Pharma Science Monitor 6(4), Oct-Dec 2015

PHARMA SCIENCE MONITOR

AN INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES

Journal home page: http://www.pharmasm.com

PROSPECTIVE VALIDATION OF TABLET MANUFACTURING PROCESS OF ORODISPERSIBLE TABLETS BY DIRECT COMPRESSION

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ABSTRACT

Validation of product should be performed as per the protocol. The protocol describes the process stages, control variables & measuring responses with justification, sampling plan, acceptance criteria, summary& conclusion. During the validation, samples were withdrawn according to sampling plan. The manufacturing of orodispersible carbamazepine tablet 100 mg by direct compression was validated successfully considering the following parameters. Mixing performed in a planetary mixture for 5, 10 and 15 min at slow speed. Mix blend were sifted through 40 mesh sieve using vibratory sifter. Compression was performed on a 12 station compression machine at 13, 18, 22, 28 RPM. All the analytical data derived during process validation of carbamazepine 100 mg tablet. Hence the process is validated.

KEYWORDS: Carbamazepine, process validation, orodispersible, direct compression..

INTRODUCTION

The prime objective of any pharmaceutical plant is to manufacture products of requisite attributes and quality consistently, at the lowest possible cost. In an environment of increasing global cutting edge competition where countries with lower production cost quickly catch up technology, a new thinking required in ordered to meet competition. A protective way to meet the increasing competition is to focus on maximizing the utilization of existing technology, being able to continuously introduced and make use of new technology. Validation is a concept that has evolved in United States in 1978.The concept of validation has expanded through the years to grip a wide range of activities from analytical methods used for quality control of drug products to computerized systems for clinical trials, labelling or process control, validation is founded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part cGMP.

The supportive data should show the pharmaceutical equivalence between the product manufactured at the manufacturer and the recipient site. The data should show that the process is under control with no significant variation in the critical parameter. Manufacturers decide to

validate the process to improve the overall quality, and reduce cost and to improve the customer satisfaction or other reason.[1]

BENEFITS OF VALIDATION

1. Assurance of quality.
2. Process optimization.
3. Reduction of cost.
4. Reduces the risk of regulatory noncompliance.
5. Increased output.
6. Easier maintenance of equipment.
7. Government regulation. (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new product.)

IMPORTANCE OF PROCESS VALIDATION:

Assurance of product quality is derived from careful attention to a number of factors including selection of parts and materials, adequate product and process design, control of the process and in-process and end-product testing. Process validation is a key element in assuring the quality. It is through careful design and validation of both the process and process controls that a manufacturer can establish a confidence that all manufactured units from successive lots will be acceptable. Successfully validating a process may reduce the dependence upon intensive in-process and finished product testing.[2, 3.]

Orodispersible tablets:

Drug delivery through oral route is the most common and preferred route of drug administration both for solid and liquid dosage forms. However, solid dosage forms are popular because of the ease of administration, accurate dosage, self-medication, pain avoidance, and most importantly the patient compliance. Tablets and capsules are the most popular solid dosage forms.[4]

Direct compression of tablets:

Direct compression (DC) is by far the simplest means of production of a pharmaceutical tablet. It requires only that the active ingredient is properly blended with appropriate excipients before compression. Apart from simplicity of formulation and manufacture, the key advantages of direct compression include reduced capital, labour and energy costs for manufacture and the avoidance of water for granulation for water sensitive drug substances.[4]

Applicability of direct compression:

The most obvious factor in determining whether DC is applicable to a certain drug substance is dose.Three key factors for successful tableting are flow and compact ability of the compression

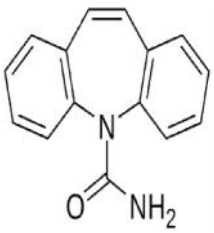
mix, and drug content uniformity in the mix and the final tablets. All of these factors are likely to be affected by drug dose.In this guide, low dose is taken 10 mg or below, medium dose is taken 10 mg to 50 mg and high dose is taken above 50 mg.For low dose drugs, flow and compaction of the compression mix are largely conferred by the excipients and the primary concern is likely to be achievement of good content uniformity in the blend and in the tablets. For medium dose drugs flow of the compression mix may become a critical factor, and for high dose drugs the flow and compaction are highly dependent on the properties of the drug substance.[5, 6.]

MATERIALS AND METHOD

Table: list of materials

SR NO.	NAME OF MATERIAL	NAME OF SUPPLIERS
1	Carbamazepine	Sun Pharmaceutical Industries Ltd., Mumbai
2	Crospovidone	Sulab Laboratory, Baroda
3	Avicel pH-102	Sulab Laboratory, Baroda
4	Vaniline	Sulab Laboratory, Baroda
5	Sodium saccharine	Sulab Laboratory, Baroda
6	Sodium stearyl fumarate	Nikita Pharmaceutical Specialities Pvt. Ltd., Nagpur
7	Talc	Sulab Laboratory, Baroda
8	Mannitol	Sulab Laboratory, Baroda

Drug Profile:

Drug Name	Carbamazepine
Chemical structure	
IUPAC Name	2-azatricyclo[9.4.0.0{3,8}]pentadeca-(1,1),3(8),4,6,9,12,14-heptaene-2-carboxamide
Trade Name	Tegretol, Carzine, Mazetol, Tegrital, Tegrita,

	Zeptol
Molecular Formula	$C_{15}H_{12}N_2O$
Category	• Anticonvulsant • Analgesics • Antimanic agents • Analgesics, non-narcotic
Molecular weight	236.269 g/mole
Dosage	100-1200 mg once or twice in a day
Solubility	Partially soluble in water (170mg/lit.), freely soluble in ethanol
Route of Administration	Oral
Melting point	191 c
Appearance	White crystalline powder
Adverse Reaction	drowsiness, dizziness, unsteadiness, nausea Vomiting, headache, anxiety memory problems, diarrhea Constipation, heartburn dry mouth, back pain

Methods:

1. Preformulation:

It is the first step in rational development of dosage forms of drug substance. Preformulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass-produced.

Following preformulation was study check on carbamazepine orodispersible tablets.

1.1 Colour, odour and appearance:

The drug sample was evaluated for his colour and odour. The result is shown in the table.

1.2 Melting point determination:

Melting point of the drug sample was determined by capillary method by using melting point apparatus. The reported and observed melting point was shown in table.

1.3 Solubility:

The solubility of carbamazepine was checked under water and various solvents. The result is shown in the table.

1.4 Determination of λ max:

10 mg of drug was first dissolved in 50 mL of methanol and was then diluted up to 100 mL with distilled water to obtain a stock solution of 100 µg/mL concentration. Then from the stock solution 1 µg/mL and 2 µg/mL test solution were prepared diluting with hydro alcoholic solvent i.e., methanol. The solutions were scanned in spectrum mode for absorbance between 200-600 nm using spectrophotometer.

2. Preparation of calibration curve of drug:

2.1 Preparation of standard calibration curve of Carbamazepine with phosphate buffer pH 6.8:

Procedure: 10 mg of drug (carbamazepine) was weighed accurately and placed into a 100 ml volumetric flask. The concentration was 100 mcg/mL. From the above solution 0.2, 0.4, 0.6, 0.8, 1.0, 1.2 ml solution is pipette out and volume make up with the help of phosphate buffer pH 6.8 so the final concentration was 2 mcg/mL to 12 mcg/mL.

3. Compatibility study:

Infrared spectra of pure drug Carbamazepine, sodium stearyl fumarate, crospovidone, were taken by KBr pellet technique and were recorded in the range of 4000 – 400 $cm^{-1}$by using FT-IR spectrophotometer Shimadzu.

4. Bulk density: it is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (pass through the standard sieve #20) into a measuring cylinder and initial weight was noted. Initial volume was called the bulk volume. Bulk density was calculated according to the formula mentioned below. It was expressed in gm. /ml and was given by Db = M/Vb

Where, M and Vb are mass of powder and bulk volume of the powder respectively.

5. Tapped density: it is the ratio of total mass of the powder to tapped volume of the powder. Volume was measured by tapping the powder and the tapped volume was noted if the difference between these two volumes was less than 2 %. If it was more than 2%, tapping was continued and tapped volume was noted. Tapping was continued until the difference between successive volumes was less than 2%.

It was expressed in gm. / ml and was given by

Dt = M/Vt

Where, M and Vt are mass of powder and tapped volume of the powder respectively.

6. Compressibility Index & Hausner Ratio: The Compressibility Index & Hausner Ratio is measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index & Hausner Ratio. The Compressibility Index & Hausner Ratio may be calculated using measured values for bulk density and tapped density as follows.

Compressibility index = tapped density- bulk density/ tapped density * 100

Hausner ratio = tapped density / bulk density

7. Angle of repose (q): the powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Tan (q) = h/r

Where, h and r are the height and radius of the powder cone.

8. Assay at mixing stage:

Assay of mixing blend was carried out by the HPLCs.

Procedure: as per the Indian Pharmacopoeia.

9. Formulation of tablets:

Formulation of tablet was prepared with crospovidone, avicel PH-102, sodium saccharine, vanillin, talc, sodium stearyl fumarate and mannitol. The dose of drug was taken 100 mg per tablet. Different batches were prepared at different compression speed and mixing time.

10. Compression:

The compression machine was set on the following parameter and compress tablet.

At four different speeds:

- 13 RPM
- 18 RPM
- 22 RPM
- 28 RPM

10.1 Uniformity of weight: the weights were determined to within ± 2% mg by using balance. Weight control was based on a sample of 20 tablets.

10.2 Tablet hardness: the hardness of the tablets was determined by Monsentro hardness tester. Hardness of tablet should not be less than 1.5 k.g/cm².

10.3 Tablet thickness: Tablet thickness can be measured using a simple procedure. Some tablets are selected randomly and their thickness was measured using Vernier Calipers.

10.4 Tablet diameter: Some tablets are selected randomly and their thickness was measured using Vernier Calipers.

10.5 Tablet friability: The friability of tablets was measured in a friability tester. 20 tablets are placed in a drum for a fixed time. (100 revolutions) and weighed again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.

(Friability: W1= Initial weight, W2 = final weight, %,

Friability = W 1 – W2 / W1 x 100)

(Acceptance Criteria: Not more than 1.0 %).

10.6 Disintegration time: Disintegration time of tablets was measured with the help of disintegration test apparatus. Required tablets selected randomly.

10.7 Wetting time: Circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimetres of water containing eosin, a water soluble dye, was added to petridish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

10.8 Dissolution study: Dissolution study was carried out with the help of dissolution test apparatus. pH 6.8 buffer was placed in a bowl. And type 1 (paddle type) apparatus was used and % CDR was calculated.

RPM – 100

Temperature - 37 c

11. Stability studies:

The stability study was carried out for optimized formulation as per ICH guidelines (Feb. 2003). Various ICH storage conditions are available which are as 40 c ± 75% RH and at room temperature for six weeks.

Formula for carbamazepine tablet:

INGREDIENTS	SPECIFICATION	STD. QTY (mg)	FOR 2000 TABLETS (gm.)	CHARAECTERISTICS
Carbamazepine	BP	100	200	API
Crospovidone	BP	8	16	Super disintegrant
Avicel pH-102	IP	110	220	Filler / binder
Vaniline	IP	4	8	Flavour
Sodium saccharine	-	4	8	Sweetener
Sodium stearyl fumarate	IP	4	8	Lubricant
Talc	IP	4	8	Glidant
Mannitol	IP	116	232	Diluent
Total		350	700	

Table: batches under validation.

Sr. no.	Batch no.	Batch size	Batch started	Batch completed
1.	X	2000	17/01/2014	18/01/2014
2.	Y	2000	20/01/2014	21/01/2014
3.	Z	2000	22/01/2014	23/01/2014

RESULT & DISCUSSION

Preformulation study:

Table: Organoleptic properties of carbamazepine

Sr. No.	Parameter	Characteristics
1	Colour	White
2	Odour	Odourless
3	Appearance	Crystal

Table: melting point

Reported Melting point	Observed Melting point
191-192 C	190-191 C

Table: solubility.

Sr. No.	Solvent	Solubility (mg/mL)
1	Acetone	41
2	DCM	28
3	Chloroform	18
4	Methanol	45
5	Phosphate buffer pH 7.4	1
6	Phosphate buffer pH 6.8	2
7	0.1 N HCL	0.2
8	0.1 M NaOH	-

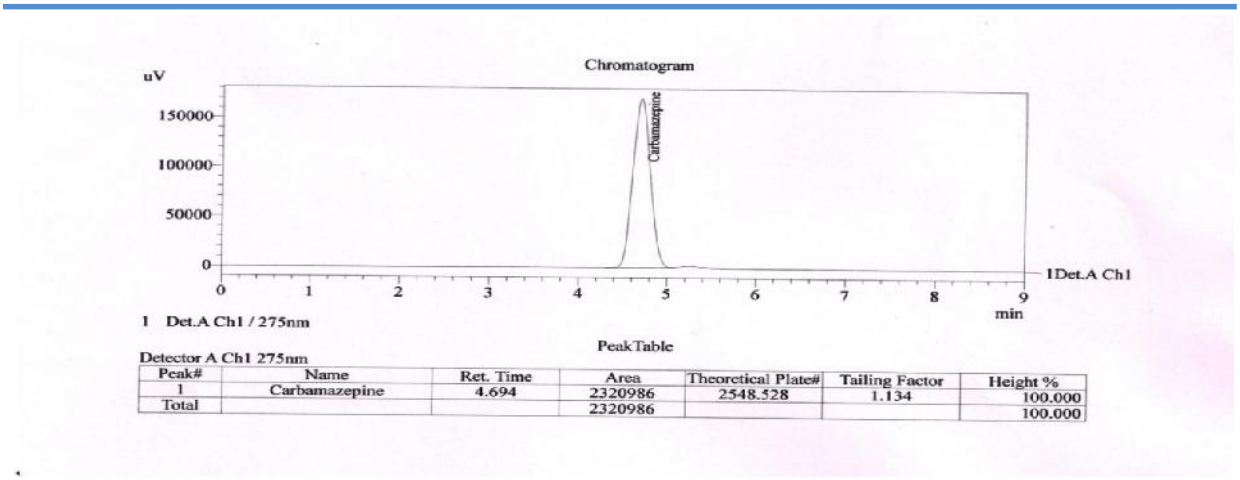
Table: determination of λmax.

Drug	Reported λmax (nm)	Observed λmax (nm)
Carbamazepine	285.4	284

IR of carbamazepine:

HPTLC:

Chromatogram of Carbamazepine. (Pure drug)

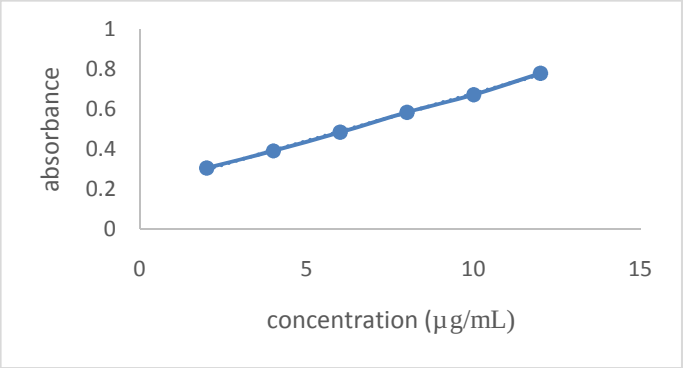


PeakTable

Detector A Ch1 275nm

Peak#	Name	Ret. Time	Area	Theoretical Plate#	Tailing Factor	Height %
1	Carbamazepine	4.694	2320986	2548.528	1.134	100.000
Total			2320986			100.000

Calibration curve:



DIFFERENT PROCESSING STEP:

1. Mixing: Dry mixing in planetary mixture for 5, 10, 15 minute respectively. (Batch X, Y, Z)
2. Compression: At different speed 13, 18, 22, 28 RPM/Min. (Batch Y1, Y2. Y3, Y4)

Table: Characterization of trial blends.

Batch No.	Bulk Density(g/mL) ± SD	Tapped Density(g/mL) ± SD	Compressibility Index (%)	Hausner Ratio	Angle of Repose
X	0.608±0.04	0.700±0.01	13	1.15	35
Y	0.681±0.02	0.750±0.03	9.09	1.10	23
Z	0.583±0.05	0.700±0.04	10.66	1.20	26

Table: assay results of mixing blends

BLEND UNIFORMITY			
SAMPLING LOCATION	X (% assay)	Y (% assay)	Z (% assay)
Top left	96.2	100	99.5
Top right	97.4	99.7	99.7
Middle	96.7	99.6	100
Bottom left	97.7	100	100
Bottom right	97.8	100	100
AVERAGE	97.16	99.86	99.84
RSD	0.707853	0.195209	0.230586
Acceptance Criteria: 95.0 % to 105.0 % of target Assay and RSD NMT 2.0 %.			

CONCLUSION

So depending upon all three batches results, it was concluded that 10 min dry mixing time gave the most satisfactory results, which were well within the acceptance limit.

So dry mixing time for further step of Process Validation was accepted as 10 min and for further manufacturing dry mixing was carried out for 10 min.

Compression:

Equipment Name: Compression Machine 12 stations

At four different compression speed

- Y1: 13 RPM
- Y2: 18 RPM
- Y3: 22 RPM
- Y4: 28 RPM

Evaluation:

Table: Evaluation of mixed blend of drug and excipients

Batch no.	Bulk density (gm/mL) ± SD	Tapped density (gm/mL) ± SD	Compressibility Index (%)	Hausner Ratio	Angle of repose
Y1	0.484±0.02	0.512±0.03	5.8	1.051	29
Y2	0.679±0.02	0.718±0.05	5.799	1.061	24
Y3	0.578±0.78	0.657±0.04	11.71	1.131	21
Y4	0.565±0.03	0.642±004	11.79	1.133	28

Loss on drying:

1 gram of powder is weighed and placed into an oven at 105 c for 2 hrs.

Table: loss on drying results for powder blend

Sample location	% loss (%w/w)			
	Y1	Y2	Y3	Y4
Top left	0.3	0.2	0.3	0.2
Top right	0.3	0.3	0.3	0.3
Middle	0.3	0.2	0.3	0.2
Bottom left	0.3	0.3	0.3	0.3
Bottom right	0.2	0.3	0.3	0.3
NMT 0.5 % w/w				

Table: Evaluation of compressed tablets of batch Y1.

	Weight of Tablet (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)
Avg.	349.5	9.5575	4.508	2.4
SD	1.820208	0.018311	0.089537	0.091766
RSD	0.520134	0.191654	1.986176	3.823596

Table: Evaluation of compressed tablets of batch Y2.

	Weight of Tablet (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)
Avg.	350.25	9.55	4.5475	2.5
SD	0.850696	0.009177	0.004443	0.032444
RSD	0.242883	0.09609	0.097694	1.29771

Table: Evaluation of compressed tablets of batch Y3.

	Weight of Tablet (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)
Avg.	347.75	9.5675	4.547	2.485
SD	10.68632	0.03726	0.004702	0.036635
RSD	3.072988	0.38942	0.103401	1.474236

Table: Evaluation of compressed tablets of batch Y4.

	Weight of Tablet (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)
Avg.	355.35	9.57	4.5455	2.475
SD	10.91245	0.023396	0.025849	0.044426
RSD	3.070902	0.244471	0.568667	1.794997

Table: % Friability.

% Friability	Y1	Y2	Y3	Y4
%	0.2898	0.43352	0.581395	0.4304

Table: Disintegration time (Seconds)

	Y1	Y2	Y3	Y4
AVG	27.6	21.8	21.7	21.6
SD	1.646545	0.421637	0.674949	0.699206
RSD	5.965743	1.934115	3.110362	3.237064

Table: % Assay.

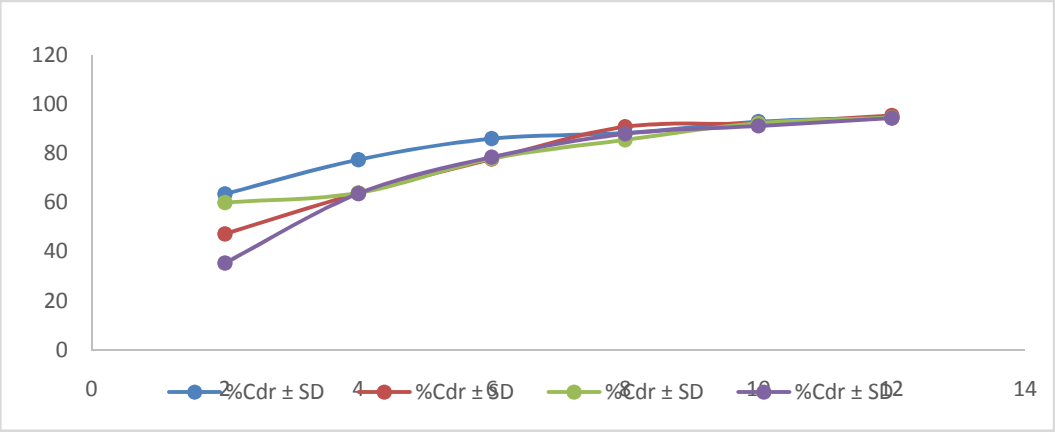
% Assay	Y1	Y2	Y3	Y4
%	99.8	100	100	100

Table: Wetting time. (Seconds)

	Y1	Y2	Y3	Y4
AVG	21.7	20.1	20.2	20.3
SD	0.483046	0.316228	0.421637	0.483046
RSD	2.226018	1.573272	2.087312	2.379536

Table: Dissolution study:

Time	**%Cdr ± SD**			
	Y1	**Y2**	**Y3**	**Y4**
0	-	-	-	-
2	63.505±0.02	47.2±0.02	59.925±0.02	35.395±0.03
4	77.43±0.01	63.75±0.03	63.875±0.03	63.645±0.01
6	86±0.01	77.675±0.02	77.8±0.02	78.475±0.02
8	88.28±0.03	90.77±0.01	85.465±0.01	87.955±0.02
10	92.88±0.03	92.17±0.01	92.265±0.01	91.15±0.02
12	94.61±0.01	95.385±0.03	94.574±0.02	94.36±0.03



Conclusion

So, depending upon all four batches results, it was concluded that at 18 RPM batch Y2, weight variation, thickness, hardness, assay and friability gave optimum results.

Assay was obtained 100% which was within the acceptance criteria i.e. 95% to 105%.

So, here it was concluded that, at 18 RPM all parameters were optimum.

10min time for dry mixing was optimum.

Stability study:

Condition at which tablets are kept for the stability study:

At room temp. For six weeks (A)

45 c and 75% RH for six weeks (B)

Table: Evaluation of compressed tablets of batch A.

	Weight of Tablet (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)
Avg.	349.9	9.574	4.509	2.49
SD	1.651156	0.024581	0.088609	0.044721
RSD	0.471894	0.256744	1.965162	1.796039

Table: Evaluation of compressed tablets of batch B.

	Weight of Tablet (mg)	Diameter (mm)	Thickness (mm)	Hardness (Kg/cm^2)
Avg.	350.15	9.5715	4.5475	2.46
SD	0.812728	0.0224121	0.02673	0.50262
RSD	0.232108	0.252013	0.587788	2.04319

Table: % Friability.

% Friability	A	B
%	0.0727	0.723

Table: Disintegration time. (Seconds)

	A	B
Avg.	21.9	21.2
SD	0.316228	0.421637
RSD	1.443962	1.988854

Table: wetting time of the tablets (Seconds)

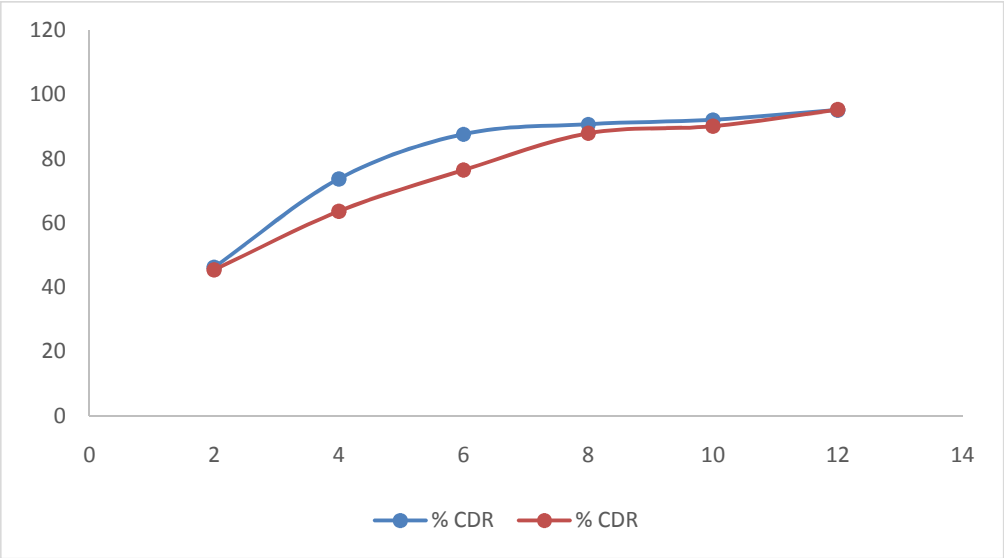
	A	B
Avg	21.83333	22.16667
RSD	1.869839	1.841722

Table: Assay results

Batch no.	% assay
A	100
B	100

Table: Dissolution study.

Time	% CDR	
	A	B
0	-	-
2	46.2±0.01	45.395±0.03
4	73.75±0.01	63.645±0.01
6	87.675±0.03	76.475±0.01
8	90.77±0.02	87.935±0.02
10	92.167±0.02	90.15±0.01
12	95.225±0.02	95.326±0.01



FINISHED PRODUCT ANALYSIS RESULTS:

Table: Analytical results of finished product

Sr. No.	Parameter	Specification	Batch No.
			Y2
1.	Appearance	White colour standard concave round shaped uncoated tablet plane on both sides.	White colour standard concave round shaped uncoated tablet plane on both sides.
2.	Weight of 20 Tablets (gm)	7gm ± 2% (6.86 gm to 7.14 gm)	7.005gm

3.	Individual Weight Variation (mg)	350±5% (332.5mg to367.5mg)	350.25mg
4.	Diameter (mm)	9.50 mm ± 0.2 mm (9.30 mm to 9.70 mm)	9.5575mm
5.	Thickness (mm)	4.50 mm ± 0.2%(4.30mm to 4.70mm)	4.54
6.	Hardness (Kg/cm^2)	NLT 1.5 Kg/cm^2	2.5k.g/cm²
7.	Friability	NMT 1.0 % w/w	0.26 % w/w
8.	Disintegration time (min)	NMT 3min	22 second
9.	Identification test By HPLC	Carbamazepine tablets complies as per Assay; the principle peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the standard solution.	Complies
10.	Assay	95% to 105%	100%

CONCLUSION

Mixing: In order to fix the optimum/ satisfactory mixing time, samples were collected from the pre-designed location at different time intervals (5, 10, 15 min) and was analysed &10 minute time was found to be satisfactory and meets the predetermined specification and quality attribute.

Compression: compression was carried out on different RPM. (13, 18, 22, 28 RPM/MIN) From the results obtained, the physical characteristics Hardness, Thickness and Friability was found to be satisfactory, the assay and dissolution of samples collected at predetermined time intervals found to be within the limits and meets predetermined specification and quality attribute.

Finally, it can be concluded that 10 minute mixing time and 18 RPM gave the satisfactory results regarding all parameters for tablet manufacturing process.

All the analytical data derived during prospective validation of Carbamazepine orodispersible tablet within limits.

Hence the process is validated.

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