Comparison of dissolution release of commercially available extended release carbamazepine tablets in Iraqi drug market using in vitro USP II method

Tara Abdulrahman Abdullah *   **Adnan Burhan Qader ***

Abstract

Background and objective: Carbamazepine is widely used as an anti-epileptic drug, primarily for the treatment of partial and tonic-clonic seizures. The drug is absorbed slowly and variably after oral administration due to its limited water solubility. In clinics, single daily dosing of conventional dosage forms of carbamazepine is insufficient; effective levels are provided by the multiple-dose administration. A multiplicity of dosage causes inconsistent plasma levels leading to side effects because of its narrow therapeutic range and toxicity levels. A single dose of extended release dosage forms is suggested to keep levels within the therapeutic concentrations. This study aimed to compare the in vitro behavior of generic tablets containing carbamazepine with the brand product.
Methods: Basket apparatus was used to evaluate in vitro behavior of the different products and similarity test was applied to evaluate the differences between generic products and the brand. The study and test were carried out in Jun 2014 at the College of Pharmacy, Hawler Medical University.
Results: There was a significant difference between the in vitro behavior of one of the generic products in the study and the in vitro behavior of the brand product.
Conclusions: The in vitro study using basket apparatus could be considered as an effective method to evaluate the in vitro behavior of the majority of pharmaceutical dosage forms. In vitro behavior is a direct indicator for in vivo one. Therefore the quality of the medicaments could be evaluated and the risk to the patients could be significantly reduced.
Keywords: Anti-epileptics; Carbamazepine E.R.; Dissolution rate; Brand product; Generic products.

Introduction

Carbamazepine was initially approved for use as an anti-seizure agent. It has been employed for the treatment of trigeminal neuralgia and is now considered a primary drug for the treatment of partial and tonic-clonic seizures.[1] Carbamazepine has also been used to treat various psychiatric disorders, including acute mania, bipolar disorder, and borderline personality disorder.[2,3] Furthermore, carbamazepine has been reported to be useful in the augmentation of antidepressant drug responses in treatment-resistant depression.[4] Carbamazepine is available for oral administration as chewable tablets 100 mg, immediate release tablets of 200 mg, extended release tablets of 200 and 400 mg and as a suspension of 100 mg/5 ml.[5] The conventional immediate-release forms of carbamazepine require frequent (three or four times daily) dosing, and there are reports of considerable variability in carbamazepine drug levels in the blood. Both of these issues are problematic.[6-8] Extended release formulations of carbamazepine have been introduced into drug therapy with a twofold purpose: to reduce the number of single doses during the day, and to decrease the fluctuation of serum levels in view to obtain better therapeutic efficacy and diminished toxicity.[9] Controlled–release formulations

* Department of Pharmaceutics, College of Pharmacy, Hawler Medical University, Erbil, Iraq.

have been one of the primary focuses in pharmaceutics.[10] Most anticonvulsants must be taken several times a day because of short half-lives and narrow therapeutic indices. This frequency of administra-tion results in decreased compliance and increased fluctuations in plasma concentrations of the anticonvulsant. Large fluctuations in plasma concen-tration place patients at risk of subtherapeutic and/ or toxic concentrations of their medication (s), leading to an increase in seizures in-cluding status epileptics and/or adverse effects. Extended release formulations would re-duce dose frequency and minimize fluctuations in plasma drug concentrations, resulting in fewer peaks to trough fluctuations. This should decrease adverse effects and seizure frequency, and may allow for a higher total daily dose of medication. There-fore, extended release medications can offer many advantages for patients with epilepsy.[11] Extended release formulations are dosage forms designed to reduce the number of times per day that the drug needs to be administered with the aim of maintaining a constant blood concentration extended release technolo-gies include depot injection, topical patches, and controlled- or sustained-release formu-lations for oral drug administration.[11] In vitro testing is still the main step in studying the drug dosage form behavior before proceeding to in vivo tests. It becomes highly important when an innovative drug dosage form has to be investigated in human volunteers before the validation and in this stage, a high reliable in vitro method for forecasting in vivo performance is strongly recommended.[11] Several methods are available and described in different pharmacopoeia for conducting in vitro test, USP II and IV are considered as the methods widely used in the field of pharmaceutical research. USP II is not expensive for conducting in vitro dissolution and it is highly used in the control of pharmaceutical products.[12] In vitro dissolution test is the most common method for the evaluation of extended release dosage forms and to predict their behavior in vivo.[11] This study aimed to evaluate the behavior of three generic products of extended release tablets containing 200 mg carbamazepine with the brand product using USP II method and Similarity test f1f2 was used to compare between the behaviors of each generic product with the branded product.[11]

Methods

This study was performed in the Department of Pharmaceutics, Collage of Pharmacy, Hawler Medical University in the academic year 2014-2015.

Drug dosage form

Carbamazepine is largely used as an antiepileptic. It is commercially available in different formulations. Three brands of carbamazepine that are available in Iraqi markets were chosen as models for this study as shown in Table 1.

Table 1: Three brands of carbamazepine 200 mg extended release tablets.

Product name	Manufacturer	Manuf. Date	Exp. Date	Batch No.
Tegretol ® CR200mg (RF)	Novartis Pharma S.p.A., Torre Annunziata, Italy	06/ 2013	05/ 2016	T1450
Tegretol ® CR200mg (T1)	Novartis , Kurtkoy-Istanbul	02/ 2013	02/ 2016	K0091
Carbamazepine ARISTO® (T2)	Advance Pharma GmbH, Berlin, Germany	08/ 2013	08/ 2016	14605633

Weight variation test:
Regarding USP, twenty tablets are weighed using sensitive balance individually and a compendia weight is taken. The average weight is obtained by dividing the compendia weight by 20. Then, the average weight was compared to the individual weight of tablet.[13]

Hardness Test:
Hardness indicates the ability of a tablet to withstand mechanical strength while handling. Measuring the force required to break the tablet across tests the force is measured in kg/cm by using hardness tester (handheld, digital hardness tester, pharma test, Germany).[13]

Friability Test:
Roche friabilator was used. This is made up of a plastic drum fixed with a machine, which rotated at 25 rpm for 100revolutions. During each revolution, the tablets fall from a distance of six inches to undergo shock. Then the twenty tablets fall from a distance of six inches to undergo shock. Then, the twenty tablets, which were weighed prior to the test, were taken out of the drum and cleaned with a cloth and weighed once again (Pharma Test, PTB, Germany).[13]

Paddle (USP apparatus II) method
The dissolution characteristics were studied using a paddle apparatus (ERWEKA) based on a method described in the USP (XXVI edition). The dissolution medium was 900 ml in volume, maintained at 37.0 ± 0.5 C°. A rotation speed of 60 rpm was used. Samples of 3 ml were withdrawn from the dissolution medium at appropriate time intervals and filtered through a membrane filter (pore size 0.45 µm). Each experiment was carried out using six tablets. The samples were appropriately diluted in a fresh quantity of the dissolution medium. The absorbance was measured by a spectrophotometer (SHIMADZU UV-160A) at 288 nm. The experiment was carried out in a phosphate buffer medium at pH= 5.8 and repeated at pH= 1.3. The dissolution media were prepared according to the USP method.[13]

Results

Physical characteristics
Weight Variation
The results are given in Table 2. The weights of the tablets of different commercial brands were within the acceptance limits.
Hardness Test
The results are shown in Table 2, which show that hardness was satisfactory for all commercial carbamazepine brands.
Friability Test
All brands were within the allowed friability limit as shown in Table 2.

Paddle (USP apparatus II) method:
Figure1 shows the percentage of carbamazepine dissolved and released after 24 hr from RF, T1 and T2 which is equal to 100.8%, 91.7% and 61.1%, respectively. The variability between the dissolutions profiles of the six tablets studied for each experiment was within the accepted limits (±10%).

Table 2: Physical parameters of the different dosage forms used in the study.

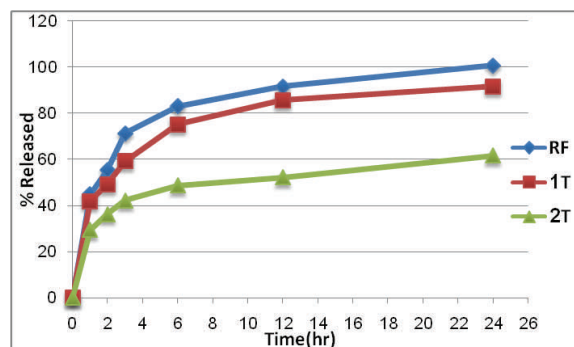| Product name	Mean of weight	Hardness	Friability%
(RF)	306 ±1	7.8 ± 1.11	0.012
(T1)	301 ±2.1	7.1 ± 1.36	0.08
(T2)	299.7 ±.2.3	6.8 ± 1.87	0.13

Figure1: Percentage dissolved and released of carbamazepine from the reference product (**RF**), **T1** and **T2**.

Similarity Factor (f2)[14,15]

As the name specifies, it stresses on the comparison of the closeness of two comparative formulations. Generally, similarity factor in the range of 50-100 is acceptable according to US FDA. It can be computed using the formula:

f2= 50xlog {[1+ (1/n) S t=1n (Rt-Tt) 2] -0.5 x100}....(1)

where, n is the number of dissolution sample times,
Rt and Tt are the individual or mean percent dissolved at each time point, t,

for the reference and test dissolution profiles, respectively. Similarity factor of 50 -100 ensures sameness of two products.

Difference Factor (f1)[14,15]

Difference factor focuses on the difference in percent dissolved between reference and test at various time intervals. It can be mathematically computed by using:

f1= {[S t=1n |Rt-Tt|] / [S t=1n Rt]} x100................(2)

Difference factor of 0-15 ensures minor difference between two products.

Table 3: The results of F1 and F2 for T1versus RF, and F1 and F2 for T2 versus RF.

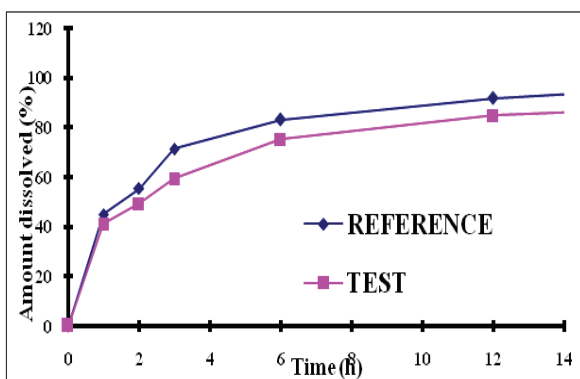| Time (h)	T1 versus RF		T2 versus RF	
	F1 %	F 2%	F1%	F2%
1	8.9	76.1	34.2	48.0
2	9.9	68.4	34.3	42.4
3	12.9	57.2	37.0	35.9
6	11.8	56.7	38.5	31.9
12	10.6	56.9	39.7	28.8
24	10.4	55.6	39.7	26.9

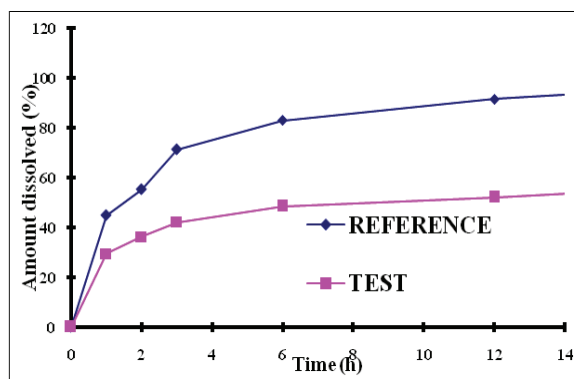**Figure 4:** F1 and F2 between T1 with the reference one RF

Figure 5: F1 and F2 between T2 with the reference one RF

Discussion

Weight variation of (RF, T1 and T2) is within the normal range according to the USP.[13] The weight of each individual tablet should be within the allowed percentage limit (7.5%) of the average weight (if the average weight is between 130 and 324 mg). Hardness of all the brands was within the accepted limits. High values of hardness could delay disintegration and dissolution. Conversely, hardness should not be so low that tablets are soft and friable.[13] In terms of friability, the values were within the accepted limits 0.5–1%.[16] The dissolution profile of T1 is compared to the reference product; difference factor f1 is equal to 7.8%, which is less than 10%. This result means that there is no difference between the test product and the reference one. At the same time, similarity factor F2 equal to 69%, which is more than 50% and this means that the two products are similar. The application of similarity test between the dissolution profile of T2 and the reference one RF showed a significant difference between the two products: f1 equal to 29.6% which is more than 10% and f2 equal to 35.6% which is less than 50%. Between two generic products, there is one product, which is not similar to the branded product, and the consequence of this difference is of high risk to the patient. Dissolution test, which is a simple test could be applied to all dosage form to investigate the similarity between the generic and brand one.

Conclusions

This study demonstrated the similarity between two generic products and the brand product for the same drug carbamazepine. This procedure is very simple to be applied to the different dosage forms available in Iraqi markets for routine control. The recommendation is to apply the same study to other molecules and dosage forms.

Conflicts of interest

The authors report no conflicts of interest.

References

1. McNamara JO. Drugs effective in the therapy of the epilepsies. In: Hardman JG, Limbird LE. The Pharmacological Basis of Therapeutics, 10th ed.; McGraw-Hill: New York Goodman & Gilman's; 2001. P. 533-4.
2. Beghi E. Carbamazepine: clinical efficacy and use in other neurological disorders. In: Levy R, Mattson R, Meldrum B, Penry J, Dreifuss F. Antiepileptic drugs, 5th ed. Lippincott, Philadelphia: Williams & Wilkins; 2002. P. 273-7.
3. Trimble MR. Carbamazepine: clinical efficacy and use in psychiatric disorders. In: Levy R, Mattson R, Meldrum B, Penry J, Dreifuss F. Antiepileptic drugs, 5th ed. Lippincott, Philadelphia: Williams & Wilkins; 2002. P. 278-84.
4. Ernst CL, Goldberg JF. Antidepressant properties of anticonvulsant drugs for bipolar disorder. J Clin Psychophar-macol 2003; 23:182-92.
5. Wael A, Alia B, Mahmoud M, Hanan E N. Formulation and evaluation of carbamazepine 200 mg chewable tablets using cyclodextrins. IJPPS 2012; 4(4):472-80.
6. Geradin AP, Abadie FV, Campestrini JA, Theobald W. Pharmacoki-netics of carbamazepine in normal humans after single and repeated oral doses. J Pharmacokinet Biopharm 1976; 4:521-35.
7. McKauge L, Tyrer JH, Eadie MJ. Factors influencing simultaneous concentrations of carbamazepine and its epoxide in plasma. Ther Drug Monit 1981; 3:63-70.
8. Levy RH. Cytochrome P450 isozymes and antiepileptic drug interactions. Epilepsia 1995; 36 (Suppl. 5):S8-13.
9. Koester LS, Ortega GG, Mayorga PP, Bassani VL. Mathematical evaluation of in vitro release profiles of hydroxyl-propyl methylcellulose matrix tablets containing carbamazepine associated with B-cyclodextrin. Eur J Pharm Biopharm 2004; 58(1):177-9.
10. Barakat NS, Elbagory IM, Almurshedi AS. Formulation, release characteristics and bioavailability study of oral monolithic matrix tablets containing carbamazepine: AAPS Pharm Sci Tech 2008; 3:931-8.
11. Bialer M. Pharmacokinetic evaluation of sustained release formulations of antiepileptic drugs. Clin Pharmacokinet 1992; 22(1):1-21.
12. Ikegami K, Tagawa K, Kbayashi M, Osawa T. Prediction of in vivo drug release behaviour of controlled-release multiple-unite dosage forms in dogs using a flow-through type dissolution test method. Int J Pharm 2003; 258:31-43.
13. Pharmacopeia U. United States Pharmacopeia And National Formulary (Usp 28–Nf 23). The United States Pharmacopeial Convention, Inc.: Rockville; 2005. 341-4, 2411-20, 2501-10, 2670.
14. Yuksel N, Kanik AE, Baykara T. Comparison of in vitro dissolution profiles by ANOVA-based,

model-dependent and -independent methods. Int J Pharm 2000; 209:57-67.

15. Costa P, Jose MSL. Modeling and comparison of dissolution profiles. Eur J Pharm Sci 2001; 13:123 -33.

16. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles. Pharm Tech 1996; 20 (6):64-70.