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# Formulation and evaluation of immediate-release capsules of pregabalin

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## Abstract

The aim is to develop and evaluate capsules with various excipient compositions that satisfy the reference product's specifications to achieve an in-vitro correlation with the reference product after that. Pregabalin I.R. capsules were formulated using Corn starch, Dibasic calcium phosphate, Lactose anhydrous, and Avicel pH 102(Microcrystalline cellulose). After compatibility studies for the capsule blend were completed, the Drug was determined to be compatible with all excipients used in various formulations. After the blend was put into capsules, several metrics were examined, including average weight, disintegration, and assay. The formulation containing D.C.P. disintegrates at a faster rate than other formulations. It was discovered that the percentage of drug release in the F7 invitro dissolving profile was equal to that of the innovator product. Finally, it was concluded that the F7 formulation is better and similar to the innovator product.

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## INTRODUCTION

Infusions of entire plants have become less common as medical advances. Parts of plants, such as leaves and roots, are being ground up more and more, and by the 19th century, some of their active components were being recognized and chemically created. Novel compounds and minerals with therapeutic potential were found. Powdered and liquid forms of several medications were made. The capsule and tablet, today's most widely used and precise dosing systems, are the products of methods to hide the taste of these drugs, make them more pleasant, and facilitate swallowing. Large-scale commercial production is carried out these days. Previously, the chemist made these items on a limited scale in the pharmacy. Hard and soft capsules are the two types of capsules available. Use hard capsules for powdered or semi-solid formulations; for liquids, use soft capsules [1]. In France, hard capsules were first created in 1833. They had two parts, a body, and a lid, and were (and still are) made of gelatin; the pharmacy filled them once they were

**Table 1 Formulation table from F1 to F5 of Pregabalin I.R. capsules - 75 mg blends A) Blends without glidant (Aerosil)**

| S. No | %w/w | Ingredient | Qty per capsule (mg) | | | | |
|---|---|---|---|---|---|---|---|
| | | | F1 | F2 | F3 | F4 | F5 |
| I | 75 | Pregabalin | 75 | 75 | 75 | 75 | 75 |
| II | 0.75 | Aerosil (Colloidal silicon dioxide) | 0.5 | 0.75 | 1.0 | 0.5 | 0.75 |
| III | 5 | Corn starch | 5 | 5 | 5 | 5 | 5 |
| IV | 19.25 | Dibasic calcium phosphate | 20 | -- | -- | 19.50 | -- |
| V | -- | Lactose anhydrous | -- | 20 | -- | -- | 19.25 |
| VI | -- | AVICEL PH 102 (MicrocrystallineCellulose) | -- | -- | 20 | -- | -- |
| 100 | | Total | 100 mg | 100 mg | 100 mg | 100 mg | 100 mg |

**Table 2 Formulation table from F6 to F9 of Pregabalin I.R. capsules Trails for optimizing the concentration of glidant in the formulation by using hydrophilic diluents (Lactose anhydrous)**

| S. No | %w/w | Ingredient | Qty per capsule (mg) | | | |
|---|---|---|---|---|---|---|
| | | | F6 | F7 | F8 | F9 |
| 1 | 75 | Pregabalin | 75 | 75 | 75 | 75 |
| 2 | 0.75 | Aerosil (Colloidal silicon dioxide) | 1.0 | 0.75 | 0.75 | 0.75 |
| 3 | 5 | Corn starch | 5 | 5 | 5 | 5 |
| 4 | 19.25 | Dibasic calcium phosphate | -- | 19.25 | -- | -- |
| 5 | | Lactose anhydrous | -- | -- | 19.25 | -- |
| 6 | | AVICEL PH 102 (MicrocrystallineCellulose) | 19.00 | -- | -- | 19.25 |
| 100 | | Total | 100 mg | 100 mg | 100 mg | 100 mg |

delivered ready-made. A wooden base pierced with holes the same size as the capsule would make up an essential filling device. A tiny funnel could be used to inject amounts of weighed powder. Semi-solid preparations were rolled into a pipe, sliced, weighed, and trimmed to the appropriate length before being put inside a capsule [2]. The capsules were packaged and labeled, and the caps were put on. The pharmacy may manufacture soft capsules. The device was a dipper made from different-sized metal molds placed into a base. After inverting the dipper and dipping it into a molten gelatin/glycerin mixture, the capsules were taken from it once it cooled. Afterward, the capsules may be carefully sealed with a heated rod or filled with a predetermined volume of liquid using a syringe and sealed with a glob of the melted glycerin/gelatin combination applied with a glass rod [3].

## METHODOLOGY

### Preparation of capsule blends

Mixing pregabalin and # 60 passed colloidal silicon dioxide in a poly bag for 5 min to provide the dry-coating of particles of pregabalin [Table 1-3]. Then add dibasic calcium phosphate / Lactose anhydrous/ Avicel PH 102 and corn starch into this mixture & blend for 5 min. A second mixing step is performed, and the capsules are filled [4].

**Table 3 Trails for optimizing the type/Nature Of Diluent**

| S. No | Diluent | Nature |
|---|---|---|
| 1 | Dibasic calcium phosphate | Lipophilic |
| 2 | Lactose anhydrous | Hydrophilic |
| 3 | AVICEL PH 102 (MicrocrystallineCellulose) | Moderate |

## EVALUATION OF CAPSULE BLEND

### Angle of Repose

It is the highest possible angle that can be formed between a powder pile's surface and the horizontal plane [5]. The funnel method was used to calculate the granules' angle of Repose. A

precisely measured powder mixture was placed inside the funnel. The funnel's height was modified so that its tip barely touched the powder blend's apex. The powder mixture was free to pour through the funnel and onto the surface [Table 4]. The following formula was used to estimate the powder cone's diameter and determine its angle of Repose.

$\theta = \tan^{-1} (h/r)$

The flow characteristics of solids have been described using the angle of Repose. Interparticulate friction, or the resistance to particle movement, is associated with this feature [6].

**Table 4 Angle of repose limits**

| Flow Property | The angle of Repose (degrees) |
|---|---|
| Excellent | 25–30 |
| Good | 31–35 |
| Fair—aid is not needed | 36–40 |
| Passable—may hang up | 41–45 |
| Poor—must agitate, vibrate | 46–55 |
| Very poor | 56–65 |
| Very, very poor | >66 |

**Bulk density**

It is the powder's bulk volume proportion to its overall mass. Weigh precisely 25 g of granules put into a 100 ml graduated cylinder after passing through a 22-sieve. Without compacting, carefully balance the powder and note the disturbing apparent volume [7]. Use the following formula to get the measurable bulk density in gm/ml.

Bulk density = weight of powder/ Bulk volume.

$$D_b = \frac{M}{V_0}$$

**Tapped density**

The formula is the powder's total mass ratio to its tapped volume. Accurately weigh 25 grams of granules through a 22-inch sieve before transferring them to a 100-millilitre graduated tap density testing cylinder [8]. The tester is run for a set number of taps until the powder bed volume reaches a minimum, as determined by a formula.

Tapped density = weight of powder / Tapped volume

$D_t = (M) / (V_f)$.

**Carr's Index**

The powder blend's compressibility index was ascertained using Carr's compressibility index [9]. To assess a powder's B.D., T.D., and packing down rate, an easy test is required [Table 5]. Carr's index formula is as follows:

$$\textbf{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

**Hausner's Ratio**

The flow ability of a powder is associated with a value called Hausner's Ratio [10].

$$\textbf{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

**Table 5 Limits of the compressibility index**

| Compressibility Index (%) | Flow Character | Hausner's Ratio |
|---|---|---|
| ≤ 10 | Excellent | 1.00-1.11 |
| 11-15 | Good | 1.12-1.18 |
| 16-20 | Fair | 1.19-1.25 |
| 21-25 | Passable | 1.26-1.34 |
| 26-31 | Poor | 1.35-1.45 |
| 32-37 | Very Poor | 1.46-1.59 |
| > 38 | Very, very Poor | > 1.60 |

**Evaluation of commercial capsules**

**Content uniformity**

A total of thirty capsules are chosen, and ten of them undergo separate assays [11]. Nine out of them have a minimum of 85–115% drug content, and none have less than 75–125%. The remaining 20 capsules are separately tested if one or three of them deviate from the 85–115% range. The requirements are satisfied if at least 27 contain 85–115% of the medication and none contain less than 75–125%.

**Weight Uniformity**

Twenty capsules must be used for this test, which applies to all capsules. Weigh a whole capsule. Carefully extract the capsule's contents and open it so no part of the shell is lost. Assess the shell's weight. The disparity between the weighing and the contents weight is the contents [12]. Carry out

steps 5 through 9 with an additional 19 randomly chosen pills. Establish the mean weight. The percentage deviation of each weight from the average weight is displayed in the table below, with no weight deviating from the average by more than two times that amount.

**Table 6 Average weight of capsule content**

| Average Weight of Capsule Content | Percentage Deviation |
|---|---|
| Less than 300 mg | 10 |
| 300 mg or more | 7.5 |

### Disintegration

It pertains to both soft and hard capsules under the B.P. Place one capsule into each tube and hang the setup over a beaker of 600 ml of 37 °C water. The discs may be inserted if the hard capsules float on the water's surface. After 30 minutes of operation, take the assembly out of the liquid. The capsules pass the test without residue on the apparatus's screen. If there is, it is a soft mass without a palpable core or comprised of shell pieces.

If the disc is used, the only remnant left on its lower surface should be shell pieces [13].

### Dissolution

**Table 7 Dissolution parameters**

| Parameter | Details |
|---|---|
| Dissolution apparatus | U.S.P. -Type I (Basket) |
| Medium | 0.06NHcl. |
| Volume | 900 ml |
| Speed | 50rpm |
| Temperature | 37± 0.5 ºC |
| Sample volume withdrawn | 5ml |
| Time points | 5,10,15,20,30,45 and 60 minutes |
| Analytical method | Ultraviolet-Visible Spectroscopy |
| $\lambda_{max}$ | 210nm |

The dissolving equipment authorized by the N.F. and U.S.P. is used to conduct the dissolution test. The capsule is placed within a basket of stainless steel cloth with a mesh size 40. The basket has a stirrer shaft attached to it, and it rotates at a predetermined speed while submerged in the dissolving media [14]. An appropriate constant-temperature water bath is used to maintain the dissolving media at 37°C ± 0.5°C, and it is contained in a covered 1000 ml glass vessel. The specific monograph contains information on the dissolving liquid and the speed of the stirrer.

### In vitro Release Kinetics Studies [15]

**Zero Order Release Kinetics:** It establishes a linear link between the drug release fractions and time.

$$Q=k_0t.$$

**First Order Release Kinetics:** Wagner proposed that first-order kinetics could adequately characterize the drug release from most slow-release tablets based on the assumption that a tablet's exposed surface area is reduced exponentially throughout the breakdown process. The equation describes first-order kinetics.

$$\text{Log } C = \text{Log } C_o - kt/2.303$$

## RESULTS AND DISCUSSION

### EVALUATION OF CAPSULE BLENDS

The mix of Pregabalin I.R. capsules was assessed for its flow characteristics; Table 8 displays the results for the I.R. capsule blends. It was discovered that the tapped and bulk densities were nearly identical for every formulation [Table 8]. The blends showed satisfactory flow and compressibility, with Carr's index and Hausner's ratios in the range of < 18 and 1.0 to 1.56, respectively. All of the formulations' angles of Repose were determined to be within the range of 9.92–12.35˚, suggesting passable flow (adding a glidant will improve the flow).

### *In vitro* Dissolution

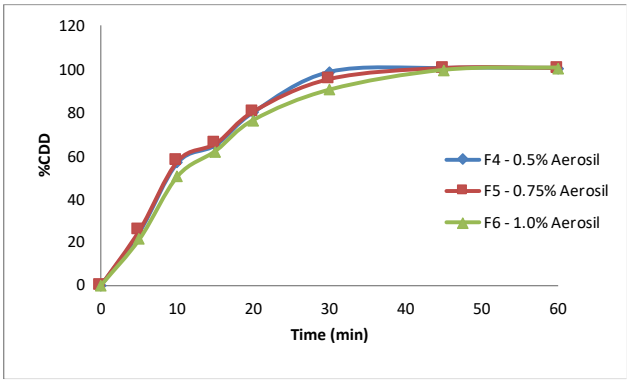


**Figure 1 Comparative dissolution profile for F4, F5 and F6 formulations of Pregabalin IR capsules**

**Table 8 Evaluation of Capsule Blends**

| Formulation Code | Bulk density (Kg/cm³) | Tapped density (Kg/cm³) | Carr's index | Hausner ratio | The angle of Repose (˚θ ) |
|---|---|---|---|---|---|
| F1 | These batches without glidant show poor flow properties and have not been studied for post-compression evaluation studies. | | | | |
| F2 | | | | | |
| F3 | | | | | |
| F4 | 0.39±0.02 | 0.47±0.03 | 17.0±1.2 | 1.56±0.41 | 12.23±0.11 |
| F5 | 0.37±0.01 | 0.41±0.03 | 9.75±0.2 | 1.1±0.03 | 12.35±0.12 |
| F6 | 0.43±0.04 | 0.52±0.01 | 17.3±1.03 | 1.41±0.02 | 11.62±0.67 |
| F7 | 0.44±0.03 | 0.50±0.04 | 12±1.02 | 1.1±0.01 | 9.92±0.54 |
| F8 | 0.41±0.01 | 0.45±0.02 | 8.8±2.03 | 1.0±0.02 | 11.85±0.23 |
| F9 | 0.39±0.01 | 0.48±0.02 | 18±2.01 | 1.23±1.01 | 11.96±0.81 |

**Table 9 Evaluation of I.R. capsules**

| Formulation Code | % weight variation | %Drug Content± SD n=3 |
|---|---|---|
| F1 | These batches without glidant showed poor flow properties and were not studied for post-compression evaluation studies. | |
| F2 | | |
| F3 | | |
| F4 | pass | 100.7 ±1.1 |
| F5 | pass | 99.6±1.5 |
| F6 | pass | 98.9 ±2.3 |
| F7 | pass | 100.2± 1.7 |
| F8 | pass | 100.5± 1.4 |
| F9 | pass | 99.2±1.1 |

The weight fluctuation stayed within the parameters [Table 9]. According to the findings, the drug content was between 98 and 102%. Note: Every time, 5 ml of sample was drawn and replaced with the same volume of 0.06 N HCl that had been heated to 37±0.5 ºC [Table 10].

**Table 10 Dissolution profile of Pregabalin I.R. Capsules**

| Parameter | Details |
|---|---|
| Dissolution apparatus | U.S.P. -Type I (Basket) |
| Medium | 0.06N HCl. |
| Volume | 900 ml |
| Speed | 50rpm |
| Temperature | 37± 0.5 ºC |
| Sample volume withdrawn | 5ml |
| Time points | 5, 10, 15, 20, 30, 45, 60mins |
| Analytical method | Ultraviolet-Visible Spectroscopy |
| $\lambda_{max}$ | 214nm |

It was discovered that the percentage of drug release in the F7 In-vitro dissolving profile was equal to that of the innovator product [Table 11]. Ultimately, it was determined that the F7 formulation is superior to the innovator product [Figure 1, 2, 3].

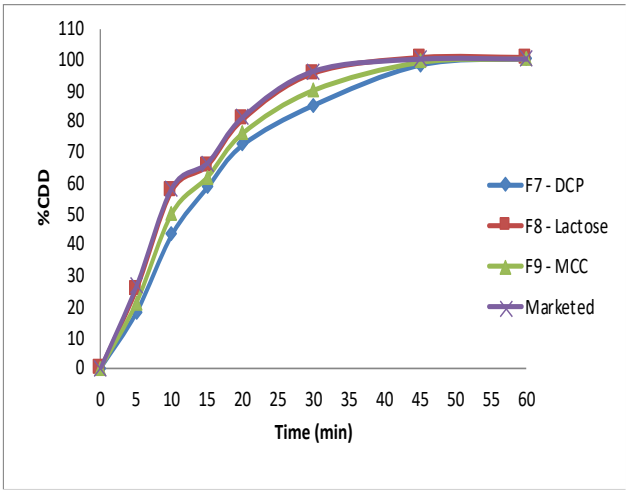


**Figure 2 Comparative dissolution profile for F7, F8, F9 and Marketed formulations of Pregabalin IR capsules**

**Table 11 In vitro Dissolution results for Pregabalin I.R. capsules**

| Time (min) | % Drug Released | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | Glidants concentration | | | Diluents concentration | | | Marketed Product |
| | | | | 0.5% | 0.75% | 1.0% | 0.5% | 0.75% | 1.0% | |
| | | | | F4 | F5 | F6 | F7 | F8 | F9 | |
| 0 | These batches without glidant showed poor flow properties and were not studied for post-compression evaluation studies. | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | | | | 24.48 | 25.34 | 21.25 | 18 | 25.34 | 21.25 | 26.51 |
| 10 | | | | 56.42 | 57.2 | 50.24 | 43.21 | 57.2 | 50.24 | 58.23 |
| 15 | | | | 64.53 | 65.32 | 61.95 | 58.57 | 65.32 | 61.95 | 66.37 |
| 20 | | | | 79.85 | 80.25 | 76.3 | 72.35 | 80.25 | 76.3 | 81.23 |
| 30 | | | | 98.34 | 95.22 | 90.23 | 85.24 | 95.22 | 90.23 | 96.12 |
| 45 | | | | 100.1 | 100.24 | 99.28 | 98.32 | 100.24 | 99.28 | 99.98 |
| 60 | | | | 100.1 | 100.24 | 100.34 | 100.52 | 100.24 | 100.34 | 99.98 |

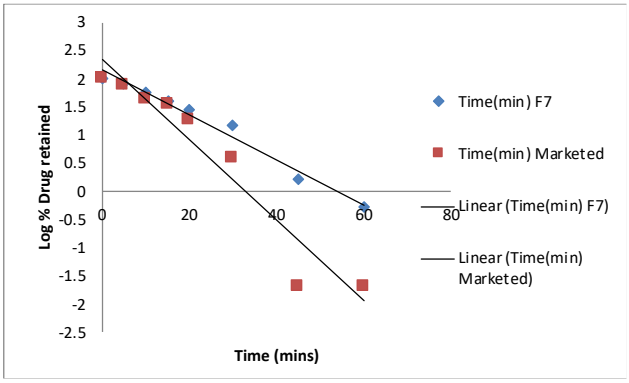


**Figure 3 First order plot for best formulation F7 & Marketed formulation**

## CONCLUSION

Pregabalin I.R. capsules were formulated using Corn starch, Dibasic calcium phosphate, Lactose anhydrous, and Avicel pH 102 (Microcrystalline cellulose). After compatibility studies for the capsule blend were completed, the Drug was determined to be compatible with all excipients used in various formulations.

After placing the blend into capsules, several metrics were examined, including average weight, disintegration, and assay. The formulation containing D.C.P. disintegrates at a faster rate than other formulations. It was discovered that the percentage of drug release in the F7 *In vitro* dissolving profile was equal to that of the innovator product. Ultimately, it was determined that the F7 formulation is superior to the innovator product.

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## Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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