Revista de Ciências Farmacêuticas Básica e Aplicada
Journal of Basic and Applied Pharmaceutical Sciences

Rev Ciênc Farm Básica Apl., 2010;31(1):25-31
ISSN 1808-4532

Pharmaceutical equivalence of gabapentin tablets with various extragranular binders

Swati Jagdale[1]*; Bhanudas Kuchekar[1]; Jibanananda Satapathy[1]; Aniruddha Chabukswar[1]

[1] MAEER's Maharashtra Institute of Pharmacy, Pune 411 038, Maharashtra, India

Recebido 23/08/2009 / Aceito 14/06/2010

ABSTRACT

Gabapentin is widely used as an oral anti-epileptic agent. However, owing to its high crystallinity and poor compaction properties, it is difficult to form tablets of this drug by direct compression. The aim of this study was to develop gabapentin tablets, pharmaceutically equivalent to the brand-name pioneer product Neurontin® (marketed in USA). Gabapentin 800mg tablets were produced by wet granulation with a constant concentration of intragranular binder and a varying concentration of extragranular binders (A = polyvinylpyrrolidone K30, B = hydroxypropylmethylcellulose 15 cps, C = Kollidon VA64, D =Klucel EXF). The tablets that did not vary in weight, thickness or hardness and had appropriate friability and disintegration profiles were coated with a 3% film-coating solution. Seven formulations F1 (A 3%), F2 (A 6%), F3 (B 3%), F4 (B 6%), F5 (C 3%), F6 (C 3%) and F7 (D 3%) were prepared. Among these, F6 exhibited adequate hardness, friability, disintegration, uniformity of content and total drug dissolution after 45minutes. Comparing the F6 dissolution profile with that of the brand-name tablets, the difference factor (f1) was 5.93 and the similarity factor (f2) 67.85. Hence, formulation F6 was found to be equivalent to Neurontin®.

Keywords: Dissolution. Gabapentin. Tablet. Binder. Pharmaceutical equivalence.

INTRODUCTION

Gabapentin is slowly and partially absorbed from the gut. It is taken orally in the form of tablets of 300mg, 400mg, 600mg and 800mg. A unique feature of gabapentin oral absorption is that its bioavailability is not proportional to dose (such that as dose increases, bioavailability decreases). For example, a 400mg dose is about 25% less bioavailable than 100mg dose (Orangebook FDA). Food has no effect on the rate and extent of absorption of gabapentin.

Corresponding Author: Dr. Swati Jagdale, MAEER's Maharashtra Institute of Pharmacy, MIT Campus, Paud Road, Pune 411 038, Maharashtra, India tel:91-9881-478118 - fax:91-20-2546-0616 - e-mail:jagdaleswati@rediffmail.com

The mechanism by which gabapentin exerts its anticonvulsant action is unknown. Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid), but its mechanism of action is different from that of several other drugs that interact with GABA synaptic receptors, including valproate, barbiturates, benzodiazepines, GABA agonists, GABA uptake inhibitor and GABA prodrugs. *In vitro* studies with radiolabelled gabapentin have characterised a novel peptide binding site in rat brain tissue, including the neocortex and hippocampus, that may relate to the anticonvulsant activity of gabapentin and its structural derivatives. However, the identity and function of the gabapentin binding site remain elusive. Gabapentin at normal clinical concentrations does not bind to many common drug or neurotransmitter receptors of the brain, such as $GABA_A$, benzodiazepine, glutamate, glycine, aspartate or $GABA_B$ receptors (Chen et al., 2005). Gabapentin does not interact with sodium channels *in vitro*. The relevance of the various activities of gabapentin to its anticonvulsant effects remains to be established (Tripathi, 2004). Dose proportionality of gabapentin gastric retentive extended release tablets has been studied in beagle dogs (Cowles et al., 2006).

For prosthetic neuralgia, gabapentin treatment is initiated as a single 300mg dose on day one, followed by 600mg on day two (300mg twice a day) and 900mg on day three (in three doses). The dose can subsequently be titrated up as needed for pain relief to a daily dose of 1800mg (600mg three times a day). For epilepsy, the effective dose is 900-1800mg/day. This may be increased up to 2400mg-3600mg/day. In the bioavailability classification system, gabapentin is classified as a class 3 drug because of its high water solubility (1 part gabapentin in 2 parts water) and its low permeability and partition coefficient, log P(n-octanol/buffer, pH 7.4) being 1.25.

Tableting behavior, flowability and the tendency to stick to the punches can be affected by the choice of crystal form (Martino et al., 1996) or degree of crystallinity (Rasenack and Muller, 2002). For example, monolithic crystals lead to unstable tablets with high capping tendency, owing to the rigid molecular structure in the crystal, while orthorhombic crystals show better compression behavior (Martino et al., 1996). Amorphous particles are likely to

show plastic deformation upon compaction, substantial lubrication sensitivity (Eissens et al., 2002) and stronger bonding than crystalline forms, resulting in higher mechanical strength (Bozic et al., 2008). On the other hand, highly crystalline materials generally fragment, leading to a larger surface area and increased number of contact points suitable for bond formation. In both stages of compression, adequate tablet strength can be obtained (Aldeborn & Nystrom, 1996).

Therefore, successful compaction depends on a combination of crystallinity-related properties and these should be first ascertained by studying the physics of compaction of each drug. Despite the importance of such information, in the case of gabapentin, it is only known that its crystallinity is high on account of its poor compatibility with excipient. The diverse absorption, distribution and elimination profiles of gabapentin make it interesting and challenging to prepare suitable oral dosage forms of the drug. However, a survey of the literature shows that very few data on oral formulations of gabapentin are available for study. Given that gabapentin is a high-dose drug that is hard to compress directly into tablets, the objective of this study was to develop tablet formulations of gabapentin by wet granulation, with the intragranular binder content fixed at 800 mg, pharmaceutically equivalent to Neurontin®. The proposed method would make the process more consistent and therefore feasible for industrial production, while maintaining pharmaceutical equivalence to the USA reference standard pharmaceutical form.

MATERIAL AND METHODS

All pharmaceutical grade material was bought from Pharmaceutical suppliers. Gabapentin (active) (98.0% -102.0% pure, as required in the USA Pharmacopoeial Forum) was bought from Shasun Chemicals (Chennai, India). Kollidon VA 64, Corn starch 400L, HPC Klucel-LF, PVPK 30, HPMC 15 cps, Klucel EXF, L-HPC-11, magnesium stearate, polyethylene glycol-6000 and talc were all bought from Signet Chemicals (Mumbai).

Preformulation study

Preformulation study is the first step in the rational development of dosage forms. The detailed physical and chemical properties of a drug substance, alone and in combination with excipient, are evaluated in preformulation studies.

Procedure for drug and excipient incompatibility study

Gabapentin drug was mixed with excipients in various ratios. Aliquots of these mixtures and the drug alone were kept in open 5mL glass vials, exposed to 40°C and 75% relative humidity for one month and, at intervals of 2 weeks and 4 weeks, the samples were withdrawn to make physical observations and analyze for related substances formed after the exposure of the drug and excipient.

a) **Physical observation** - Significant color changes were observed after exposure of drug and excipient to 40°C and 75% relative humidity for 2 and 4 weeks.

b) **Related substance observation** - Related substances were observed by chromatography, with a Shimadzu VP Series HPLC system (HP 1050 HPLC C 18) (Wilmington, DE). Samples were tested for related substances before and after the period of exposure (to 40°C and 75% RH for 2 weeks and 4 weeks) of drug & excipient. Related substances were analyzed by the following method.

Procedure for gabapentin-related substance quantitation

i) Diluent preparation – 2.32 g of monobasic ammonium phosphate was dissolved in 1000mL of water and adjusted with phosphoric acid to a pH of 2.0.
ii) Mobile phase preparation – A filtered mixture of buffer solution and acetonitrile (76:24) was degassed by passing it through a filter.
iii) Buffer solution preparation – 0.58g of monobasic ammonium phosphate and 1.83g of sodium perchlorate were dissolved in 1000mL of water and adjusted with perchloric acid to a pH of 1.8.
iv) Impurities solution preparation – Suitable quantities of USP gabapentin-related compound A RS and USP gabapentin-related compound B RS were dissolved in methanol to obtain a solution containing about 1.4 mg per mL and 0.84 mg per mL, respectively.
v) System suitability solution preparation – A suitable quantity of USP gabapentin RS was dissolved in diluent and an appropriate volume of impurities solution was added, to obtain a solution containing about14.0 mg per mL, 0.014mg per mL and 0.0084mg per mL of USP gabapentin RS, USP gabapentin-related compound A RS and USP gabapentin-related compound B RS, respectively.
vi) Standard preparation - Accurately weighed quantities of USP gabapentin RS and USP gabapentin-related compound E RS were dissolved in diluent, and diluted quantitatively (stepwise if necessary) with diluent, to obtain a solution having known concentrations of about 14.0 mg per mL and 0.0084mg per mL, respectively.
vii) Assay preparation - About 350mg of gabapentin was transferred to a 25 mL volumetric flask, dissolved in diluent, diluted to volume and mixed.
viii) Chromatographic system - The liquid chromatograph was equipped with a detector set at 210nm and a 4.6mm x 25cm column that contained L1 packing. The flow rate was maintained at 1mL per minute and the column temperature at 400C. The system suitability solution was chromatographed and the peak responses were recorded and measured as in the procedure below, the relative retention times being about 2.75 for gabapentin-related compound A, 3.3 for gabapentin-related compound B and 1.0 for gabapentin, while the resolution, R, between gabapentin-related compound A and gabapentin-related compound B was not less than 2.3. The standard preparation was then chromatographed and the peak responses recorded as directed in the procedure, the relative retention times being about 2.7 for gabapentin-related compound E and 1.0 for gabapentin, with a relative standard deviation for replicate injections not more than 2.0% for the gabapentin peak.
Procedure - Equal volumes (about 20µL) of standard preparation and assay preparation were injected separately

into the chromatograph, the chromatograms were recorded and the responses for major peaks measured. The quantity (in mg) of $C_9H_{17}NO_2$ in the portion of gabapentin injected was calculated by the formula $25C(r_u / r_s)$, in which C is the concentration, in mg per mL, of USP gabapentin RS in the standard preparation and r_u and r_s are the respective peak areas for the assay and standard preparations.

Preparation of Gabapentin Tablets

The tablets were prepared by wet granulation. In each formula described in Table 1 the intragranular binder was kept constant, while the extragranular binders were varied between higher and lower concentrations.

Table 1. Composition (mg) of gabapentin 800mg tablet formulations.

Name of ingredient	F1	F2	F3	F4	F5	F6	F7
Intragranular							
Gabapentin	803.27	803.27	803.27	803.27	803.27	803.27	803.27
Corn starch 400L	159.23	159.23	159.23	159.23	159.23	159.23	159.23
HPC Klucel-LF	33	33	33	33	33	33	33
Water	qs	Qs	Qs	qs	Qs	qs	qs
Extragranular							
PVK 30	33	66					
HPMC 15 cps			33	66			
Kollidon-VA64					33	66	
Klucel EXF							33
Corn starch 400L	33	16.5	33	16.5	33	16.5	33
L-HPC-11	33	16.5	33	16.5	33	16.5	33
Magnesium stearate	5.5	5.5	5.5	5.5	5.5	5.5	5.5

qs: Sufficient quantity

The binder solution was prepared by adding HPC to warm water with continuous stirring until a clear solution was obtained. The intragranular ingredients, gabapentin API and cornstarch 400L, were passed through sieve #40 and dry mixed for 10 minutes at a chopper speed of 150 rpm in a rapid mixer granulator (Cadmach, Ahmedabad, India). This mixture was granulated with binder solution, keeping the chopper speed at 150 rpm and impeller speed at 2000 rpm, for 10 minutes. The wetted granules were then dried in a rapid drier (Remi Motors, Mumbai, India) until moisture fell to the limit of detection (≤2%). Dried granules were passed through sieve #20. All extragranular ingredients were passed through sieve #40 (sieve #60 for magnesium stearate, due to its small particles). The dried granules were mixed with all the extragranular ingredients except magnesium stearate for 20 minutes. These mixed granules were lubricated with magnesium stearate for 5 minutes. Lubricated granules were assessed for bulk density, tap density, compressibility index and Hausner ratio, to check their flow properties. For this purpose, an accurately weighed 50g of the granules (M) was carefully poured into a graduated cylinder and the initial volume (Vo) was measured. The graduated cylinder was then closed with a lid and set in a bulk density determination apparatus (Electro lab, Mumbai). After the density apparatus had executed the required number of taps, the final volume (Vf) was measured and the operation continued until two consecutive readings were equal. Bulk density, tapped density, compressibility index and Hausner ratio were determined with the following formulas:

True density = M/Vt

Bulk density = M/ Vo

Tapped density = M/Vf

Compressibility index (Ci) = 100 x (Vo – Vf / Vo)

Hausner Ratio = Tapped density / Bulk density

where M = Weight of the powder (granules) taken

Vo = Initial volume

Vt = True volume

Vf = Final volume.

The lubricated granules were compressed in a tablet press (Cadmach, Ahmedabad, India).

Well-compressed tablets having no perceptible variation in weight or thickness, with good hardness, friability and disintegration time, were coated with the 3% film coating solution described next.

Preparation of 3% coating solution

Table 2. Coating solution composition

Sr. N°	Ingredients	%w/w	mg/tablet	Qty/batch in g
1	HPMC 15 cps	(76%)	25.08	25.08
2	Polyethylene glycol-6000	(12%)	3.96	3.96
3	Talc	(12%)	3.96	3.96
4	Distilled water	(6% solution)	6%w/w	344.6

The coating solution formula is described in Table 2. Half of the water was heated to a temperature of 60-70°C and HPMC 15 cps was added to the warm water under stirring, to obtain a clear solution. Talc was added to a second portion of water and homogenized in a Pharma R&D homogeniser (Remi Motor, Mumbai, India). PEG-6000 was added to the rest of the water. All three solutions were mixed and stirred for 30 minutes with a mechanical stirrer (Remi Motor, Mumbai, India). The coating solution was passed through nylon cloth (100 mesh). Tablets were then coated in a Pharma R & D Coater (Ideal Cure Pvt Ltd, Mumbai) under appropriate conditions: inlet temp=65°C, bed temp=50°C, coating pan speed=22 rpm, atomization air pressure=2 kg/cm^2, peristaltic pump =1 rpm.

Characteristics of Tablet formulations

The tablets were characterized by weight, hardness, disintegration, friability, content uniformity of dose and dissolution profile. The average weight was measured over 20 minutes, as recommended by the United State Pharmacopoeia (U.S.P), 2006. The hardness was determined in a Schleuniger Hardness Tester over 10 tablets. For each formulation, the friability was tested in a friabilator over a sample of 20 tablets and the acceptance criterion was a maximum loss of 2% of initial weight (U.S.P. 2006). The disintegration was carried out in a disintegrator (Electro Lab, Mumbai, India), the time taken being compared with the acceptance criterion for a conventional tablet. The drug content of each batch was assayed by high performance liquid chromatography. Samples were analyzed on a Hewlett-Packard 1050 HPLC (Wilmington, DE) with UV detection at 210 nm. Separation was performed on a Brownlee (Boston, MA) Spheri-5 cyano column with a mobile phase of phosphate buffer (pH=6.2), acetonitrile and tetrahydrofuran (92:5:3%), delivered isocratically (1mL/min) (Ciavarella USA Patent).

Dissolution Assay

Tablet dissolution was assessed in a standard USP 24 apparatus II in 900 mL of 0.06 N HCL. The stirring speed was 50 rpm. A total of 6 tablets were used in the test. Temperature was maintained at 37°C±0.5°C throughout the experiment. Dissolution was monitored for 60 min, samples being taken at 5 min, 10 min, 15 min, 30 min, 45 min and 60 min. After the collection of each sample, the dissolution medium was replenished with the same volume of fresh medium. The samples were diluted to 100mL with dilution medium and analyzed for drug content by HPLC. A calibration curve was generated from HPLC chromatograms of standard solutions.

The standard deviation (SD) and the relative standard deviation (RSD) were calculated for each interval, for each tablet tested and the reference drug. From all the above data, the difference (f_1) and similarity (f_2) factors of the dissolution profiles were calculated, employing Excel 6.0 software.

Stability study

The tablets were exposed to 40°C/75% relative humidity for 1 month, 2 months and 3 months. Tablets were withdrawn at these times to analyze properties such as color, water content, dissolution, assay etc.

RESULTS

Table 3. Physical observations in preformulation drug and excipient exposure study.

Drug & Excipient	Initial	40°C & 75% RH for 2 weeks	for 4 weeks
Drug	White crystalline powder	No change	No change
Drug+ sodium lauryl sulphat	White crystalline powder	Off-white crystalline powder	Light yellow crystalline powder
Drug+ Talc	White crystalline powder	No change	No change
Drug+ Magnesium stearate	White crystalline powder	No change	No change
Drug+ Microcrystalline cellulose	Off-white crystalline powder	No change	No change
Drug+ Kollidon VA 64	White crystalline powder	Slight off white	Slight off white
Drug+ Maize starch	White crystalline powder	No change	No change
Drug+ Lactose	Off-white crystalline powder	White crystalline powder	Blackish white crystalline powder
Drug+ PEG 400	Off white lumpy mass	Pale yellow lumpy mass	Pale yellow lumpy mass
Drug+ PEG 6000	White crystalline powder	Pale yellow lumpu mass	Pale yellow lumpy mass
Drug+ LHPC 11	White crystalline powder	Pale yellow lumpy mass	
Drug+ Lactose DCL21	Off-white crystalline powder	Slightly off-white	Slightly off-white
Drug+ Klucel LF	White crystalline powder	No change	No change
Drug+ Corn starch 400 L	White crystalline powder	No change	No change
Drug+ Titanium dioxide	White crystalline powder	No change	No change
Drug+ HPMC 15 CPS	Off-white crystalline powder	No change	No change
Drug+ Kollidon CLM	Off-white crystalline powder	White crystalline powder	White crystalline powder
Drug+ PVP K 30	White crystalline powder	Slightly off-white	Slightly off-white

RT-room temp, RH- relative humidity (±5%)

As can be seen in Table 3, no color change was observed in any excipient except in sodium lauryl sulphate and lactose. It was thus expected that there might be interaction between these two excipients and gabapentin. As Table 4 shows, excepting sodium lauryl sulphate and lactose, all the combinations exhibited impurity profiles within the reference limit (after exposing the drug excipient combination to 40°C for 2 weeks and 4weeks, the total impurity should not be more than 0.3%).

Table 4. Related substance observations in preformulation study.

Drug & Excipient	Initial total impurity (%w/w)	Total impurity after 2 weeks at 40°C (%w/w)	Total impurity after 4 weeks at 40°C (%w/w)
Drug+ Sodium lauryl sulphate	0.058	1.23	1.97
Drug+Talc	0.001	0.004	0.004
Drug+ Magnesium stearate	0.003	0.004	0.005
Drug+ Micro crystalline cellulose	0.0002	0.0005	0.0005
Drug+ Kollidon CLM	0.1	0.16	0.27
Drug+ Kollidon VA 64	0.543	0.601	0.655
Drug + corn starch 400L	0.0008	0.0008	0.0008
Drug+ Lactose	0.641	1.652	1.890
Drug+ PEG 6000	0.006	0.006	0.006
Drug+ LHPC 11	0.009	0.089	0.127
Drug+ Klucel LF	0.055	0.076	0.078
Drug+ Titanium dioxide	0.0001	0.001	0.007
Drug+ HPMC 15 CPS	0.0007	0.0007	0.0007
Drug+ PVP K 30	0.099	0.012	0.014
Drug+ PEG 400	0.006	0.006	0.006
Drug+ Maize starch	0.0073	0.0075	0.0075

Thus, it was confirmed that sodium lauryl sulphate and lactose interact with gabapentin and hence cannot be used in the formulation. All the exipients were compatible except sodium lauryl sulphate and lactose. The compatibility study report is shown in Table 5.

Table 5. Drug-excipient compatibility report.

Name of the Excipient	Category	Remarks
Corn starch	Disintegrant	Compatible
L-HPC-11	Anticapping/ Disintegrant	Compatible
Sodium starch Glycolate	Disintegrant	Compatible
Kollidone VA 64	Binder	Compatible
Kollidone CLM	Disintegrant	Compatible
Klucel LF	Binder	Compatible
Polaxomer-407	Solubuliser	Compatible
MCC	Diluent	Compatible
Sodium laruylsulphate	Surfactant	Incompatible
Magnesium stearate	Lubricant	Compatible
Talc	Anti adherent	Compatible
Klucel-EXF	Binder	Compatible
HPMC 15 CPS	Polymer for coating	Compatible
Titanium dioxide	Opacifier	Compatible
Ethyl cellulose	Polymer for coating	Compatible
Poly ethylene glycol 6000	Plasticizer	Compatible
PVP K 30	Binder	Compatible
Lactose	Diluent	Incompatible

The characteristics of the granules are shown in Table 6.

Table 6. Characteristics of granules.

No	Parameters	F1	F2	F3	F4	F5	F6	F7
1	Loss on drying or water content % w/w	1.75%	1.43%	1.87%	1.90	1.76	1.87	1.91
2	Bulk density gm/mL	0.4711	0.4955	0.5384	0.530	0.500	0.5166	0.573
3	Tapped density gm/mL	0.5341	0.5627	0.6181	0.590	0.560	0.5776	0.620
4	Compressibility index %	11.79	12.44	12.94	10.16	11.50	10.56	7.58
5	Hausner' s ratio	1.13	1.13	1.14	1.11	1.13	1.11	1.08

They clearly indicate that the granules were all of the free-flowing type, as their compressibility indices (Ci) were within the range 5-12 and Hausner ratios within 1.0-1.2 (USP 2009) The characteristics of the tablets are shown in Tables 7 and 8.

Table 7. Characteristics of 800mg gabapentin core tablets.

Batch No.	Hardness (N)	Thickness (mm)	Friability %	Weight Variation % w/w	Disintegration time (min)
F1	170-180	7.48-7.52	Capping	NA	20
F2	170-180	7.48-7.52	0.52	±1.09%	27
F3	170-180	7.48-7.54	Capping	NA	23
F4	170-180	7.48-7.54	0.63	±1.25%	25
F5	170-180	7.48-7.52	Capping	NA	20
F6	170-180	7.48-7.52	0.72	±1.2%	21
F7	170-180	7.48-7.52	0.45	±1.1%	22

Table 8. Characteristics of 800mg gabapentin coated tablets.

Batch No.	Hardness (N)	Thickness (mm)	Friability %	Weight Variation % w/w	Disintegration time (min)
F1	NA	NA	NA	NA	NA
F2	200-220	7.54-7.58	NA	±1.1%	28
F3	NA	NA	NA	NA	NA
F4	200-220	7.54-7.59	NA	±1.30%	27
F5	NA	NA	NA	NA	NA
F6	200-220	7.49-7.55	NA	±1.2%	23
F7	NA	NA	NA	±1.42%	NA

Formulation 1 (F1) clearly showed capping. In formulation 2 (F2), the drug release was relatively slow and failed to match that of the reference drug, as the release remained below 90% after 45 min (as shown in Tables 7 and 8 and Figure 1).

Similar results were obtained for formulations 3 (F3) and 4 (F4) (Tables 7 and 8 and Figure 1). The similarity and difference factors of some of the formulations are shown in Table 9.

Table 9. Similarity (f_2) and difference (f_1) factors of several formulations.

F Value	F2	F4	F7	F6
f_1	25.81	18.60	31.93	5.93
f_2	34.84	42.91	32.36	67.85

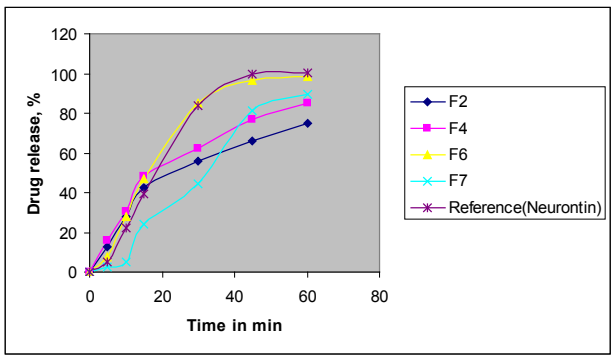

Figure 1. Comparative drug release profiles of various formulations.

In formulation 5 (F5), capping was also observed (Table 7). Only in the case of formulation 6 (F6), which had a higher concentration of extragranular binder (Kollidon VA 64) was an adequate result obtained. There was no capping and the drug release exceeded 90% withn 45 minutes, like that of the reference drug, as shown in Table 10 and Figure 1.

In formulation 7 (F7), the drug was also released more slowly than from Neurontin®, as shown in Figure 1. It was thus decided not to test this extragranular binder (Klucel EXF) at the higher concentration, as the drug release would be even slower.

Table 10. Dissolution profile of F6.

Time (min)	Tab-1	Tab-2	Tab-3	Tab-4	Tab-5	Tab-6	Mean	SD	RSD
5	5.6	4.6	5.3	6.8	5.3	4.3	5.3	±0.88	16.60
10	24.0	19.7	22.8	24.8	21.2	19.9	22.0	±2.14	9.73
15	43.4	35.7	40.9	43.1	37.1	37.0	39.5	±3.37	8.53
30	86.7	76.8	87.2	86.6	82.7	82.3	83.7	±4.02	4.80
45	99.5	97.3	100.7	100.2	100.2	99.7	99.6	±1.20	1.20
60	99.9	99.4	101.1	100.7	101.0	100.2	100.4	±0.69	0.69

Table 11. Calculation of difference (f_1) and similarity (f_2) factors of F6.

Time t (min)	Rt	Tt	Rt-Tt	(Rt-Tt)^2
0	0	0	0	0
5	7.5	5.3	2.2	4.84
10	28	22	6	36
15	47	39.5	7.5	56.25
30	84.8	83.7	1.1	1.21
45	96.7	99.6	2.9	8.41
60	98.7	100.4	1.7	2.89
∑	362.7	350.5	21.4	109.6
Number of points		6		
f_1	5.93			
f_2	67.85			

Rt: mean % drug dissolution from innovator tablets at time t

Tt: mean % drug dissolution from F6 tablets at time t

As adequate results were obtained only for F6, its dissolution profile alone is reported in Tables 10 and 11. These clearly indicate that the drug release from F6 was greater than 90% after 45 min, like that of the reference drug, and that its similarity factor exceeded 50%, while its difference factor was less than 10%, placing it well within the reference limits Pharmacopoeial forum, 2006.

Uniquely among the seven formulas, the F6 tablets showed adequate hardness, thickness, friability and disintegration, as well as a dissolution profile close to that of the reference drug. The results of tests on the stability of F6 are given in Table 12.

Table 12. Stability study results for F6.

Conditions	Period	Description	Avg wt (mg)	Hardness	Disint time (min)	Moisture (%w/w)	Avg drug release in 45 min	Assay
Room temp	Initial	White	1133	230N	25	1.58	99.6%	101%
40°C/75 %RH	1 month	White	1133	220N	26	1.67	98.2%	100.87%
40°C/75 %RH	2 months	White	1133	265N	26	1.67	97.4%	100.87%
40°C/75 %RH	3 months	White	1133	270N	26	1.67	97.2%	100.85%

It was found that all the tablets of F6 showed expected hardness, disintegration time and moisture content. Also, their dissolution in 45 minutes was more than 90% and the drug assay was 100%.

DISCUSSION

Drug dissolution testing is an integral part of drug product development and manufacturing and is also used as a quality control tool, to monitor batch-to-batch consistency

of the drug release from a product (Qureshi & McGilveray, 1999). It is desirable to have an *in vitro* method of testing dissolution that is sensitive to formulation factors that affect the dissolution process and thus bioavailability. As a result, the reliability and discriminatory capabilities of dissolution tests for tablets has attracted much attention in recent years. (Dumont et al., 2007).

In standard tests, the dissolution rate is proportional to the stirring rate, since the higher this rate is, the thinner the surface diffusion layer becomes (Banakar, 1992). Therefore, the dissolution profiles were produced and compared at a constant stirring rate of 50 rpm, using the basket method.

According to Graffner (2006), when a dissolution test method is developed for the market, the official standards of the pharmacopoeia should be adopted. Alternative methods are justified only when official methods are shown to be unsatisfactory and the alternative is and proved capable of distinguishing between batches with acceptable and unacceptable performance.

The comparative analyses of the *in vitro* performance of the formulations were based on the kinetic parameters calculated from dissolution profiles. A quantitative interpretation of the dissolution results was facilitated by mathematical model-based equations (Costa & Lobo, 2001).

The Excel 6.0 software used here provides a very sensitive and accurate method of calculating the values of f_1 and f_2.

Kollidon VA 64 is a polyvinyl pyrrolidone that was used both as a tablet binder and disintegrant. It has suitable flow and compression characteristics that allow it to be used in both roles.

The methods used in the dissolution study and the comparison parameters can be used to compare and identify the differences between formulations, in order to establish acceptance criteria and preview how alterations in manufacturing would affect bioavailability. The comparison of dissolution profiles in terms of f_1 and f_2 proved to be most discriminatory when apparatus I (basket) was used at 50 rpm, in 900 mL of dissolution medium. The values of the formulations indicated pharmaceutical equivalence to the reference tablet.

In this experiment it was seen that in F1, in which PVPK 30 (3%) was used as extragranular binder, capping was observed, but that this problem was solved by increasing this binder concentration from 3% to 6% (F2). However, at 6% PVPK 30, only 65.83% of the drug was released in 45 minutes; this compared poorly with the innovator tablet, which attained a drug release of more than 90% in 45 minutes.

In F3, in which HPMC 15 cps (3%) was used as extragranular binder, capping was observed. Again, by increasing this binder concentration from 3% to 6% (F4), this problem was solved, but only 77.1% of the drug was released in 45 minutes, much less than from the innovator tablet in the same time.

In F5, in which Kollidon VA 64 (3%) was used as the extragranular binder, capping was again observed, but, by increasing this binder concentration from 3% to 6% (F6), this problem was solved. In this case, the drug release matched that of the innovator tablet, being more than 90% in 45 minutes

In F7, in which Klucel EXF (3%) was used as extragranular binder, the drug was released more slowly than in the reference, reaching 81% in 45 min. As there was incomplete drug release in 45 minutes with 3% of the binder, it was decided not to test this binder at the higher concentration, since the release rate would be still lower.

Since acceptable results were obtained with F6, tablets of this batch were kept for stability tests. In these tests, no degradation was observed over 3 months. Hence, this product could be stored for a period of one year or more.

From the good results obtained with F6, it could be concluded that Kollidon VA 64 is the extragranular binder of choice for development of a gabapentin tablet. This choice was confirmed by the stability study, in which the F6 tablets fully met the specifications.

In the stability study, F6 tablets showed the expected hardness, disintegration time and moisture content throughout the 3-month period. Also, the dissolution rate (over 90% in 45 min) and assay (100%) remained good until the end. This product can thus be kept for a period of one year or more, but further stability studies, up to 6 months, will be needed to determine the exact shelf life.

According to official and regulatory guidelines, F6 (formulation 6) is pharmaceutically equivalent to the reference dosage form and could be adopted as an alternative tablet for production in official laboratories, in order to fulfill the objectives of public health policies that seek to provide ready access to rational dosage forms of adequate quality.

ACKNOWLEDGMENTS

The authors are grateful to Mr. Dhananjay Sahoo, Research Scientist, R&D, Alkem Laboratory, Taloja, Mumbai, India for his valuable suggestions from time to time during the work.

RESUMO

Equivalencia farmacêutica de comprimidos de gabapentina com vários ligantes extragranulares

Gabapentina é uma droga de alta dosagem por via oral amplamente usada como agente antiepilético. Devido a sua alta cristalinidade e baixo poder de compactação é difícil formar comprimidos por compressão direta. O objetivo desse estudo foi desenvolver comprimidos de gabapentina, farmaceuticamente equivalente ao produto de referencia Neurontina (vendido nos Estados Unidos). Comprimidos de gabapentina de 800 mg foram produzidos por granulação molhada usando concentrações constantes e variáveis dos ligantes intragranulares (A=PVPK 30, B=HPMC 15 cps, C=Kollidon VA 64, D=Klucel EXF). Os comprimidos sem variação de peso, densidade , dureza , com friabilidade e com perfil de desintegração apropriados foram revestidos com uma solução de revestimento de 3%. Foram feitas sete formulações: F1 (A em baixa concentração), F2 (A em alta concentração), F3 (B em baixa concentração) , F4 (B em alta concentração), F5 (C em baixa concentração), F6 (C

em alta concentração), F7 (D em baixa concentração). Dentre essas formulações a F6 demonstrou dureza adequada, friabilidade, desintegração, uniformidade de conteúdo e total dissolução após 45 minutos. O fator de dissimilaridade (f_1) foi de 5,93 e o fator de similaridade (f_2) foi de 67,85. Portanto, F6 pode ser considerado equivalente a Neurontina.
*Palavras-chave:*Dissolução. Gabapentina. Comprimidos. Ligantes. Equivalência farmacêutica.

REFERENCES

Alderborn G, Nystrom C. Pharmaceutical powder compaction technology. New York: Marcel Dekker; 1996. 610p.

Banakar UV. Pharmaceutical dissolution testing. NewYork: Marcel Dekker; 1992. 437p.

Bozic DZ, Dreu R, Vrecer F. Influence of dry granulation on compactibility and capping tendency of macrolide antibiotic formulation. Int J Pharm. 2008; 357:44-54.

Chen PE, Geballe MT, Stansfeld PJ, Johnston AR, Yuan H, Jacob AL, Snyder JP, Traynelis SF. Structural Features of the Glutamate Binding Site in Recombinant NR1/ NR2A N-Methyl-D-aspartate Receptors Determined by Site-Directed Mutagenesis and Molecular Modeling. Mol. Pharmacol. 2005; 67(5):1470-84.

Ciavarella AB, Gupta A, Khan M., Sayeed V, Volpe D, FaustinoP. A development and validation of stability indicating method for Gabapentin. United states patent. 4, 894, 476.

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

Cowles V, Gusler G, Gu r, Louie-Helm J, Hou E, Berner B. Dose proportionality of gabapentin gastric retentive extended-release tablets in beagle dog. AAPSJ Annual Meeting 2006.

Different market scenario of Gabapentin. Available from: http://www.fda.gov/orangebook

Dumont ML, Berry MR, Nickerson B. Probability of passing dissolution acceptance criteria for an immediate release tablet. J Pharm Biomed Anal. 2007; 44(1):79-84.

Eissens AC, Bolhuis GK, Hinrichs WLJ, Frijlink, HW. Inulin as filler-binder for tablets prepared by direct compaction. Eur J Pharm Sci. 2002; 15(1):31-8.

Graffner C. Regulatory aspects of drug dissolution from a European perspective. Eur Pharm Sci.2006; 29:288-98.

Martino P, Guyot-Hermann AM, Conflant P, Drache M, Guyot JC. A new pure paracetamol for direct compression: the orthorhombic form. Int J Pharm. 1996; 128:1-8.

Qureshi SA, McGilveray IJ. Typical variability in drug dissolution testing: study with USP and FDA calibrator tablets and marketed drug (glibenclamide) product. Eur J Pharm Sci. 1999; 7:249-58.

Rasenack N, Müller BW. Crystal habit and tableting behavior. Int J Pharm.2002; 244(1-2):45-57.

The J of standards development and official compendia revision, Pharmacopoeial forum. 2006; 32(6):1695.

Tripathi KD. Essentials of medical pharmacology. 5th ed. New Delhi: Jaypee Brothers Medical Pub; 2004. p.304-5.