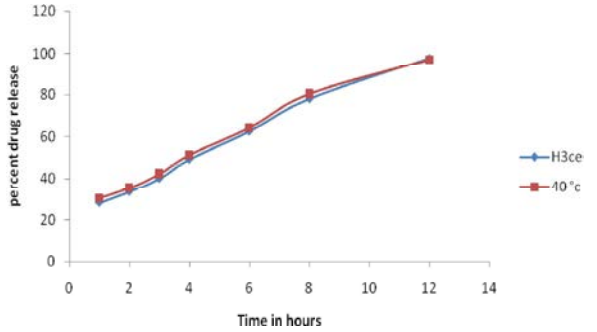

Fig. 5: Effect (mean ± SD) of storage temperatures on the release of carbamazepine from HPMC (H3ce) matrix tablets (n=3)

the formulation at 40 ± 2°C temperatures and 75 ± 5 % relative humidity. But it was observed that there were no significant changes in the properties like hardness, friability, thickness and weight variation. The drug content before storage was 97.89 %, while after 4 months duration it was 97.47 % as depicted in Figure 4. The dissolution profiles studies also showed no significant differences after storage for 4 months as depicted in Figure 5. So it was reflected from the aforementioned discussion, that HPMC can be used as an effective polymer for the preparation of matrix tablets, to extend the release of carbamazepine for prolong period of time [22]. So this suggests that the HPMC K100 matrix formulations have the ability 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 carbamazepine 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 carbamazepine 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 is stable in HPMC based matrix tablets. So HPMC was selected the best polymer to formulate the sustained release formulation of carbamazepine for 12 hours.

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