Int J Pharm Bio Sci 2012 July; 3(3): P 32 – 43

Research Article Pharmaceutics

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

FORMULATION PARAMETERS CHARACTERIZATION & COMPARATIVE STUDY OF CARBAMAZEPINE TABLETS

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ABSTRACT

This research analyses the concept of formulations in epilepsy and evaluates marketed available formulations of carbamazepine. ER formulations are usually designed to reduce dose frequency and maintain relatively constant or flat plasma drug concentration. Epilepsy is a single-episode disease, and the convenience and possible better compliance associated with once-daily administration must be weighed against the shorter 'forgiveness' period and possible higher risk of breakthrough seizure due to sub-therapeutic plasma levels and/or omitted doses. Several literature reports show that up to 30% of epileptic patients may not respond to drug therapy, or inadequate control of their seizures, even if there is increasing prevalence and incidence rates of epilepsy. In this investigation, trial has been undertaken for the prediction of the reasons of treatment failures by virtue of controlling the drug quality aspects. Evaluation studies provide a means of identifying quality differences between same products obtained from various manufacturers. Quality analysis and evaluations are the most important tasks to be performed when various reports of therapy indicate problems and failures of treatment. Data suggest that all the tablets met the quality specification with respect to hardness, friability, disintegration, dissolution, assay and dosage form uniformity (weight variation and/or content uniformity). With respect to drug content (assay), from the carbamazepine tablets analyzed, ZEN was found to be out of the specified tolerance limit, while the other carbamazepine tablets evaluated were within the tolerance limits of content.

KEYWORDS : Antiepileptic, carbamazepine, anticonvulsants.

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INTRODUCTION

The anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder, since many seem to act as mood stabilizers, and in the treatment of neuropathic pain. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure.. While an anticonvulsant is a fair description of AEDs, it neglects to differentiate the difference between convulsions and epilepsy.Convulsive non-epileptic seizures are quite common and these types of seizures will not have any response to an antiepileptic drug. In epilepsy an area of the cortex is typically hyperirritable that can often be confirmed by completing an EEG. Antiepileptic drugs function to help reduce this area of irritability and thus prevent epileptiform seizures. The major molecular targets of marketed anticonvulsant drugs are voltage-gated sodium channels and components of the GABA system, including $GABA_A$ receptors, the GAT-1 GABA transporter, and GABA transaminase. Additional targets include voltage-gated calcium channels, SV2A, and α2δ. The drug class was the US's 5th-best-selling in 2007. Some anticonvulsants have shown antiepileptogenic effects in animal models of epilepsy. That is, they either prevent the expected development of epilepsy or can halt or reverse the progression of epilepsy. However, no drug has been shown to prevent epileptogenesis (the development of epilepsy after an injury such as a head injury) in human trials[1,2,3,4,5,6,7,8].

MATERIALS AND METHOD

MATERIALS

MARKETED PREPARATIONS

The following tablets of Carbamazepine were purchased from drug retail outlets and used for evaluation was shown in (Table 1)

Table 1
Carbamazepine 200mg tablets

Brand	Manufacturer	Mfg. Date	Exp. Date
TEGRITAL®200mg	Novartis Pharma	01/2009	12/2012
ZEN®200mg	Intas Pharma	12/2008	11/2013
CARBATOL®200mg	Torrent Pharma	01/2007	12/2012

INSTRUMENTS AND THEIR MANUFACTURERS

The instruments and their manufacturers shown in (Table 2)

Table 2
Instruments and their manufacturers

Sr.No.	Instrument/Apparatus	Model with Make
1.	UV Visible Spectrophotometer	Lamada 25, Perkin Elmer
2.	Dissolution Apparatus, Type II	Model-TDT 08L, Electrolab
3.	Tablet Hardness Tester	Dolphin Tablet Hardness Tester
4.	Single pan electronic Balance	Unibloc, Shimadzu.
5.	Disintegration Tester (USP)	Model ED-2AL, Electrolab
6.	Friability tester	Model EF-1W, Electrolab

METHODOLOGY

Validation of UV spectroscopic analytical method [18]

i) LINEARITY

A series of solutions of Carbamazepine in ethanol (96%) of concentrations 2-20 µg/ml was prepared. The absorbance of all the solutions was measured using ethanol (96%) as blank at 285 nm using double beam spectrophotometer. A standard plot of absorbance v/s concentration of drug in µg/ml was plotted. Correlation coefficient and regression equation were obtained from the calibration curve.

ii) PRECISION

For checking method precision, a standard solution of Carbamazepine of concentration 10 µg/ml was prepared and the absorbance was recorded in 6 replicates. From the data obtained standard deviation (SD) and % RSD were calculated.

iii) ACCURACY

To check the accuracy of the method, a solution of three different concentrations 5, 10 and 15 µg/ml was prepared. The absorbance of each solution was measured and concentration was estimated from the regression equation. Percent accuracy was calculated from the data obtained.

iv) LIMIT OF DETECTION (LOD)

Limit of detection is the minimum quantity of the drug which can be detected by the method. Limit of detection is calculated as

$$LOD = 3.3 (\sigma/S)$$

Where σ is the standard deviation of the constant and S is the mean of slope of the calibration curve equation.

v) LIMIT OF QUANTIFICATION (LOQ)

Limit of quantification is the minimum quantity of the drug that can be quantified by the method.

Limit of quantification is calculated as

$$LOQ = 10 (\sigma/S)$$

Where σ is the standard deviation of the constant and S is the mean of slope of the calibration curve equation.

TABLET EVALUATION PARAMETERS [23]

The following quality parameters were evaluated using Indian Pharmacopeia.

i) HARDNESS

Six tablets were individually placed carefully in a hardness tester and the degree of force required to break the tablets was recorded.

ii) FRIABILITY

A number of tablets, equivalent to 6.5gm, were weighed. The tablets were then placed in the drum of the friability tester and rotated at 25 revolutions per minute (100 times). The tablets from each product batch were dedusted and reweighed. The percent loss of total weight was calculated.

iii) WEIGHT VARIATION

20 tablets from each product were individually weighed, and the average weight was calculated. The percent deviation was calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in (Table 3) and none deviates by more than twice that percentage.

Table 3
Acceptance criteria for weight variation

Average weight of tablet	Percentage deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

iv) CONTENT OF ACTIVE INGREDIENTS

The content of the active ingredient in each of the 20 tablets was calculated from the results of the assay obtained as directed in the individual monographs assuming homogeneous distribution of the active ingredient.

v) DISINTEGRATION

The mean disintegration times of six tablets from each product were determined using ELECTROLAB disintegration apparatus. The disintegration media for all the products comprised of distilled water maintained at 37±1˚C. Tablets were considered completely disintegrated when all particles passed through the wire mesh.

vi) ASSAY

Twenty tablets from each brand product were weighed and powdered. A quantity of the powder containing 60 mg of carbamazepine was boiled with 25 ml of 96% ethanol for a few minutes. The hot mixture was stirred in a closed flask for 10 minutes and filtered through sintered glass. The flask and the filter were washed with 96% ethanol and sufficient 96% ethanol was added to the cooled filtrate to produce 100 ml. 5 ml of this solution was diluted to 250 ml with 96% ethanol and the absorbance of the resulting solution was measured using an ultraviolet spectrophotometer at the wave length maximum, λmax, of 285 nm. Then the content of carbamazepine $C_{15}H_{12}N_2O$ was calculated taking 490 as the value of A (1%, 1cm) at the λmax of 285 nm.

vii) DISSOLUTION [18]

The dissolution rates of the tablets (carbamazepine) were determined according to USP specifications. The dissolution medium consisted of 900 ml of 1% sodium lauryl sulfate in a thermostatically controlled water bath at 37±0.5˚C that was being stirred at 75 rpm for the different brands of carbamazepine tablets using dissolution apparatus II.

The amount of carbamazepine released from the respective tablet products put in dissolution media were determined by sample withdrawal at different times. Samples (5 ml) were withdrawn after 5, 15, 20, 30, 45, and 60 minutes for carbamazepine tablets, and an equivalent amount of water and 1% sodium lauryl sulfate solution were immediately introduced, respectively, as replacement. The

samples were filtered and suitably diluted with 1% sodium lauryl sulfate for carbamazepine samples.
The assay for carbamazepine released from the tablets was performed by measuring the absorbance at 285 nm using UV Spectrophotometer. 1% sodium lauryl sulfate was used as a blank and the necessary correction for dilution was made when calculating the amounts of drug released. The drug content was calculated using comparison method with the reference standard of carbamazepine.

RESULT & DISCUSSION

VALIDATION OF UV SPECTROSCOPY ANALYTICAL METHOD
LINEARITY

Calibration curves were constructed in ethanol (96%). Beer's law was obeyed in the concentration range of 2-20 µg/ml. The high values of regression coefficients (0.9472) estimated the linearity of relationship between concentration and absorbance (Table 4 & Figure.1).

Table 4
Absorbance values for Linearity

Sr. No.	Concentration (µg/mL)	Absorbance (nm)
1.	2	0.0950
2.	4	0.1799
3.	6	0.2800
4.	8	0.3790
5.	10	0.4745
6.	12	0.5683
7.	14	0.6635
8.	16	0.7501
9.	18	0.8500
10.	20	0.9472

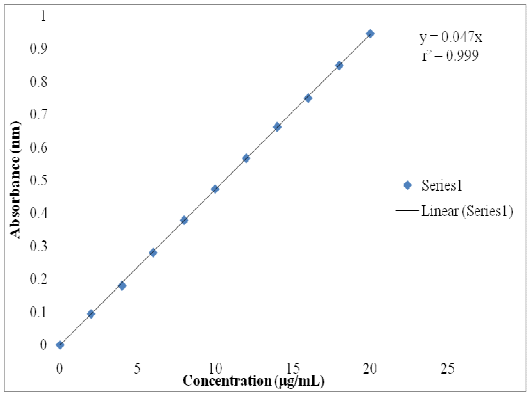

Figure 1
Calibration curve of Carbamazepine (API)

PRECISION

From the data presented in Table 5, it was observed that the method was precise for detection of Carbamazepine. RSD values were found less than 2%. There was good reproducibility of the results.

Table 5
Precision Values

Mean of 6 Absorbances	0.4868
Standard deviation (SD)	0.0043
% Relative standard deviation (RSD)	0.8930

ACCURACY

Accuracy studies were carried out using solutions of Carbamazepine at three different levels in ethanol (96%). The % accuracy was as per (Table 6). The accuracy is the closeness of the best result obtained by the method to the true value. The concentration recovered should be within ±2% to the true value. The % accuracy was found to be within acceptance criteria

.

Table 6
%Accuracy Values

Concentration (µg/ml)	**05**	**10**	**15**
Mean absorbance	0.2349	0.4788	0.7121
Concentration recovered	4.99	10.18	15.15
Mean % Accuracy	99.97	101.87	101.01

LIMIT OF DETECTION (LOD)

LOD was found to be 0.0992µg/ml for detection of Carbamazepine.

LIMIT OF QUANTIFICATION (LOQ)

LOQ was found to be 0.3008µg/ml. Thus the UV-Spectroscopic analytical method was found to be linear, precise and accurate. The method could detect and quantify Carbamazepine in concentration as low as 0.3µg/ml.

TABLET EVALUATION PARAMETERS

HARDNESS

The mean hardness values of the tablets of Carbamazepine in this study is shown in (Table 7). It is indicated that for the carbamazepine tablets studied the lowest hardness is that of ZEN which is 3.83 kg/cm^2, and the highest is that of CARBATOL (6.33 kg/cm^2). TEGRITAL showed a hardness of 5.91 kg/cm^2. Usually, tablets require a certain degree of strength and resistance to friability to withstand mechanical shocks of handling during manufacturing, packaging, shipping, storage and finally consumption by the patient. Adequate tablet hardness as well as reasonable friability is the necessary requisites for a consumer acceptance.

Table 7
Summary of hardness tests of the tablets

Sr. No	Brand Name	Hardness (kg/cm^2)
1.	TEGRITAL	5.9166
2.	ZEN	3.8333
3.	CARBATOL	6.3333

FRIABILITY

The weight loss of the tablets, after friability test expressed as percent friability, is also indicated in Table 8. The lowest percent friability for the carbamazepine tablets has been obtained for ZEN (0.04%) while TEGRITAL and CARBATOL percent friability are 0.21% and 0.58% respectively. For conventional compressed tablets, a hardness of 50N is the minimum requirement for a satisfactory tablet product and must not lose more than 1% of its weight after friability test. Limits of < 1% friability are often set, but < 0.1% is a realistic goal

.

Table 8
Summary of friability tests of the tablets

Sr. No	Brand Name	Friability (%F)
1.	TEGRITAL	0.21
2.	ZEN	0.04
3.	CARBATOL	0.58

WEIGHT VARIATION

As illustrated in Table 9, the average weight of the tablets varies from product to product. For Carbamazepine tablets, the average weight is 231.89 mg (ZEN), 241.40 mg (CARBATOL) and 282.0 mg (TEGRITAL) where the official standard strength for all the three products is 200 mg. The variations in average weights of the tablets could be accounted due to the use of different kinds and/or amounts (varying proportions) of excipients in the tablets investigated. In case of the analyzed

Table 9
Weight Variation of Carbamazepine Tablets

Sr. No	ZEN		CARBATOL		TEGRITAL	
	Weight (mg)	% deviation	Weight (mg)	% deviation	Weight (mg)	% deviation
1.	228.5	1.462	241.3	0.043	284.6	0.922
2.	235.1	1.384	241.1	0.126	275.8	2.199
3.	229.8	0.901	243.1	0.702	286.8	1.702
4.	229.3	1.117	244.0	1.075	280.0	0.709
5.	233.9	0.867	238.1	1.369	281.2	0.284
6.	232.0	0.047	240.0	0.582	281.7	0.106

7.	243.7	5.093	242.3	0.371	282.5	0.177
8.	230.0	0.815	242.7	0.536	281.2	0.284
9.	230.1	0.772	239.7	0.706	282.9	0.319
10.	229.5	1.031	240.1	0.541	280.1	0.674
11.	229.0	1.246	242.8	0.578	282.2	0.071
12.	233.8	0.824	240.6	0.333	281.6	0.142
13.	231.0	0.384	239.3	0.872	283.3	0.461
14.	230.2	0.729	242.3	0.371	282.4	0.142
15.	233.4	0.651	244.9	1.448	281.9	0.035
16.	231.5	0.168	242.0	0.246	282.1	0.035
17.	229.7	0.944	243.2	0.744	283.2	0.426
18.	232.2	0.134	239.5	0.789	280.7	0.461
19.	233.8	0.824	240.0	0.582	282.3	0.106
20.	231.3	0.254	241.1	0.126	283.5	0.532
MEAN	**231.89**		**241.40**		**282.0**	

brands of carbamazepine tablets analyzed, the weight variation may be because of the use of different kinds/varying proportion of excipients by manufacturers.

Not more than two of the individual weight deviate from the average weight by more than the 7.5 (ZEN & CARBATOL), 10 (TEGRITAL) and none deviates by more than twice that percentage. From the results of weight variation of carbamazepine tablets, all the tablets were found within the acceptance criteria.

CONTENT OF ACTIVE INGREDIENT

The percentage contents of different brands of carbamazepine tablets calculated using content uniformity method is indicated in Table 10. The content of active ingredient should be within 95% – 105%. The percentage contents for the carbamazepine tablets are TEGRITAL (95.5-96.9%), ZEN (86.2-87.8%), CARBATOL (100.5-101.6%) and ZEN New Batch (98.1-100.7).

From the results of content uniformity of carbamazepine tablets, TEGRITAL (95.9%) and CARBATOL (101%) passed the IP specification i.e. they contain the required amount of carbamazepine while ZEN (86.8%) fail to pass the specification on percentage content as it has lower percentage than the IP specification limit. The New ZEN batch, however, was found to be within IP specification limits.

Table 10
Content uniformity of Carbamazepine Tablets

Sr. No	Brand Name	Content of Active Ingredient (Average)
1.	TEGRITAL	95.98%
2.	ZEN	86.82%
3.	CARBATOL	101.01%
4.	ZEN New Batch	99.32%

DISINTEGRATION

Carbamazepine tablets, like any other solid dosage forms, need to disintegrate in the gut and go into solution before they are completely absorbed. Disintegration, therefore, is an important process in making the drug available for absorption. The official requirement in the Indian Pharmacopoeia disintegration test is that uncoated tablets should disintegrate in less than 15 minutes. As shown in Table.11, the disintegration times for the studied Carbamazepine tablets are: TEGRITAL (1.5 - 2.0 minute), ZEN (25 – 40 seconds) and CARBATOL (3.0 - 4.0 minutes).

Table 11
Disintegration Time of Carbamazepine Tablets

Sr. No.	Brand Name	Disintegration Time
1.	TEGRITAL	1.5 – 2.0 minutes
2.	ZEN	25 – 40 seconds
3.	CARBATOL	3.0 – 4.0 minutes

As evident from the results, all the tablets pass the IP specification. The results indicate that disintegration time for carbamazepine tablets increases in the order ZEN (25-40 seconds), TEGRITAL (1.5-2.0 minutes) and CARBATOL (3.0-4.0 minutes). The values from the hardness test of the tablets also increase in the same order: ZEN (3.83 kg/cm^2), TEGRITAL (5.91 kg/cm^2) and CARBATOL (6.33 kg/cm^2) for carbamazepine tablets. Thus, the results of the study indicate that there is direct relationship between disintegration time and hardness.

ASSAY

The Indian Pharmacopoeia states that carbamazepine tablets must contain not less than 95.0% and not more than 105.0% of carbamazepine stated on the label. The results of analysis of the three brands of carbamazepine tablets analyzed according to the IP methods are represented in Table 12. From the results of assay of carbamazepine tablets, TEGRITAL (95.6%) and CARBATOL (100.75%) passed the IP specification i.e. they contain the required amount of carbamazepine while ZEN (86.5%) fail to pass the specification on percentage content as it has lower percentage than the IP specification limit. The highest content has been achieved for CARBATOL tablets. The New ZEN batch, however, was found to be within IP specification limits

.

Table 12
Assay Results of Carbamazepine Tablets

Sr. No.	Brand Name	Content of Active Ingredient (Average)
1.	TEGRITAL	95.63%
2.	ZEN	86.56%
3.	CARBATOL	100.75%
4.	ZEN New Batch	99.37%

DISSOLUTION

The dissolution profile of carbamazepine tablets is depicted in (Figure 2 & table 13). The USP specification for the release of carbamazepine from the brands of carbamazepine tablets is that between 45% and 75% of the label claim of carbamazepine should be dissolved in 15minutes; and not less than 75% of the labeled amount of carbamazepine is dissolved in 60minutes. All the three brands of carbamazepine tablets analyzed and passed the above USP requirement to release its contents in the tolerance limits specified as a dissolution requirement. TGRITAL tablet released 82.7% of its content at the 15th minute and 95.8% at the 60th and ZEN tablets released 79.4% at the 15th minute and 88.1% at the 60th minute. CARBATOL tablet has released 59.9% of its content at the 15th minute and 89.9% at the 60th minute

.

Table 13

Percent drug release of different brands of carbamazepine tablets at different times

Time (minute) of Sampling	% Carbamazepine Released		
	CARBATOL	TEGRITAL	ZEN
0	0	0	0
5	30.82	62.46	71.84
15	59.90	82.71	79.41
20	70.22	89.39	82.97
30	79.91	92.38	85.40
45	84.82	94.28	87.05
60	89.98	95.68	88.16

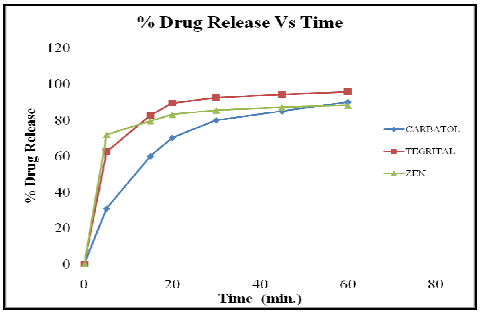

Figure 2

Dissolution profiles of different brands of carbamazepine tablets

DISSOLUTION PARAMETER

The $t_{50\%}$ and $t_{80\%}$ are the dissolution parameters that can be utilized to analyze dissolution profile of different pharmaceutical products. The $t_{50\%}$ is the time required for release of 50% of the contents of the tablets analyzed and $t_{80\%}$ is the time required for the release of 80% of the contents. Very long $t_{50\%}$ and $t_{80\%}$ values of pharmaceutical products dissolution profile indicate that the product may manifest lower rate and extent of bioavailability in the body.

CONCLUSION

In general, the overall aspect of the study has attempted to make a comparative assessment of the quality in terms of physical properties and

in vitro bioequivalence of some antiepileptic drug products, carbamazepine. All the tablets met the quality specification with respect to hardness, friability, disintegration, dissolution, assay and dosage form uniformity (weight variation and/or content uniformity). With respect to drug content (assay), from the carbamazepine tablets analyzed, ZEN was found to be out of the specified tolerance limit, while the other carbamazepine tablets evaluated were within the tolerance limits of content. As ZEN tablets did not comply with the content uniformity test and assay and their values were found to be outside the specified tolerance limits mentioned in IP, we decided to repeat the above tests using another batch of ZEN tablets. The repeat test results were found to comply with the IP specifications. Therefore, one possible cause of the inadequate control of seizures and tolerance developments to antiepileptic drugs may be attributed to the quality aspect of the drugs.

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