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RESEARCH ARTICLE

Orally disintegrating tablet containing carbamazepine and levetiracetam: formulation and *in vitro* and *in vivo* characterization

Busra Kandilli[a], Afife Busra Ugur Kaplan[a], Meltem Cetin[a], Numan Taspınar[b], Sidika Genc[c], Yesim Yeni[c], Muhammed Sait Ertugrul[c,d], Ismail Cagri Aydin[c] and Ahmet Hacimuftuoglu[c]

[a]Department of Pharmaceutical Technology, Faculty of Pharmacy, Ataturk University, Erzurum, Turkey; [b]Department of Medical Pharmacology, Faculty of Medicine, Usak University, Usak, Turkey; [c]Department of Medical Pharmacology, Faculty of Medicine, Ataturk University, Erzurum, Turkey; [d]Department of Pharmacology, Faculty of Pharmacy, Agri Ibrahim Cecen University, Agri, Turkey

ABSTRACT

This study aimed to prepare and characterize the orally disintegrating tablet (ODT) formulations containing the combination of levetiracetam (LEV) and carbamazepine (CBZ) (CBZ + LEV combination) for the treatment of epilepsy. The ODT formulations were prepared using the lyophilization (L) and direct compression (DC) methods. The flowability of the mixed powders used for DC formulation was evaluated. The quality control tests for the ODTs were performed. Also, the antiepileptic effects of pure drugs, their combination, and the suspension of CBZ + LEV-DC-ODT formulation were evaluated in the rats with pentylenetetrazole (PTZ)-induced epilepsy model. The obtained results for the mixed powders of the DC formulation (angle of repose: 26.18 ± 0.794°; compressibility index: 15.24 ± 0.764%) suggest that the flow properties of the powder blend were suitable for the preparation of CBZ + LEV-ODT using DC method. The mean values of diameter and hardness of L-ODTs and DC-ODTs were found to be 16.87 mm and 16.18 mm and 11.96 N and 30.11 N, respectively. The friability of both formulations was <1%. Both formulations were disintegrated in seconds. Drugs in L-ODT had faster dissolution than those in DC-ODT. Compared to the seizure scores obtained for the groups treated with LEV or CBZ, generally, there was a higher decrease in seizure scores in the groups treated with CBZ + LEV combination or the suspension of CBZ + LEV-DC-ODTs. Consequently, the ODT formulations containing the CBZ + LEV combination might be beneficial in the treatment of epilepsy.

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Introduction

The tablets orally administered are very much preferred due to flexibility and compactness in manufacturing and also easy transporting and easy administration. But, especially pediatric and geriatric patients may have some problems such as difficulty in swallowing during the administration of an intact tablet. Several dosage forms (fast disintegrating tablets, chewing tablets, etc.) were developed to overcome these problems [1]. The orally disintegrating tablet (ODT) is a solid dosage form, which has the advantages of both solid and liquid dosage forms such as accurate dosing, good stability, easy manufacturing, convenient administration, enhanced patient compliance, quick drug dissolution, and fast drug absorption. Besides, the use of ODTs reduces the dose of the active substance and increases its bioavailability by causing the pregastric absorption of the active substance and reducing hepatic metabolism. It might be an important advantage for active substances that undergo a great deal of hepatic metabolism [2,3].

The United States Food and Drug Administration (FDA) has used the ODTs term for tablets which disintegrates rapidly (within seconds) when placed upon the tongue. However, the European Pharmacopoeia defined ODT as the tablets disperse in the mouth within 3 min before swallowing [3]. ODTs provide an alternative to overcome the swallowing problems of especially pediatric and geriatric patients; therefore, these tablets are widely accepted dosage forms for pediatric and geriatric, and psychiatric patients with dysphasia [2,4]. The most commonly used preparation methods for ODTs are direct compression (DC), lyophilization (L)/freeze-drying. L-ODTs show a very porous structure. The porous structure leads to quick penetration of saliva into ODTs in the mouth [1].

Epilepsy, which is characterized by recurrent seizures (two/more unprovoked seizures) and cognitive, social neurobiological, and psychological consequences, is the most common neurological disease. It affects about 50 million people of all ages worldwide. Also, an epileptic seizure occurs because of the temporary disturbance of electrical activity and abnormal/excessive stimulation of neuronal activity in the brain [5–7]. Unknown, generalized, focal, and also combined epilepsy (generalized and focal) are the types of epilepsy classified by 'the International League Against Epilepsy (ILAE)' in 2017 [5]. Epilepsy has significant economic implications in terms of premature death, health-care needs, and lost work productivity [7].

There are several treatment options for epilepsy such as the use of antiepileptic drugs (AEDs), ketogenic diet, surgery, vagus nerve stimulation, and chiropractic therapy [8,9]. AEDs such as carbamazepine (CBZ), lamotrigine, sodium valproate, and levetiracetam (LEV), have an important role in epilepsy treatment and help control the seizures in about 70% of epilepsy patients. However, nearly 30% of epilepsy patients are refractory to

CONTACT Meltem Cetin melcetin@hotmail.com; melcetin@atauni.edu.tr Department of Pharmaceutical Technology, Faculty of Pharmacy, Ataturk University, Erzurum, Turkey