RESEARCH ARTICLE

HPMC Extended-Release Multi-Composite Matrix for Co-delivery of Oxcarbamazepine and Vitamin D

Sarah K Amer[1], Walaa Alaa[2], AG Eshra[3]

[1]*Department of Pharmaceutics, Division of Pharmaceutical Sciences, College of Pharmacy, Arab Academy for Science, Technology and Maritime Transport, Alexandria, Egypt.*
[2]*College of Pharmacy, Arab Academy for Science, Technology and Maritime Transport, Alexandria, Egypt.*
[3]*Department of Pharmaceutics, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt.*

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ABSTRACT

Background: Carbamazepine (CBZ) is considered as first-line treatment for epilepsy. The literature has signified a history of non-uniform drug performance and clinical failures. However, many studies suggested that Oxcarbazepine (OXC), a structural analog of CBZ, may have an equivalent antiepileptic effect. OXC follows a different metabolic pathway other than CBZ. However, both share the same mechanism of action by blocking voltage-gated sodium channels.

Objectives: This study aimed to form hydroxypropyl methylcellulose (HPMC) extended-release tablets containing OXC combined with vitamin D.

Methods: These formulated tablets were tested for their dissolution rate, tablet hardness, friability, thickness and pharmacokinetic parameters (Cmax and Cmin). Blood sodium levels were additionally investigated to ensure the absence of hyponatremia; the main side effect of long-term use of CBZ and some of its derivatives.

Results: The use of HPMC inhibited the formation of dihydrate OXC form thus offering a significant extended-release profile. OXC also showed a highlighted capability to attain high bioavailability. Microcrystalline cellulose (MCC) was also added to tablets formed to inhibit polymorphic transformation. Tablets containing OXC co-delivered with vitamin D ensured significantly decreased susceptibility to hyponatremia, and an extended-release profile was evident. Lower amounts of OXC were loaded in formed tablets containing vitamin D owing to the synergistic effect between vitamin D and antiepileptic drugs.

Conclusion: Conclusively, employing these newly HPMC-constructed tablets of OXC co-delivered with vitamin D appeared to be a promising option for the effective management of epilepsy with least side effects.

Keywords: Oxcarbamazepine, Extended-release tablets, Epilepsy, Vitamin D, Hyponatremia.

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INTRODUCTION

Epilepsy is identified by the World Health Organization (WHO) as a major public health issue owing to its high rates of morbidity and mortality. It is defined as a neurological disorder marked by two or more unprovoked seizures occurring more than 24 hours apart or a single seizure with a high chance of recurrence. Epidemiological studies show high prevalence rates of epilepsy in Arab countries, including Egypt, Saudi Arabia, and Lebanon.[1] Carbamazepine (CBZ) is widely used as a first-line antiepileptic drug (AED) for managing epilepsy. However, traditional CBZ formulations often fail to achieve optimal systemic delivery and are linked to significant side effects and clinical failures.[2]

Oxcarbazepine (OXC), a structural analogue of CBZ, has shown antiepileptic efficacy with similar mechanisms of action and clinical advantages, including a lower side effect profile.[3] Upon administration, OXC is rapidly converted by hepatic enzymes to its active monohydroxy derivative (MHD), leading to a lower enzyme induction profile and fewer drug interactions.[4] Hydroxypropyl methylcellulose (HPMC), a semi-synthetic cellulose polymer, is used in pharmaceutical formulations to create swellable extended-release dosage forms. HPMC quickly hydrates upon contact with water, forming a gelatinous barrier that prevents dose dumping and enhances drug loading.[5] Microcrystalline cellulose (MCC) is added to formulations to stabilize CBZ and its derivatives

**Author for Correspondence: sarah7_amer@hotmail.com*

like OXC. Studies show that MCC enhances stability, prevents polymorphic changes, and improves compaction and tableting properties. In addition, MCC's high crystallinity and small particle size reduce the risk of polymorphic transitions and enhance the wettability and deaggregation of particles.[6,7] Cholecalciferol, a precursor of active vitamin D, has shown anticonvulsant and neuroprotective properties in the brain. Studies are exploring its potential to work synergistically with existing antiepileptic drugs, particularly OXC. Vitamin D is crucial for the nervous system, regulating cell growth and differentiation. Deficiency in vitamin D may be linked to seasonal affective disorders, schizophrenia, and epilepsy, with reduced levels leading to neural hyperexcitability and severe convulsions. Vitamin D also helps regulate electrolyte balance, preventing hyponatremia, a common side effect of CBZ and its derivatives, including OXC. Integrating cholecalciferol into these formulations has not resulted in significant adverse effects, suggesting that HPMC multi-composite matrices co-delivering OXC and vitamin D could offer a promising pharmacotherapeutic strategy for epilepsy management.[8,9]

Aim of the Work

This study provides a new pharmaceutical formulation of HPMC multi-composite construct for extended release of OXC combined with vitamin D that would be of great influence on seizure control offering better therapeutic effects regarding the management of epilepsy.

MATERIALS AND METHODS

Materials

OXC powder was acquired from Sigma-Aldrich Co. LLC, Germany, and its identity was confirmed through melting point analysis, infrared (IR), and ultraviolet (UV) spectroscopy, showing no deviations from the reported standards. Tetrahydrofuran and HPMC K100M CR were also sourced from Sigma Aldrich, International Trade Pharmaceutical Chemicals Co. Other chemicals such as lactose, microcrystalline cellulose (MCC), silicon dioxide (SiO2), magnesium stearate, formic acid, triethylamine, sodium lauryl sulfate (SLS), acetone, and nitrogen were procured from Elgomhoria Pharmaceutical Chemicals Co. Methanol (HPLC-grade) was obtained from Merck, Germany. Distilled water, produced by the Distiller AC-L8 (Barcelona, Spain), was utilized for all experiments.

Tablet Manufacturing

OXC tablets were prepared by thoroughly blending 60 mg of OXC with 40 mg of HPMC, 60 mg of lactose, 38 mg of MCC, and 15 mcg of vitamin D. A polyvinylpyrrolidone (PVP) binder solution was then added to form a wet mass, which was subsequently sieved to produce granules and then dried. The dried granules were milled to ensure a uniform particle size. Afterward, 1-mg each of silicon dioxide and magnesium stearate were gently incorporated into the mixture. The final blend was compressed into tablets using a tablet press. Quality control assessments were conducted on the tablets, including evaluations of weight, uniformity, hardness, friability, and dissolution profile. The finished tablets were stored in containers designed to shield them from moisture and light.[10,11]

Tablet Quality Control Testing

High-performance liquid chromatography (HPLC) assay

An HPLC method was employed for the assay, content uniformity evaluation, and monitoring of dissolution rates. The HPLC system followed the guidelines specified in the USP 2019 monograph for OXC tablets. This system utilized a Spheri-Cyano column (250 x 4.6 mm) with a particle size of 5 µm. The mobile phase was a mixture of methanol, tetrahydrofuran, and water in a 12:3:85 ratio, supplemented with 0.22 mL of formic acid and 0.5 mL of triethylamine per liter. The standard preparation involved dissolving 10 mg of standard OXC in a 50 mL volumetric flask, followed by the addition of 20 mL of methanol, sonication for 10 minutes, and dilution to the final volume with methanol. A diluent of methanol and water in a 50:50 ratio was used. UV detection was performed at 230 nm, with a flow rate of 1.5 mL/min and an injection volume of 10 µL.[12]

Uniformity of content and assay (Potency)

Ten OXC tablets were selected at random, weighed, and finely ground using a mortar. The resulting powder was placed in a 100 mL volumetric flask, and 30 mL of methanol was added. The mixture was sonicated for 10 minutes to achieve complete dissolution. After sonication, the solution was brought to the 100 mL mark with methanol. A 5 mL portion of this solution was then transferred to a 50 mL volumetric flask and diluted to the final volume with the designated diluent.[12]

Dissolution rate testing

The dissolution rate was assessed using a dissolution test system (SR8-plus, HANSON Research Corporation, USA). The test was conducted in triplicate on three tablets, following the guidelines of USP 2019 and FDA regulations for dissolution apparatus (Apparatus II, with a rotating paddle at 75 rpm and a temperature of 37°C). The dissolution medium consisted of 900 mL of phosphate buffer at pH 6.8. Samples were collected at time intervals of 5, 10, 15, 30, 45, 60, and 90 minutes.[12]

Hardness

Following USP guidelines, the hardness test was conducted on 10 tablets using the DR.SCHLEUNIGER® Pharmatron AG Switzerland, Model SY Tablet Hardness Tester, version 4.22, USA. The average hardness value was then documented.[13]

Friability

The experiment was carried out using a COPLEY Friability Tester (FRV 2000, USA) with 100 drops applied over 4 minutes. In line with USP guidelines, each tablet had an approximate weight of 6.5 g. The initial weight of the tablets (Winitial) was accurately measured before placing them into the friability tester drum, which was set to rotate at 25 rpm for 4 minutes. After the test, the tablets were carefully removed, de-dusted, and reweighed to determine their final weight (Wfinal). The weight loss was calculated, and the percentage of friability (F)

was determined using the formula: F = (Winitial - Wfinal) / Winitial × 100.[13]

Thickness

The test was conducted on five randomly chosen tablets, with the average value being recorded. The thickness of each tablet was measured using a Vernier caliper, and the measurements were documented.[13]

In-vivo studies

Monitoring and laboratory tests (Diagnosis criteria)

The effectiveness of the extended-release OXC tablets was evaluated by tracking seizure frequency and measuring both OXC and sodium plasma levels throughout the study. Thirty Swiss albino mice were used, with seizures induced using the Pentylenetetrazol (PTZ) model. Fifteen mice were treated with the formulated OXC tablets, while the other fifteen received a placebo. Seizure frequency was recorded, and 100 µL blood samples were collected using sterile needles after the start of treatment. These samples were stored as plasma at -20°C until they were analyzed. The primary parameter monitored was the OXC plasma level, with samples taken at 1, 2, 3, 4, 6, 8, 12, and 24 hours after treatment. The secondary parameter monitored was sodium plasma levels, measured before PTZ induction as a baseline, after the PTZ procedure to evaluate potential electrolyte changes due to intense neuronal activity, and after treatment initiation to assess the impact of the formulated anticonvulsant on electrolyte balance.[13-15]

Analysis of blood samples

OXC plasma levels were determined using the OXC ELISA Plate kit from Eurofins Abraxis, Warminster, USA, conducted in the laboratory of the Medical Research Institute at Alexandria University. Sodium plasma levels were measured in the laboratory of the Main Alexandria University Hospital.

Statistical analysis

A two-way analysis of variance (ANOVA) was utilized to evaluate the differences in OXC plasma levels and sodium plasma levels. This approach was selected to identify any significant differences or interactions between the groups for the parameters being measured.

RESULTS

Inter-tablet variability of outer appearance and thickness of formulated OXC tablets

The formulated OXC tablets exhibited an oval shape with a smooth surface, which facilitates ease of administration and minimizes the risk of esophageal irritation. The tablets were characterized by a white color, as shown in Figure 1. The thickness measurements of the formulated OXC tablets, presented in Table 1, indicated no statistically significant differences ($p > 0.05$). The tablets maintained a consistent average thickness of 0.365 cm, with uniformity observed in the recorded values ($p > 0.05$).

Figure 1: Outer appearance of formulated OXC tablets

Table 1: Thickness values of formulated tablets

Tablet no.	T_1	T_2	T_3	T_4	T_5	*Mean value*	*p-value*
Thickness in cm	0.363	0.363	0.365	0.364	0.365	0.365	$p > 0.05$

Tablets Assay (potency) and Uniformity of Content

Figure 2 displays the assay (potency) results of the formulated OXC tablets, showing that all values met the USP 2019 acceptance criteria (92–108%). The tablets consistently demonstrated a mean potency of 101.72 ± 1.93, with no statistically significant differences observed among the mean potency values ($p > 0.05$). The uniformity of content, expressed as a percentage of the label claim, was also evaluated across various tablets and found to be in compliance with USP standards (92–108%), as shown in Figure 3. Assays of ten individual tablets revealed variability in content uniformity, ranging from 98.22 to 105.95%. However, this variation was not statistically significant ($p > 0.05$).

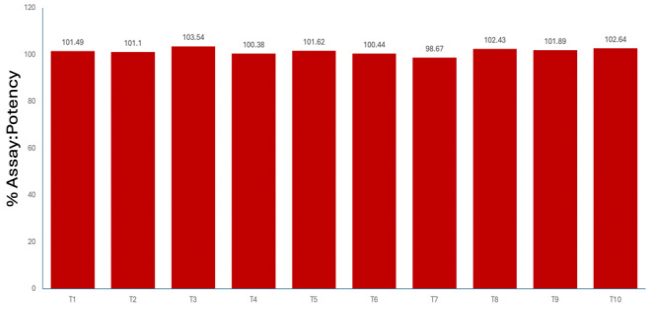

Figure 2: Variability in assay (potency) of ten individual randomly selected tablets determined according to the USP 2019

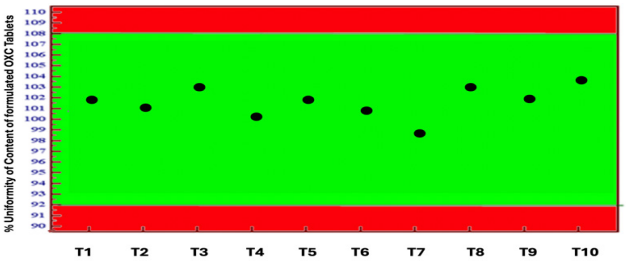

Figure 3: Intra-tablets variability in uniformity of content of randomly selected tablets determined according to the USP 2019. Acceptance range from 92–108% (Green area)

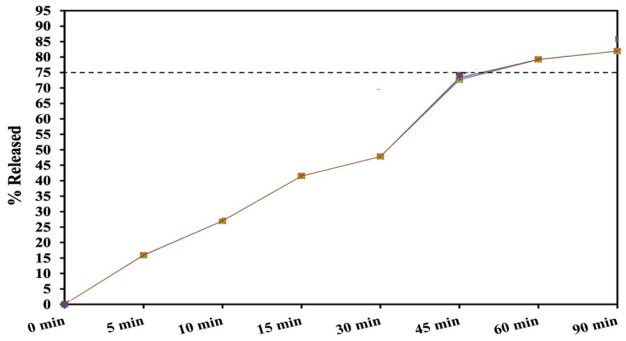

Figure 4: Mean dissolution profile of OXC tablets in phosphate buffer dissolution medium at 25°C and 45%RH (USP 2019)

Dissolution Profiles in Phosphate Buffer Dissolution Medium

The dissolution profile analysis of the formulated OXC tablets demonstrated an extended-release mechanism, marked by a slow initial drug release that gradually increased, reaching 75% within 45 minutes. Statistical analysis showed no significant differences in the dissolution behavior of the formulated OXC tablets, which was further supported by a high similarity factor (f2) value of 69.52. This high f2 value confirms the consistency in the dissolution profiles across all tested tablets, thereby validating the uniform extended-release properties, as depicted in Figure 4.

Tablet hardness and friability

Table 3 shows the hardness values for the formulated OXC tablets, where ten tablets were tested and displayed almost identical results, with no statistically significant differences ($p > 0.05$). However, tablet T6 exhibited capping during the hardness test, likely due to the polymorphic transformation of OXC in that specific tablet. Despite this, all tablets met the acceptance criteria, within the 4-10 Kp range, as specified by USP 2019. Additionally, Table 1 provides the friability results for the formulated OXC tablets, showing an average initial weight of 279.3 mg and an average friability of 0.330%. The friability values were consistent across all OXC tablets, with no statistically significant differences ($p > 0.05$). However, some tablets with higher initial weights indicated a greater tendency to absorb moisture, suggesting a potentially increased susceptibility to high temperature and humidity. Overall, all OXC tablets met the acceptance criteria, with friability percentages remaining below the USP 2019 limit of ≤ 1.5%.

Efficacy of Treatment

The study provided important insights into the pharmacokinetics of OXC, revealing a sustained release profile. This profile was marked by an initial minimum concentration (Cmin) within the first hour after administration, followed by a gradual increase, with peak plasma levels of OXC tablets reached at 8 hours. Therapeutic levels were consistently maintained up to 24 hours post-dosing. The highest peak plasma OXC concentrations recorded were 1.47 and 1.45 µg/100 µL. ANOVA analysis showed that the within-subject variations among Swiss albino mice treated with the formulated OXC tablets were not statistically significant ($p > 0.05$). Additionally, it was observed that mice receiving the placebo had a higher average seizure frequency compared to those treated with the formulated OXC tablets. Notably, no seizures occurred in the group receiving the OXC tablets, demonstrating effective seizure control. This difference was statistically significant according to ANOVA ($p < 0.05$).

Blood sodium level after administration of formulated OXC tablets

The blood sodium levels, as illustrated in Figure 6, were initially measured in all Swiss albino mice before the PTZ procedure to establish a baseline for tracking changes due to induced seizures and subsequent treatment with the formulated OXC tablets. To reduce potential confounding factors, only mice without pre-existing conditions known to affect blood sodium levels were included in the study. At the outset, all

Table 3: Hardness and friability values of formulated OXC tablets at 25°C/45 % RH

Tablet no.	*Hardness in Kp*	*Acceptance Range[a] 4-10 Kp*	*W_I in mg*	*W_F in mg*	*F in %*	*Accepted limit [b] Friability ≤ 1.5%*
T1	6.6	Accepted	278.00	278.08	0.333	Accepted
T2	7.0	Accepted	277.02	277.11	0.328	Accepted
T3	7.0	Accepted	276.01	276.09	0.331	Accepted
T4	7.5	Accepted	276.02	276.11	0.328	Accepted
T5	6.8	Accepted	278.00	278.08	0.334	Accepted
T6	5.8[c]	Accepted	280.63	280.73	0.329	Accepted
T7	7.0	Accepted	279.60	279.70	0.333	Accepted
T8	7.6	Accepted	278.62	278.72	0.331	Accepted
T9	6.6	Accepted	280.60	280.70	0.328	Accepted
T10	6.8	Accepted	279.61	279.72	0.334	Accepted
Mean	6.8	Accepted	278.41	278.50	0.330	Accepted
p-value	*p > 0.05*		*p > 0.05*			

[a]acceptance limit is determined according to the specifications of USP 2019, [b]acceptance limit is determined according to the specifications of USP 2019, [c]capping during hardness measurement test, W_I is the Initial weight, W_F is the Final weight, F is the Friability

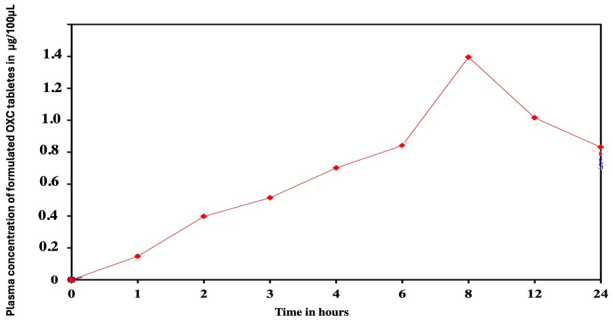

Figure 5: Time-Concentration graph of formulated OXC tablets post-treatment initiation

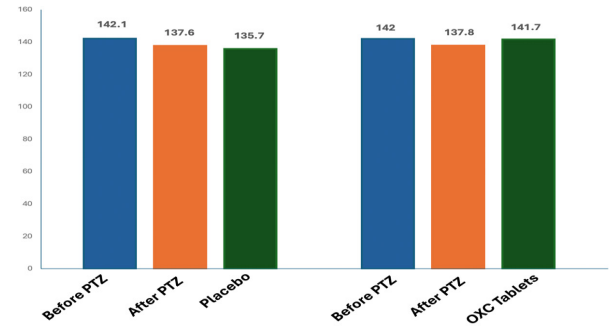

Figure 6: Blood Sodium level before and after PTZ model compared to treatment with Placebo and formulated OXC tablets

mice had normal blood sodium levels ranging from 135 to 145 mEq/L. After the PTZ procedure, some mice exhibited slight decreases in sodium levels to 136.6 mEq/L and 136.4 mEq/L ($p > 0.05$), while others showed borderline decreases of 135.5, 135.3, 135.4, and 135.0 mEq/L, which were relatively statistically significant ($p < 0.05$). However, mice treated with the formulated OXC tablets demonstrated a statistically significant normalization of blood sodium levels within the normal range of 135 to 145 mEq/L. In contrast, those receiving the placebo experienced a continued significant drop in sodium levels. This suggests that the addition of vitamin D in the formulation may contribute to stabilizing blood sodium levels and reducing the risk of hyponatremia. Moreover, all fifteen albino mice treated with the formulated OXC tablets maintained normal blood sodium levels throughout the study, indicating that the new formulation did not negatively impact electrolyte balance.

CONCLUSION

This study introduces a novel pharmaceutical formulation involving a HPMC multi-composite matrix designed for the extended release of OXC in conjunction with vitamin D. The results showed that this formulation has significant potential to enhance seizure control and improve therapeutic outcomes in the management of epilepsy by providing sustained drug release and incorporating the neuroprotective properties of vitamin D, this approach offers a promising advancement in epilepsy treatment.

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