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Comparative study of the physico-chemical properties and dissolution behavior of three Carbamazepine (200mg) brands available in the Sudanese market

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Abstract: Introduction: Carbamazepine (CBZ) is a widely used antiepileptic and anticonvulsant drug, it is considered as a golden standard therapy for many types of epilepsies, including generalized tonic colonic seizures and partial onset seizures. **Purpose**: The aim of the study was to investigate three different commercially available CBZ brands, their relative dissolution behavior, weight variations, thickness and diameter of the tablets, hardness of the tablets, content uniformity, and the cost-effectiveness of local brands compared to the imported brands that might be used as alternatives. **Methods**: The methods used to compare the physico-chemical properties and the dissolution behavior for the carbamazepine brands were taken as stated in the US pharmacopeia (2013), and additional methods that were given by Shanghai pharmaceuticals were also used. Other in-house methods were also valuable in the accomplishment of this research. **Results**: All the different brands were comparable regarding weight variations, diameter and thickness, content uniformity, friability and dissolution and met the acceptable standard limits described by pharmacopeias such as USP (2013). Conclusion: Though differences for release profiles exist, all the commercial brands released 75% of drug labeled amount within 1 hr. according to USP (2013), so they can satisfy patient need. Also the rest of the properties investigated were all conforming with the USP (2013).
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Keywords： Comparative; study; physico-chemical properties; dissolution; behavior; Carbamazepinebrands; available; Sudanese market

1. Introduction

Carbamazepine ($C_{15}H_{12}N_2O$) is a tricyclic compound that is most efficient against partial seizure with or without secondary generalization. The introduction of carbamazepine into the area of epilepsy specified a new phase to control epileptic attacks. Carbamazepine was discovered by chemist Walter Schindler in Switzerland (1953). It was first marketed as a drug to treat trigeminal in 1962 and has been used as an anticonvulsant and antiepileptic in the UK since 1965, and has been approved in the US since 1974[(1,2,3)]. Carbamazepine is a white or almost white crystalline powder which exhibits polymorphism with CAS Number 298-46-4.

The total imported quantities of carbamazepine are estimated about 200 K units in 2015, and there are currently more than four local brands manufactured by local Sudanese manufacturers. [(4,5,6,7,8).] As established by many treatment guidelines and societies' protocols, carbamazepine is indicated as first-line medicine, to be used as mono-therapy for many seizures and epileptic disorders. For example the NICE (national institute for health and care excellence) guidelines for management of epilepsy, indicates Carbamazepine, lamotrigine, oxcarbazepine and Sodium valproate as first-line AED [(4,5,6,7,8).]

2. Materials and Methods

Materials

Brands of Carbamazepine used are Tegretol, Storilat, Remedica, and Shanghai CBZ pharmaceuticals). In this study, three brands of commercial conventional CBZ tablets containing 200 mg of CBZ were used.

Analytical Methods

The methods used were primarily a combination between the USP (2013) and an in-house methods used by Shanghai pharmaceuticals. Accurately weighed carbamazepine (29 mg) was dissolved in ethanol in a100 ml volumetric flask. From the stock solution, different dilutions were prepared to generate a calibration curve by measuring absorbance using a UV spectrophotometer (Shimadzu 1202 UV spectrophotometer) at 285 nm. The uniformity of contents percentage of carbamazepine was calculated.

$$Content\ \% = \frac{Absorption\ \ of\ sample \times conc.Of\ standard \times average\ \ wt. \times assay\ \ of\ standard\ \ (99.9\%)}{Absorption\ \ of\ standard \times conc.Of\ sample \times label\ \ amount\ \ (0.2\ g)} \qquad 2.1$$

Ten tablets of each brand were chosen randomly and weighed with an electronic balance and the readings were recorded. The diameter and thickness of CBZ tablets (n = 10) from each brand were measured with a micrometer and the readings were recorded, and the degree of hardness of each tablet was tested with a hardness tester. Ten tablets from each commercial brand were weighed separately, and each set of tablets was put into the friabilator. Then the tablets were rotated at 25 rpm, and the procedure was operated for 4 min. After this, the tablets were removed, brushed and weighed again. The friability percentage was calculated for each batch using the following formula.

$$\text{Friability \%} = \frac{\text{wt.before} - \text{wt.after}}{\text{wt.before}} \times 100 \qquad 2.2$$

The dissolution rate studies on conventional CBZ tablets were carried out according to the USP paddle method at a stirring rate of 75 rpm. Three tablets from each brand were used The dissolution medium was 900 mL of distilled water containing 1% sodium lauryl sulfate at 37 ± 0.5 °C. 5 ml each 10 min were drawn then filtrated and diluted to 100 ml by the same solvent and assayed spectrophotometrically at 285 nm. The percentage of cumulative CBZ released was calculated.

$$Drug\ released\ \% = \frac{Absorption\ \ of\ sample \times conc.Of\ standard \times assay\ \ of\ standard\ \ (99.9\%)}{Absorption\ \ of\ standard \times conc.Of\ sample\ \left(0.01111\frac{mg}{ml}\right)} \qquad 2.3$$

3. Results and Discussions:

The average weights of the three brands were as follow: Tegretol =0.2802 g, Storilat = 0.25173 g, and Shanghai CBZ= 0.34626 g. The weight of each individual tablet was found to be within the allowed percentage limit (7.5%) of the average weight. The thickness and diameter for each commercial brand were found to be consistent as shown in tables 1,2,3, and 4.

Table 1 showing tablets thickness records

Tegretol (mm)	Storilat (mm)	Shanghai CBZ (mm)
3.28	**4.23**	**4.49**
3.28	**4.23**	**4.49**
3.29	**4.21**	**4.51**
3.31	**4.22**	**4.47**
3.30	**4.22**	**4.47**
3.24	**4.21**	**4.53**
3.29	**4.21**	**4.47**
3.29	**4.22**	**4.46**
3.30	**4.21**	**4.48**
3.32	**4.24**	**4.50**
STDEV. = 0.021602469	**STDEV. = 0.010540926**	**STDEV. = 0.021628171**
AVERAGE= 3.29	**AVERAGE= 4.22**	**AVERAGE= 4.487**

For a satisfactory tablet, hardness should be between 4 and 8 kg [8]. The results in **Table 5** show that hardness was satisfactory for all commercial carbamazepine brands, except for the Storilat brand which found to be harder than the other brands (mainly due to the excipients used for manufacturing).

Table 2 showing tablets diameter records

Tegretol (mm)	Storilat (mm)	Shanghai CBZ (mm)
9.1	9.03	9.04
9.1	9.03	9.02
9.1	9.04	9.02
9.09	9.04	9.04
9.09	9.03	9.02
9.09	9.04	9.03
9.1	9.03	9.04
9.1	9.03	9.03
9.1	9.02	9.02
9.09	9.03	9.02
STDEV. = 0.005163978	STDEV. = 0.006324555	STDEV. = 0.009189366
AVERAGE= 9.096	AVERAGE= 9.032	AVERAGE= 9.028

Table 3 showing tablets thickness records

Tegretol (mm)	Storilat (mm)	Shanghai CBZ (mm)
3.28	4.23	4.49
3.28	4.23	4.49
3.29	4.21	4.51
3.31	4.22	4.47
3.30	4.22	4.47
3.24	4.21	4.53
3.29	4.21	4.47
3.29	4.22	4.46
3.30	4.21	4.48
3.32	4.24	4.50
STDEV. = 0.021602469	STDEV. = 0.010540926	STDEV. = 0.021628171
AVERAGE= 3.29	AVERAGE= 4.22	AVERAGE= 4.487

Table 4 showing tablets diameter records

Tegretol (mm)	Storilat (mm)	Shanghai CBZ (mm)
9.1	9.03	9.04
9.1	9.03	9.02
9.1	9.04	9.02
9.09	9.04	9.04
9.09	9.03	9.02
9.09	9.04	9.03
9.1	9.03	9.04
9.1	9.03	9.03
9.1	9.02	9.02
9.09	9.03	9.02
STDEV. = 0.005163978	STDEV. = 0.006324555	STDEV. = 0.009189366
AVERAGE= 9.096	AVERAGE= 9.032	AVERAGE= 9.028

The friability value should be lower than 0.5–1% [9,10,11]. All brands were within the allowed friability limit, except for the tegretol brand which appears to be exactly at the limit of the friability value. As shown in **Table 6**.

Oral bioavailability of CBZ is fully dependent on dissolution of product. It has been reported that the exchange of one marketed brand for another caused seizures and the occurrence of side effects [8]. CBZ, a BCS Class II drug, is practically insoluble in water, and dissolution of this type of drug is generally done in the presence of surfactant. According to the USP [12,13,14,15], drug dissolved for all conventional CBZ tablets should be at least 75% of the labeled amount. All met the USP specification (i.e., released 75% of labeled amount within 60 min). Tables 7,8, and 9 and graphs 1, and 2 show the absorbances and percentages of the drug released for 3 tablets from every commercial brand used.

Table 5 showing tablets hardness records

Tegretol (kg)	Storilat (kg)	Shanghai CBZ (kg)
8.58	13.14	8.01
7.92	12.24	7.82
7.80	13.23	8.05
6.87	12.69	7.86
7.02	15.57	7.78
8.18	13.81	8.10
8.16	11.05	8.06
7.11	13.99	7.92
8.12	13.34	8.11
6.11	13.11	7.62

Table 6 showing the tablets friability percentage

Tegretol friability %	Storilat friability %	Shanghai CBZ friability %
0.5%	0.2%	0.16%

Table 7 showing Tegretol dissolution profile

Time	Tablet 1 Absorb.	Drug released%	Tablet 2 Absorb.	Drug released%	Tablet 3 Absorb.	Drug released%
10 min.	0.367	86.8%	0.377	88.1%	0.378	88.3%
20 min.	0.428	100.1%	0.410	95.8%	0.408	95.3%
30 min.	0.453	105.8%	0.427	99.8%	0.428	100%
40 min.	0.454	106.1%	0.481	112.4%	0.480	112.2%
50 min.	0.463	108.2%	0.494	115.5%	0.495	115.7%
60 min.	0.510	119.2%	0.478	111.7%	0.478	111.7%

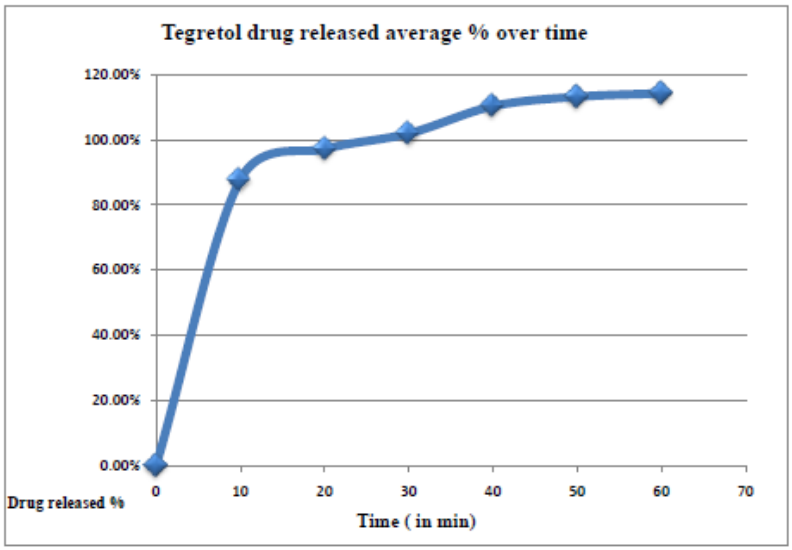

Fig 1 showing Tegretol drug released average percentage.

Table 8 showing Storilat dissolution profile

Time	Tablet 1 Absorb.	Drug released%	Tablet 2 Absorb.	Drug released%	Tablet 3 Absorb.	Drug released%
10 min.	0.174	34.4%	0.188	43.9%	0.185	43.2%
20 min.	0.353	82.5%	0.369	86.2%	0.369	86.2%
30 min.	0.455	106.3%	0.463	108.2%	0.463	108.2%
40 min.	0.499	116.6%	0.521	121.7%	0.522	121.9%
50 min.	0.533	124.5%	0.532	124.3%	0.532	124.3%
60 min.	0.543	126.8%	0.544	127.1%	0.545	127.3%

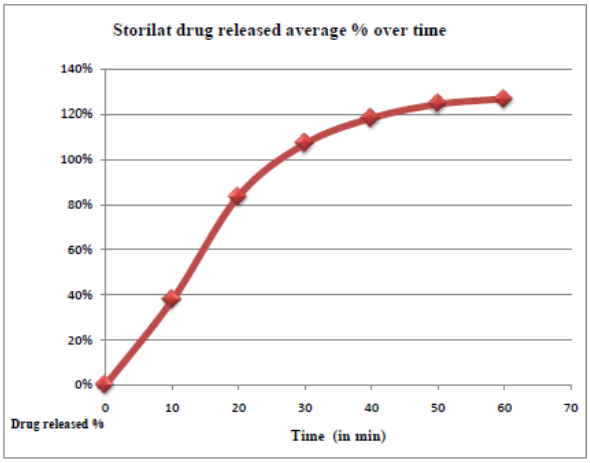

Fig 2 showing Storilat drug released average percentage

Table 9 showing Shanghai CBZ dissolution profile

Time	Tablet 1 Absorb.	Drug released%	Tablet 2 Absorb.	Drug released%	Tablet 3 Absorb.	Drug released%
10 min.	0.384	89.7%	0.374	87.4%	0.376	87.8%
20 min.	0.497	116.1%	0.496	115.9%	0.495	115.6%
30 min.	0.533	124.5%	0.522	121.9%	0.523	122.2%
40 min.	0.541	126.4%	0.554	129.4%	0.553	129.2%
50 min.	0.541	126.4%	0.563	131.5%	0.563	131.5%
60 min.	0.547	127.8%	0.570	133.2%	0.569	132.9%

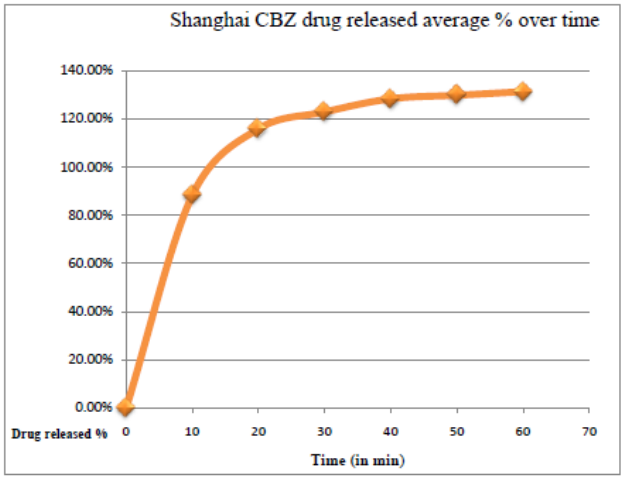

Fig 3 showing Shanghai CBZ drug released average percentage

Conclusion

After conducting weight, thickness and diameter measurements for the three CBZ brands, all found to be conforming to the USP (2013) standards. The friability measurements of the three brands are within the desired limits conforming to the USP (2013). The hardness records are within the standards (4-8kg) except for the storilat brand tablets, which gave higher hardness reading than the rest of the CBZ brands. The dissolution profiles of the three brands were conforming to the ideal standards (for all tablets they should release at least 75% of the drug in 1 hour). The local CBZ (Shanghai CBZ) was found to be conforming to the standard dissolution and physico-chemical behavior mentioned in the USP (2013).

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