



## Improvement in the Physical and Chemical Stability of Gabapentin by Using Different Excipients

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### ABSTRACT

The aim of this study was to investigate the best stable mix for gabapentin with excipients which have different physicochemical properties under different ambient conditions. Gabapentin undergoes intramolecular cyclization by nucleophilic attack for alkyl amine on carboxylate carbonyl followed by dehydration, so gabapentin needs special conditions of temperature and relative humidity during manufacturing and storage, because gabapentin turns to gabapentin lactam which has toxic effect. Mixtures of gabapentin with each of the following excipients were made: PVP K15, Aerosil K100, Avicel pH101, Mg stearate, hydroxy propyl methyl cellulose (HPMC) were used and milled for five minutes by porcelain mortar and pestle, then the mixtures were kept in open glass containers which kept in desiccators containing different saturated salt solutions to reach the required relative humidity, these desiccators were kept in dry oven to get the required temperature, the samples were withdrawn to analyze for intact gabapentin by high performance liquid chromatography (HPLC) at zero moment (directly after milling) and after the first, second, third, fourth and fifth week. Also sample of raw gabapentin milled for 5 minutes was analyzed to investigate the effect of milling on stability. The best recovery of intact gabapentin was obtained at high relative humidity and low temperature with gabapentin:mg stearate (1:5%) mixture, so it is useful to use this conditions during manufacturing and storage of gabapentin.

**Keywords:** Gabapentin lactam, milling, relative humidity, temperature, excipients.

### INTRODUCTION

Gabapentin is a useful anticonvulsant for treatment of epilepsy and postherpetic neuralgia, and also for prevention of seizures. Since gabapentin structurally resembles the  $\gamma$ -aminobutyric acid (GABA), one of neurotransmitters, it may freely cross the blood brain barrier to cause the higher level of gabapentin in the brain for treatment of seizures. Recently, gabapentin is also widely recommended to relieve pain, especially migraine headache and neuropathic pain<sup>1</sup>. Gabapentin exists as three polymorphs and monohydrate, the commercial drug substance is form II ( $\alpha$ -gabapentin), form III is  $\beta$ -gabapentin, form IV is  $\gamma$ -polymorph. Form III is reportedly unique in that intramolecular hydrogen bonding occurs between the amine and carboxylic acid groups whereas only intermolecular hydrogen bonding has been associated with the crystalline structures of forms II and IV between these groups in the  $\alpha$  and  $\beta$  forms, form I is the hydrate<sup>2</sup>. The interconversion between the polymorphic forms has been reported to occur by thermal treatment and milling<sup>3</sup>. The energetic input of solid state milling change the particle size, surface area, crystallinity of the drugs and induce polymorphic conversion of drugs, resulting in the modification of physio chemical properties of drugs and the changes in their dissolution rates and bioavailability<sup>4</sup>. Milling causes undesired phenomena such as aggregation of fine particles, formation of electrostatic force<sup>5</sup>. The presence of various excipients has been reported to induce differences in the polymorphic composition of co-milled gabapentin<sup>6</sup>.

Thermal induced polymorphic transition of GBP as follows: GBP Form I was dehydrated beyond 55° C and transformed to Form III after heating to 90° C, and then converted to Form IV up to 125° C heating, but Forms II over 126° C and Form III after heating to 75° C directly transformed to Form IV. The GBP Form IV was the last polymorph before intramolecular lactamization of GBP<sup>3</sup>. Most reactions accelerates by increasing temperature, Arrhenius equation is the most famous equation to reveal the effect of temperature on drug stability:

$$k = A \exp \left( \frac{-E_a}{RT} \right)$$

$E_a$  is the activation energy and  $A$  is the frequency factor. If the  $E_a$  for a degradation process is only 10 kcal/mol, a 10°C increase in temperature results in only a 1.76-fold change in drug reactivity. However, if the  $E_a$  is 30 kcal/mol, a 10°C increase in temperature results in about a 5.5-fold increase in the degradation rate.  $E_a$  is stable for certain degradation, so the rate of degradation increases by temperature increasing<sup>7</sup>. The lactamization rate of gabapentin samples was greatest in the presence of the lowest humidity conditions and dramatically decreased with increasing humidity, in particular gabapentin appeared to be much more stable at humidity levels greater than 31% RH. High humidity conditions facilitate the self healing of crystal defects generated by milling, so at high humidity milling damaged crystals are able of recovering or at least transitioning to a form of gabapentin that is incapable of spontaneous dehydration<sup>8</sup>.

So the purpose of this study was to investigate the stability of gabapentin with different excipients and different conditions of temperature and relative humidity after milling for 5 minutes using mortar and pestle, then samples of binary mixtures were analyzed by HPLC to determine the best stable mixture during manufacturing and storage.

## MATERIALS AND METHODS

### Materials

Gabapentin (Hangzhou,China), Polyvinylpyrrolidone (PVP K15, Fluka.Milan-Italy), Aerosil 200 (S.D Fine Chemicals, Mumbai), Hydroxy propyl methyl cellulose K100 (HPMC K100, Shin-Etsu,China), Microcrystalline cellulose PH 101 (Avicel PH101, FMC International, Ireland), Magnesium stearate (Mg stearate, Yung zip chemical, Taiwan) and all other solvents and chemicals used in the study were of analytical grade.

### Methods

Binary mixtures of gabapentin with these excipients: PVP K15- Aerosil 200- HPMC- Avicel – Mg stearate were made as following: 3g of gabapentin and 3g of each excipient were weighted and mixed to form a mixture (1:1), then 3g of gabapentin and 0.15g of Aerosil were weighted and mixed to form a mixture (1:5%), also 3g of gabapentin and 0.15g of Mg stearate were weighted and mixed to form a mixture (1:5%), then every mixture were milled by mortar and pestle for 5 minutes. Mixtures were kept in open 25mL glass containers, then containers were stored in desiccators containing saturated salt solutions to obtain the required relative humidity. The containers were stored in dry oven to obtain the required temperature. The oven temperature was detected by temperature balance, and relative humidity was detected by humidity balance, so the conditions were as following:

RH=30.5% (MgCl<sub>2</sub>), T=25°C.

RH=30.5% (MgCl<sub>2</sub>), T=40°C.

RH=74,4% (NaCl), T=25°C.

RH=74,4% (NaCl), T=40°C.

The samples were withdrawn at zero moment (directly after milling) and after the first, second, third, fourth, fifth week and analyzed by high performance liquid chromatography HPLC following USP NF 2007.

**HPLC:** Hitachi C3E15 Germany, Auto sampler L-2200, Pump L-2130, UV-VIS Detector L-2420, column Hypersil-100 C18, 150X46, part No 37105-154630, Phosphoric acid and Monobasic potassium phosphate(Merck, Germany), Water HPLC grade, Methanol HPLC grade, Acetonitrile HPLC grade. The liquid chromatograph was equipped with a 215nm detector, flow rate 2ml/min, column temperature 40° C.

**Diluent:** 2.32g of monobasic ammonium phosphate was dissolved in 1000ml of water and adjusted with phosphoric acid to PH of 2.0

**Buffer solution:** 0.58g of monobasic ammonium phosphate and 1.83g of sodium perchlorate was dissolved in 1000ml of water, and adjusted with perchloric acid to PH of 1.8

**Mobile phase:** mixture of Buffer solution and acetonitrile (76:24)

**Preparation of mixtures samples:** 140mg (equal to 70mg of gabapentin) of mixtures (1:1) (gabapentin: excipient) and 73.5mg (equal to 70mg of gabapentin) of mixtures (1:5%) (gabapentin: excipient) were weighted and dissolved in 10ml volumetric flask containing diluents, then filtrated by 0.45µm filters and analyzed by HPLC.

**Preparation of standard solution:** 70mg of raw gabapentin was weighted and dissolved in 10ml volumetric flask containing diluents, then filtrated by 0.45µm filters and analyzed by HPLC.

### Preparation samples for analyzing by Dynamic Vapor Sorption DVS

50mg of gabapentin milled for 5 minutes, mixture of gabapentin milled with Aerosil (1:1), mixture of gabapentin milled with Mg stearate (1:5%) were weighted and dried by dry nitrogen up to 0.0%, then relative humidity was increased from 0.0% to 98% by increasing humidity 10% in each step linearity ,then humidity was decreased linearity from 98% to 0.0%.

### Preparation samples for analyzing by Infrared IR

A trace amount of each sample was smeared on one piece of KBr plate (5:95) and directly compressed by a hydraulic press under 200kg/cm<sup>2</sup> for 15s.

## RESULTS AND DISCUSSION

The recovery of gabapentin and standard deviation (SD) are shown in following tables by using HPLC, where every experience was repeated three times.

### Effect of milling and co-milling

Phase changes in the solid state require three steps: molecular loosening, solid solution formation and crystallization of new phase. The stresses applied to crystals during mechanical milling can create new lattice defects in their crystal lattices and contribute to lattice disorder, leading to different packing arrangements and/or conformations within the crystal lattice. The nucleation and growth of new lattice defects may result in solid state polymorphic interconversion upon milling<sup>9</sup>.

The recovery of intact gabapentin 2 decreased after milling for 5 minutes by mortar and pestle, while another study showed that milled gabapentin 2 (using oscillatory ball mill at 20 Hz) degraded after 105 minutes<sup>9</sup>. This may be due to varying the tool that using in milling, because mortar gives shearing energy enough to cause damage in crystal and transfer gabapentin to less stable form. Mortar causes tearing and ripping of samples, much like shearing, but differs in that there is direct contact with sample<sup>10</sup>. The effects of milling could be due to the

dramatic increase in surface area associated with particle size reduction, milling clearly impacted both the generation of gabapentin lactam during this operation

and also affected the susceptibility of the milled material for further degradation by intramolecular cyclization to form gabapentin lactam<sup>8</sup>.

**Table 1:** The recovery of intact gabapentin for binary mixtures of gabapentin and each excipient

Conditions:	Zero moment	First week	Second week	Third week	Fourth week	Fifth week
<b>Gabapentin: PVP K15 (1:1), C=14 mg/ml:</b>						
RH=30.5%; T=25°C	99.14 (218890.56)	83.82 (201616.80)	75.39 (477178.45)	72.36 (558301.83)	71.75 (160857.63)	70.13 (366350.63)
RH=30.5%; T=40°C	99.14 (218890.56)	81.87 (461203.12)	76.93 (140501.98)	71.81 (198829.85)	68.03 (104354.52)	59.71 (2636.51)
RH=74.4%; T=25°C	99.14 (218890.56)	88.79 (649712.50)	88.31 (451689.65)	84.41 (414002.68)	82.12 (309501.51)	74.56 (13056.98)
RH=74.4%; T=40°C	99.14 (218890.56)	84.01 (481871.08)	77.40 (224253.42)	72.84 (192911.85)	72.51 (61109.12)	70.85 (302458.51)
<b>Gabapentin: Avesil (1:1), C=14 mg/ml:</b>						
RH=30.5%; T=25°C	99.16 (42891.00)	84.18 (160271.17)	78.00 (498974.83)	77.11 (516265.05)	75.81 (16151.90)	73.74 (103205.99)
RH=30.5%; T=40°C	99.16 (42891.00)	82.76 (423250.24)	78.25 (306142.91)	73.75 (708763.43)	79.31 (18904.89)	68.43 (125310.93)
RH=74.4%; T=25°C	99.16 (42891.00)	90.94 (324984.34)	90.14 (206377.31)	87.28 (383054.72)	83.49 (327368.30)	76.53 (9880.64)
RH=74.4%; T=40°C	99.16 (42891.00)	88.47 (461686.63)	83.80 (263021.70)	78.47 (196300.90)	75.81 (78153.51)	72.49 (55363.84)
<b>Gabapentin: Aerosil (1:1), C=14 mg/ml:</b>						
RH=30.5%; T=25°C	98.2 (26306.49)	86.10 (223744.17)	78.06 (1009764.08)	71.34 (22221.75)	70.11 (14151.80)	35.12 (80810.28)
RH=30.5%; T=40°C	98.2 (26306.49)	77.68 (194289.78)	70.54 (1627632.08)	69.47 (83674.92)	66.64 (12262.98)	41.24 (114172.72)
RH=74.4%; T=25°C	98.2 (26306.49)	87.03 (259879.62)	75.03 (1768961.81)	73.56 (9875.83)	73.32 (75364.26)	67.30 (72617.98)
RH=74.4%; T=40°C	98.2 (26306.49)	79.07 (389563.61)	73.81 (773187.27)	68.89 (67889.44)	67.19 (9335.66)	61.15 (28525.25)
<b>Gabapentin: Aerosil (1:5%), C=7.35 mg/ml:</b>						
RH=30.5%; T=25°C	99.51 (212388.71)	89.12 (206957.52)	83.10 (223040.09)	82.65 (121675.92)	80.36 (593301.65)	80.05 (221553.74)
RH=30.5%; T=40°C	99.51 (212388.71)	87.27 (433645.25)	85.19 (339023.58)	84.68 (100203.12)	74.39 (6923.75)	74.06 (101126.46)
RH=74.4%; T=25°C	99.51 (212388.71)	94.88 (299594.99)	92.26 (128656.39)	88.35 (125056.32)	85.43 (117965.24)	84.91 (240637.44)
RH=74.4%; T=40°C	99.51 (212388.71)	86.21 (297359.62)	85.47 (236460.21)	84.66 (169631.90)	84.06 (236460.41)	83.84 (119215.67)
<b>Gabapentin: Mg stearate (1:1), C=14 mg/ml:</b>						
RH=30.5%; T=25°C	99.91 (111937.83)	85.74 (215435.91)	81.74 (94026.84)	74.92 (21228.63)	67.24 (83032.91)	65.90 (294407.96)
RH=30.5%; T=40°C	99.91 (111937.83)	74.25 (71911.21)	73.89 (33708.22)	73.67 (36683.68)	72.05 (48412.47)	63.80 (392614.43)
RH=74.4%; T=25°C	99.91 (111937.83)	89.09 (782657.17)	85.71 (325094.51)	84.40 (524353.33)	82.42 (364408.99)	76.80 (6962.53)
RH=74.4%; T=40°C	99.91 (111937.83)	81.52 (85688.63)	75.79 (286664.91)	70.81 (900800.44)	68.95 (53165.16)	66.10 (89413.54)
<b>Gabapentin: Mg stearate (1:5%), C=7.35 mg/ml:</b>						
RH=30.5%; T=25°C	99.92 (256237.11)	91.33 (165684.82)	88.40 (235614.51)	83.52 (331433.56)	81.92 (351118.95)	80.96 (413763.52)
RH=30.5%; T=40°C	99.92 (256237.11)	87.27 (295551.54)	86.38 (270590.62)	82.24 (360593.99)	81.62 (217323.74)	77.54 (344391.22)
RH=74.4%; T=25°C	99.92 (256237.11)	95.78 (165437.12)	93.93 (335194.27)	89.12 (452035.07)	85.99 (54334.14)	83.30 (218860.79)
RH=74.4%; T=40°C	99.92 (256237.11)	89.84 (311632.58)	86.74 (380930.81)	84.66 (532087.76)	83.50 (161992.87)	82.61 (321729.34)
<b>Gabapentin: HPMC (1:1), C=14mg/ml:</b>						
RH=30.5%; T=25°C	99.14 (256739.15)	83.82 (201616.80)	75.39 (477178.44)	72.36 (558301.83)	71.75 (160857.63)	70.13 (366350.62)
RH=30.5%; T=40°C	99.14 (256739.15)	81.87 (461203.12)	76.93 (140501.98)	71.81 (198829.85)	68.03 (104354.52)	59.71 (2636.51)
RH=74.4%; T=25°C	99.14 (256739.15)	88.79 (649712.49)	88.31 (451689.65)	84.41 (414002.68)	82.12 (309501.50)	74.56 (13056.98)
RH=74.4%; T=40°C	99.14 (256739.15)	84.01 (481871.08)	77.40 (224253.42)	72.84 (192911.85)	72.51 (61109.11)	70.85 (302458.50)

The recovery of milled gabapentin for 5 minutes was 98.8% (SD=52759.71).

### Co-milling of gabapentin with excipients

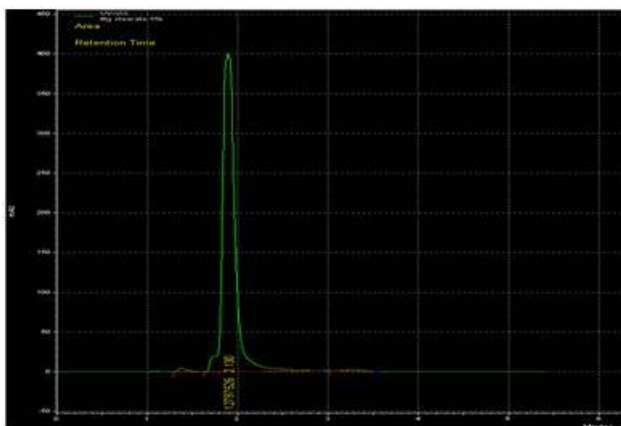
PVP K15 as binder agent in tablets– Avicel as diluents and binder agent– Mg stearate as lubricant– Aerosil as lubricant– HPMC as controlled release agent.

The co-milling effect on the polymorphic change of gabapentin<sup>2</sup> was dependent on the types of additive used. The highest recovery of intact gabapentin was

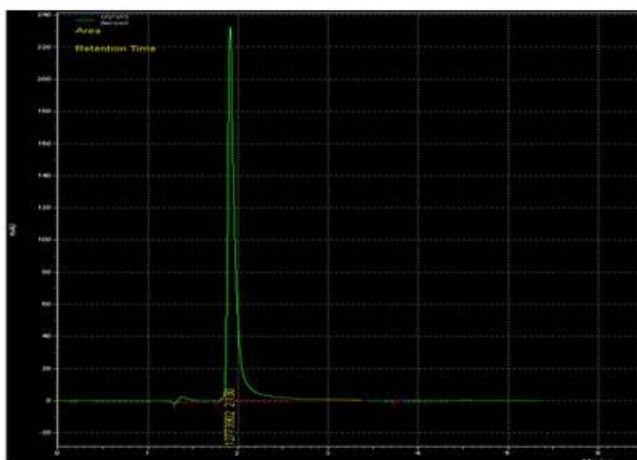
mixture of gabapentin: Mg stearate (1:5%), it was 99.92% (SD=256237.41) as shown in figure 1.

The next recovery was (gabapentin: Avicel) 99.16% (SD=60657.00), then (gabapentin: PVPK15) 99.15% (SD=218890.71), then (gabapentin: HPMC) 99.14% (SD=256738.87). The recovery was approximate the same with Avicel, PVP K15, HPMC. The lowest recovery of intact gabapentin was with (gabapentin: Aerosil) (1:1) as shown in figure 2.





**Figure 1:** HPLC chromatograms for gabapentin: Mg stearate (1:5%).



**Figure 2:** HPLC chromatograms for gabapentin: Aerosil (1:1).

The recovery of intact gabapentin after 5 minutes milling was 98.2% (SD= 26306.32).

These results were compatible with previous study that show there was almost lack of polymorphic transition for gabapentin 2 by co-milling gabapentin 2 with Mg stearate, when gabapentin 2 milled with Avicel, HPMC, gabapentin 2 transformed to gabapentin 4 alone, also gabapentin 4 and a little amount of gabapentin lactam formed after co-milling gabapentin 2 with Aerosil. It may be the coexistence of these excipients prevents the over-heat of gabapentin 2 during co-milling process<sup>9</sup>.

#### Effect of temperature

The recovery of intact gabapentin decreased with increasing temperature in all mixtures and all conditions. The recovery at 25°C was higher than recovery at 40°C and degradation increased with time at both 25°C and 40°C.

#### Effect of moisture

The recovery of intact gabapentin was less at low relative humidity (RH=30.5%) and increased by increasing relative humidity (RH=74.4%), this result was compatible with another study show that gabapentin lactamization was higher at low relative humidity and dramatically

decreased with increasing relative humidity<sup>11</sup>. It maybe explains by Le Chatelier principle:

If a chemical system at equilibrium experiences a change in concentration, temperature, volume, or partial pressure, then the equilibrium shifts to counteract the imposed change and a new equilibrium is established<sup>12</sup>, so the presence of humidity explained decreasing degradation rate so equilibrium shifts to form gabapentin:



The result of HPLC was proven by studying sorption-desorption isotherm for milled gabapentin for 5 minutes, mixture of gabapentin: Mg stearate (1:5%), mixture of gabapentin: Aerosil (1:1) using dynamic vapor sorption DVS as shown in fig 3.

Gabapentin weight increased 0.0106 at humidity 30.5% and increased 0.038 at humidity 74.4%, so that there is no significant change on gabapentin as shown in fig 3 (B).

Gabapentin: Mg stearate (1:5%) mixture weight increased 0.071 at humidity 30.5% and increased 0.314 at humidity 74.4% as shown in fig 3 (A), so that there was water uptake by the mixture in the presence of Mg stearate that causing the stabilizing effect for gabapentin. It maybe that hydrophobic faces of gabapentin crystal were faced with hydrophobic faces of Mg stearate, and hydrophilic faces for Mg stearate were susceptible to moisture which causing the stabilizing effect for gabapentin.

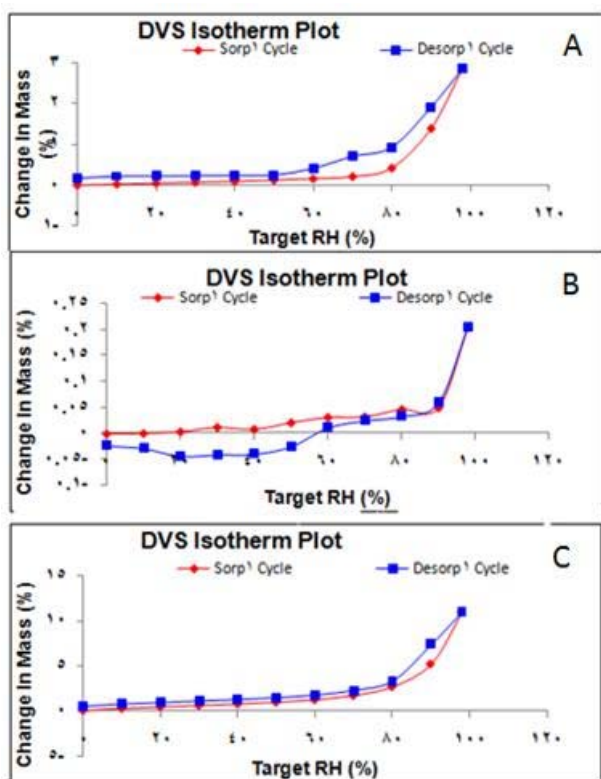
The next recovery was with (gabapentin: PVP K15) (1:1), PVP K15 is very hygroscopic<sup>13</sup>, so humidity played stabilizing effect on gabapentin. Then the next recovery was with (gabapentin: Avicel) (1:1), Avicel is hygroscopic<sup>13</sup>, so humidity played stabilizing effect on gabapentin. Then the next recovery was with (gabapentin: HPMC) (1:1), HPMC is hygroscopic. The recovery of intact gabapentin was approximate the same with PVP K15, Avicel, HPMC.

The recovery of intact gabapentin decreased with (gabapentin: Aerosil) (1:1) mixture, this result was proven by studying sorption-desorption isotherm for (gabapentin: Aerosil) mixture using dynamic vapor sorption DVS as shown in fig 3 (C), mixture weight increased 0.56 at humidity 30.5% and increased 2.165 at humidity 74.4%, so that there is moisture uptake by the mixture in the presence of Aerosil, but most of this moisture was adsorbed on Aerosil so moisture was interrupted in it's meso pores which caused gabapentin degradation.

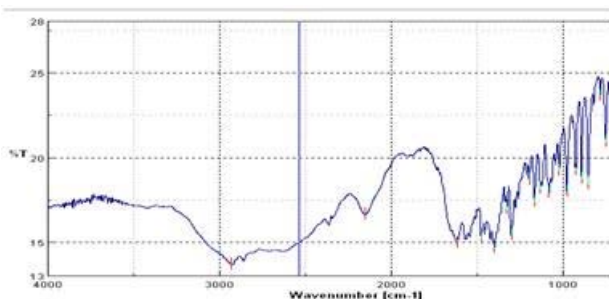
#### Degradation products were detected by IR spectrophotometer

The FT-IR spectrum of raw gabapentin 2 was compared respectively with FT-IR spectrum of milled gabapentin for 5 minutes, (gabapentin: Mg stearate) (1:5%) mixture, (gabapentin: Aerosil) (1:1) mixture. Several characteristic peaks for gabapentin 2 identified as follows: 2931, 2154, 1615, 1546, 1475, 1400, 1300, 1165 and 709  $\text{cm}^{-1}$ , and

the peaks at 3202, 2928 and 1699  $\text{cm}^{-1}$  were the unique bands of gabapentin lactam<sup>9</sup>.

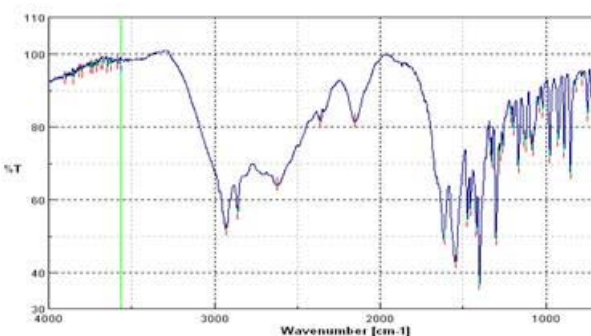


**Figure 3:** Sorption- desorption isotherm for milled gabapentin 5 minutes (A), gabapentin: Mg stearate (1:5%) mixture (B), gabapentin: Aerosil (1:1) mixture (C).



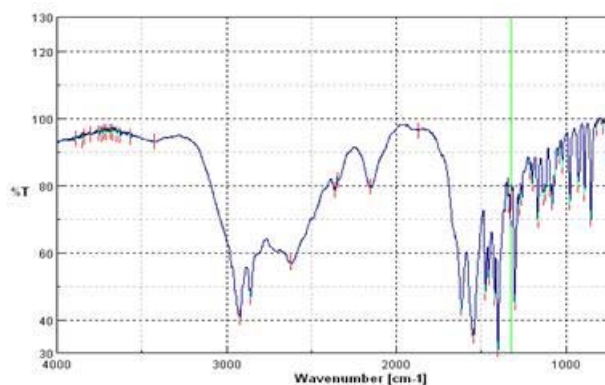
**Figure 4:** FT-IR spectra of raw gabapentin.

The peaks near 2123– 2200  $\text{cm}^{-1}$  were corresponded to the distinct side chain and/or CN stretching vibration. The IR band absorptions for gabapentin 2 within 3200– 2800  $\text{cm}^{-1}$  region were due to the  $\text{NH}_3^+$  stretching vibration.



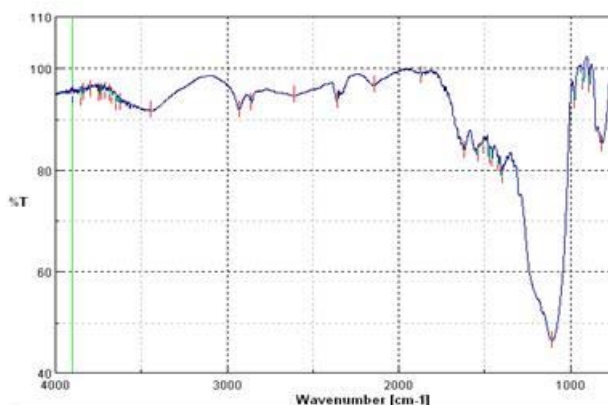
**Figure 5:** FT-IR spectra of gabapentin 5 minutes milling by mortar.

The stresses applied to crystals during mechanical milling can create new lattice defects in their crystal lattices and contribute to lattice disorder, leading to different arrangements and/or conformations within the crystal lattice. The peak near 927 $\text{cm}^{-1}$  was shifted to 922 $\text{cm}^{-1}$ , and there are no characteristic peaks for gabapentin lactam, so there is conversion between polymorphs without formation of gabapentin lactam.



**Figure 6:** FT-IR spectra of (gabapentin:Mg stearate) (1:5%).

The peak near 2931 $\text{cm}^{-1}$  was shifted to 2921 $\text{cm}^{-1}$ , and there are no characteristic peaks for gabapentin lactam, so there is conversion between polymorphs without formation of gabapentin lactam.



**Figure 7:** FT-IR spectra of (gabapentin:Aerosil) (1:1).

The peak near 3818 $\text{cm}^{-1}$  was shifted to 3837 $\text{cm}^{-1}$ , and the peak near 1400 $\text{cm}^{-1}$  was shifted to 1398 $\text{cm}^{-1}$  which was near to 1397 $\text{cm}^{-1}$  (the unique peak for gabapentin 4) and there were no characteristic peaks for gabapentin lactam, so there was conversion between polymorphs by formation of gabapentin 4 and without formation of gabapentin lactam.

We conclude (gabapentin: Mg stearate) (1:5%) is the most stable mixture, and (gabapentin: Aerosil) (1:1) is the worst stable mixture.

**CONCLUSION**

It's benefit to use Mg stearate 5% as glidant in gabapentin tablets and work at low temperature 25°C and high relative humidity 75% during manufacturing and storage.

Milling duration was studied for 5 minutes, so it's benefit to study the effect of milling for 10, 15, 20, 30, 60, 120 minutes by mortar and pestle with different excipients to provide the best conditions in manufacturing and storage for gabapentin tablets.

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