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# PREPARATION AND EVALUATION OF NON-EFFERVESCENT TABLET FOR CONTROLLED RELEASE OF PREGABLIN

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**Abstract**
A high performance liquid chromatographic approach that is straightforward, precise, and specific was developed and validated by researchers in order to measure the amount of etoricoxib present in both tablet and bulk dosage forms.Within the framework of the procedure, an LC-10 ATVP Shimadzu Liquid Chromatograph HPLC with dimensions of 4.5x250mm and a stationary phase consisting of Hyper ODS 2 C18 were utilised. A flow rate of one millilitre per minute is maintained by the solvent system, which is comprised of HPLC-grade methanol. A wavelength of 233 nm was utilised in order to investigate etoricoxib. The calibration curve for etoricoxib revealed a straight line, ranging from 20 to 55 µg/ml. Both the accuracy between days and the accuracy within a single day were found to be within acceptable ranges. The approach that has been proposed demonstrates sufficient specificity, repeatability, and sensitivity for the measurement of etoricoxib in both tablet and bulk dose quantities. In the study, it was discovered that the LOQ for etoricoxib was 0.650, whereas the LOD was 0.250. With recoveries ranging from 99.50 to 99.73 percent, we determined that the accuracy and reciprocity were satisfactory within the given parameters.
**Keywords:** pregabalin, controlled-release floating,, hplc, cox-2

## Introduction

It is a non-steroidal anti-inflammatory medicine that is also a powerful COX-2 inhibitor [1–5]. Etoricoxib belongs to this category.The action of COX-1 is not inhibited by the compound known as etoricoxib, which is classified as 5-chloro-6'-methyl-3- [4-(methyl sulfonyl) phenyl]-2, 3'-bipyridine. Depending on the dose, the amount of COX-2 that is suppressed can vary. [6,7] Research has shown that inhibiting COX-2 has both anti-inflammatory and analgesic effects. In spite of the fact that it is crystalline and only marginally soluble in water overall, it is easily dissolved in a solution of water that is mildly acidic [3]. A shade of off-white can be seen in the powder. Etoricoxib is a tablet that may be purchased in the dosages of 60, 90, and 120 milligrammes; nevertheless, it is not recognised as an official medicine by any pharmacopoeia [4]. As a treatment for primary dysmenorrhea, discomfort after dental surgery, migraines, acute gouty arthritis, rheumatoid arthritis, osteoarthritis, and cancer, as well as for the prevention and treatment of cancer, it is advised. A variety of analytical methods, including high-performance liquid chromatography, visible light, ultraviolet light, and others, have been utilised in the research that has been conducted on etoricoxib [14–16].With the help of high-performance liquid chromatography (HPLC), the purpose of this study is to find a straightforward and trustworthy method for determining the concentration of etoricoxib in tablet dosage forms as well as bulk medicine [17].

## Pre-formulation Studies

### Physicochemical characterization of drug

Ecoxib is a medicine that is classified as a non-steroidal anti-inflammatory drug and is a powerful COX-2 inhibitor [1–5].There is no evidence that etoricoxib, which is sometimes referred to as 5-chloro-6'-methyl-3- [4-(methylsulfonyl) phenyl]-2, 3'-bipyridine, effectively inhibits COX-1. Dosage has a significant impact on the effectiveness of COX-2 inhibition. Through the inhibition of COX-2, it is possible to reduce both inflammation and discomfort [6,7]. The fact that it is crystalline and only partially soluble in water does not prevent it from being quickly dissolved in a solution of water that is slightly acidic [3]. The powder has a colour that would be described as off-white.Etoricoxib is available for purchase in tablet form (60, 90, and 120 mg), despite the fact that it is not formally recognised by any of the pharmacopoeias [4]. Certain conditions, such as primary dysmenorrhea, discomfort following dental surgery, migraines, acute gouty arthritis, migraine prevention and therapy, rheumatoid arthritis, osteoarthritis, and cancer, are among the conditions that are recommended to be treated. The analytical procedures for etoricoxib have been thoroughly reported, and they include visual, ultraviolet, high-performance liquid chromatography, and a variety of other techniques [14–16].Through the utilisation of the high-performance liquid chromatography (HPLC) technique, the primary purpose of this study is to devise a straightforward and precise method for detecting the concentration of etoricoxib in both tablet dosage forms and bulk medication [17].

### Physical appearance

An examination of the drug sample was carried out visually in order to validate its colour, appearance, and various other physical characteristics.

### Melting point

For the purpose of determining the melting point of the PGB, a digital melting point equipment (LabIndia-MR-VIS, Mumbai, India) was utilised in conjunction with the capillary method. After the melting point equipment had been meticulously sealed at one end of the capillary tube, the subsequent step consisted of carefully inserting the sample into the device. It was possible to determine the melting point of the medicine by gradually raising the temperature until the sample turned into a liquid.

### Solubility

The test for solubility was one of the components that comprised the purity test. The solubility of PGB was determined by placing fifty milligrammes of the substance in a test tube and waiting for it to dissolve. Shaking the mixture allowed for the slow addition of 0.1 millilitres of solvent to be carried out. We continued to add solvent until the material was totally dissolved in the liquid in question. For the

purpose of determining the solubility of the pharmaceutical powder, the volume of solvent that was necessary to dissolve it was measured.

**Loss on Drying**

First, the weighing bottle was heated to dry it, then it was refrigerated in a desiccator over silica gel, and last, it was measured. This was done before the sample was weighed (W1). For the second weigh, one gramme of PGB was introduced to the measuring container that had been dried the previous time. After three hours at 105 degrees Celsius, we dried the vial that contained the PGB sample. As soon as the weighing bottle had been dried, it was placed in a desiccator that contained silica gel and allowed to cool down to room temperature. This was followed by the weighing of it (W3). A calculation is made to determine the amount of PGB medication that is lost when it dries up.

$$\text{Loss on drying \%} = \frac{W2 - W3}{W2 - W1} \times 100$$

**Drug – Excipient Compatibility Study (Isothermal Stress Testing)**

For the purpose of determining whether or not the excipients were compatible with pregabalin (PGB), we utilised isothermal stress testing. In order to conduct isothermal stress testing, the exact quantity was added to a volumetric flask that held the medicine along with a number of excipients and had a capacity of 25 millilitres. We utilised a vortex mixer to thoroughly combine the contents of all three flasks for a period of two minutes after they had been filled. Following the addition of water at a weight-to-weight ratio of 10% to each flask, the solution of the medication and the excipient was further mixed with a vortex mixer. After being wrapped in parafilm and sealed with a stopper, each flask was then placed in a hot air oven and kept at a temperature of fifty degrees Celsius. We checked these samples on a regular basis to see whether there was any change in hue. Using the High Performance Liquid Chromatograph (HPLC) technique, a quantitative analysis of the Pregabalin raw material was carried out three weeks after the samples had been suitably diluted and stored in the circumstances that were previously specified. Similarly, drug-excipient mixtures were kept in a refrigerator at a temperature of 8 degrees Celsius without any additional water being added as a control.

*Table 1 Ratio of Drug and Excipient blend for Isothermal Stress Testing*

| S. No. | Sample | Ratio (Drug : Excipient) |
|---|---|---|
| 1 | PGB | - |
| 2 | PGB + HPMC K100M | 1 : 1 |
| 3 | PGB + Carbopol 971P | 1 : 1 |
| 4 | PGB + Povidone | 2 : 1 |
| 5 | PGB + Crospovidone | 1 : 1 |
| 6 | PGB + Mannitol | 1 : 1 |
| 7 | PGB + Colloidal Silicon Dioxide | 3 : 1 |
| 8 | PGB + Magnesium Stearate | 3 : 1 |

**Preparation of Non-effervescent Gastro-retentive Tablets of Pregabalin**

The wet granulation process was utilised in the production of tablets containing three hundred milligrammes of pregabalin substance. For each individual recipe, the following components were each passed through a sieve with a mesh size of forty centimetres: For example, pregabalin, carbopol 971P,

mannitol, povidone, crospovidone, and HPMC K100M are all drugs that fall into this category. In order to guarantee that the components were well combined, the mixture was put through a sieve with a mesh size of forty. Following that, the following substances were mixed by hand: pregabalin, carbopol 971P, povidone, and hydroxypropyl methyl cellulose (HPMC) K100M. In order to determine the amount of moisture that was present in the powder mixture, we made use of a moisture analyzer. Granulating the mixture by hand with isopropyl alcohol was the method of choice. After heating the materials in a tray dryer to a temperature of fifty degrees Celsius until the moisture content of the grains had fallen to the same level as the powder, sieve number twelve was utilised in order to separate the grains. Crospovidone and mannitol were combined after the dry granules were combined after being passed through a sieve with a mesh size of 18 and 40, respectively. After passing the liquid through a #80 screen that contained colloidal silicon dioxide and magnesium stearate, further lubrication was added to the mixture. The Rotary Tablet Compression Machine was equipped with a concave D-tooling punch with a diameter of 10 millimetres, which was used to compress the lubricated mixture.

**Evaluation of Pre-Compression Parameters of Powder Blend**

We determined the compressibility and flow qualities of powder mixtures by measuring their bulk density, tapped density, Carr's index, and Hausner ratio, in addition to their angle of repose. This allowed us to analyse the combination of these properties.

**Angle of Repose**

The method of the stationary funnel was utilised in order to accurately determine the angle of repose. An angle of repose is created when the base and edge of a powder pile that is shaped like a cone are on the horizontal plane. We made use of a glass funnel that had a diameter of ten millimetres for the opening. While the funnel was being secured, ten grammes of powder sample was liberally put to the top of the funnel. For the purpose of determining the angle of repose (θ), we took measurements of the powder conical pile's height (h) and radius (r).

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

*Table 2 Flow Properties and Corresponding Angles of Repose as per USP* [40]

| Flow property | Angle of repose (in degree) |
|---|---|
| Excellent | 25-30 |
| Good | 31-35 |
| Fair | 36-40 |
| Passable | 41-45 |
| Poor | 46-55 |
| Very poor | 56-65 |
| Very, very poor | >66 |

**Bulk Density**

For the purpose of determining the powder's bulk density, a graduated measuring cylinder with a capacity of fifty millilitres was filled with a carefully weighed ten gramme of powder, and the volume of the powder was recorded.

**Tapped Density**

For the purpose of determining the density of powder, the tapping density device was being utilised. A graduated measuring cylinder with a capacity of fifty millilitres was loaded with a precisely measured quantity of ten grammes of powder, and the cylinder was then attached to the apparatus where it was being used. The powder was tapped in the device that measures tapped density in order to realise the goal of maintaining a consistent volume.

**Carr's Compressibility Index**

Compressibility is an indication of ease with which a material can be induced to flow.[42]

**Hausner Ratio**

Hausner ratio is a measure of the inter particulate friction, which could predict powder flowproperties.

*Table 3 Scale of Flowability as per USP*

| Compressibility Index (%) | Flow character | Hausner 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 | >1.6 |

**Evaluation of Non-effervescent Gastro-retentive Tablets of Pregabalin**

**Average Weight and Weight Variation**

There were twenty tablets that were chosen at random and then weighed as a whole.

Twenty tablets were weighed individually, and the percentage of weight difference between the tablet with the highest weight and the tablet with the lowest weight was calculated in relation to the average weight.

**Tablet Thickness**

A Vernier caliper was utilised in order to ascertain the thickness of six tablets that were chosen at random. The values of the mean are given as the standard deviation (SD) plus or minus the mean.

**Hardness of Tablet**

Within the hardness tester, one tablet was placed in a horizontal orientation, and the machine was then operated in such a way that the tablet was crushed down. We took note of the tablet's level of hardness. The operation was carried out once more with an additional five pills. All of the results are shown as the average values of six tablets.

± Standard Deviation (SD).

**Tablet Friability**

The sample consisted of ten tablets in their whole. The tablets were meticulously dedusted, and then they were weighed. It was decided to place the tablets in the drum of the Friability Tester, which had been adjusted to rotate at a speed of 25 revolutions per minute (rpm). For a total of four minutes, the drum was

rotated one hundred times. Following the removal of the tablets, they were dedusted and correctly weighed. Calculations were made to determine the percentage of weight loss seen in comparison to the initial weight.

**Drug Content**

A High Performance Liquid Chromatograph (HPLC) method was utilised in order to measure the amount of pregabalin present in tablets. This was accomplished by comparing the tablets to the reference standard of pregabalin.

**In vitro Buoyancy Study**

The floating behaviour of the tablets was evaluated visually, in duplicate, using the floating lag time approach that Rosa et al. described. Additionally, the tablets were tested three times.[46] [46] A tablet was positioned inside a glass beaker with a capacity of 250 millilitres, which was then filled with 200 millilitres of 0.06 N Hydrochloric Acid (HCl). The beaker was then kept in a water bath at a temperature of 37 ± 0.5 degrees Celsius. Recordings were made of the floating lag time, which is defined as "the time between the tablet being placed in a glass beaker with HCl and its buoyancy," as well as the total floating duration, which is defined as "the time during which the tablet remains buoyant." A tablet was placed in 900 ml of 0.06N HCl in a USP type II dissolution equipment (37 ± 0.5°C, 50 rpm) in order to assess the floating lag time and total floating time. This was done in triplicate, as stated by Gharti et al.It is [47] The floating lag time was calculated to be the amount of time it took for the tablets to rise to the surface and float. The total floating time was calculated to be the amount of time that the table remained on the surface without moving at any point.

**Tablet Adhesion Retention Period**

The adhesion retention period of the tablets was assessed using an in vitro approach that was reported by Nakamura et al., and the evaluation was performed three times.It is [48] In 0.1 N Hydrochloric Acid (HCl), an agar plate with a weight-to-weight ratio of 2% was created. 0.1 N Hydrochloride Acid (HCl) was used to wet one side of the tablet, and then a fingertip was used to provide a mild force in order to attach the tablet to the centre of the agar plate.It is [49] Following a period of five minutes, the agar plate was subsequently affixed to a disintegration test device and subsequently moved in 0.1 N Hydrochloric Acid (HCl) at a temperature of 37±2 degrees Celsius. At the lowest point, the tablet that was glued to the plate was submerged in the solution, and at the highest position, it emerged from the solution. Visual observation and recording were done in order to determine how long the tablet remained on the agar plate.

**In vitro Drug Release Study**

Using the United States Pharmacopoeia Type II (Paddle) Dissolution Test Apparatus, the drug release research of manufactured Pregabalin non-effervescent gastro-retentive tablets was carried out in accordance with the Dissolution Methods Database for Pregabalin Extended-Release Tablet that is maintained by the United States Food and Drug Administration (USFDA). In accordance with the Indian Pharmacopoeia 2022 for Pregabalin Capsules Dissolution, the High Performance Liquid Chromatograph (HPLC) method was utilised in order to conduct the analysis of the drug release from the tablets.

**Physicochemical properties**

**HPLC analysis of Pregabalin**

For the purpose of conducting an assay examination of pregabalin, the HPLC method was utilised to perform the identification of the drug sample. The retention time of the major peak in the chromatogram of the test solution, which included the drug sample that was utilised for the research, was the same as the retention time of the major peak in the chromatogram of the reference solution, which contained the pregabalin standard. Pregabalin was identified as the substance to be tested. In accordance with the requirements of the monograph of Pregabalin in the Indian Pharmacopoeia, 2022, the purity of the medicine was determined to be 99.48% (on dried basis), which falls within the range of 98.0 – 102.0% (on dried basis). It provided evidence that the medicine that was utilised in the studies was genuine.

**Enantiomeric Purity analysis**

Since the peak of R-Pregabalin was not found in the chromatogram that was generated from the enantiomeric purity study using the HPLC method, and only the peak of S-Pregabalin was obtained, this indicates that the drug sample that was utilised in the experiments is the S-Pregabalin enantiomer and does not contain R-Pregabalin. R-Pregabalin should not have a percentage composition that is higher than 0.5 percent of that of S-Pregabalin, as stipulated by the Indian Pharmacopoeia 2022.

**Drug – Excipient Compatibility Study**

During the isothermal stress test, it was found that there was no change in the physical characteristics (colour and appearance) of the stressed samples or the control samples related to the amount of drugs present. It is clear from looking at Table 4 that the amount of medication that was altered in the samples of IST was less than one percent after being stored for three weeks under stressful settings.

*Table 4: Results of isothermal stress testing study of Pregabalin after 3 weeks of storage at stressed conditions.*

| S. No. | Sample | Ratio (Drug : Excipient) | PGB content * | |
|---|---|---|---|---|
| | | | Control Sample | Stressed Sample |
| 1 | PGB | - | 99.86±0.69 | 100.04±0.53 |
| 2 | PGB + HPMC K100M | 1 : 1 | 100.21±0.47 | 99.74±0.71 |
| 3 | PGB + Carbopol 971P | 1 : 1 | 99.93±0.71 | 100.42±1.12 |
| 4 | PGB + Povidone | 2 : 1 | 100.15±0.85 | 99.43±1.06 |
| 5 | PGB + Crospovidone | 1 : 1 | 99.57±0.22 | 99.72±0.83 |

**Evaluation of Precompression Parameters**

**Moisture Content of Dried Granules**

The manufacture of Pregabalin Non-effervescent Gastro-resistant tablets was accomplished by the use of the wet granulation process. Analyses were performed on the moisture content of the powder blend both before and after the granules were in the drying process. It was necessary to dry the granules until the moisture content of the powder blend was comparable to that of the granules before the granulation process began. The medication content of a tablet can be altered with regard to its theoretical weight if the granules have a higher or lower moisture content. Granules can also impact the flow properties of powders, which can lead to tablet faults such as sticking, capping, or lamination.

*Table 5 Moisture content of pre-granulation powder and dried granules during tablet preparation*

| S. No. | Formulation | Moisture Content (%) | |
|---|---|---|---|
| | | Powder Blend (pre-granulation) | Dried Granules |
| 1 | PNEGRT-1 | 2.51 | 2.34 |
| 2 | PNEGRT-2 | 2.79 | 2.96 |
| 3 | PNEGRT-3 | 2.83 | 2.69 |
| 4 | PNEGRT-4 | 2.82 | 2.91 |
| 5 | PNEGRT-5 | 2.91 | 2.79 |
| 6 | PNEGRT-6 | 3.03 | 3.22 |
| 7 | PNEGRT-7 | 2.76 | 2.42 |
| 8 | PNEGRT-8 | 3.27 | 3.46 |
| 9 | PNEGRT-9 | 3.89 | 3.58 |

**Characterization of Pre-Compression Powder Blend**

A variety of metrics were utilised in order to assess the flow and compressibility of the powder blend of each formulation of Pregabalin tablet prior to compression. A discussion of the findings may be found in Table 6. The angles of repose of the different powders ranged from 30.15 degrees to 39.08 degrees, and they displayed a moderate flow. For a number of different formulations, the values that were obtained for Carr's Index and Hausner Ratio ranged from 11.63 to 24.16 percent and 1.13 to 1.32 percent, respectively. Flow properties and compressibility characteristics were found to be improved in a powder mix that had a low proportion of HPMC K100M and Carbopol 971P polymers, as was seen. There was a decrease in the flowability of powder as the number of matrix-forming polymers, particularly Carbopol 971P, increased. Birsan et al. and Omeh et al. [56,57] both reported observations that were comparable to this one. The very tiny particle size and static charge of Carbopol 971P could be the cause of the decreased flowability that occurs with rising concentrations of the product, which results in poor flowability.

*Table 6 Result of pre-granulation powder and dried granules during tablet preparation of various criteria:*

| S. No. | Formulation | Angle of Repose | Bulk Density | Tapped Density | Carr's Index | Hausner Ratio |
|---|---|---|---|---|---|---|
| 1 | PNEGRT-1 | 30.15 | 0.433 | 0.490 | 11.63 | 1.13 |
| 2 | PNEGRT-2 | 34.30 | 0.424 | 0.481 | 11.91 | 1.14 |
| 3 | PNEGRT-3 | 36.81 | 0.390 | 0.471 | 17.20 | 1.21 |
| 4 | PNEGRT-4 | 35.94 | 0.417 | 0.483 | 13.66 | 1.16 |
| 5 | PNEGRT-5 | 37.66 | 0.396 | 0.455 | 12.97 | 1.15 |
| 6 | PNEGRT-6 | 38.24 | 0.371 | 0.443 | 16.25 | 1.19 |
| 7 | PNEGRT-7 | 36.14 | 0.404 | 0.479 | 15.66 | 1.19 |
| 8 | PNEGRT-8 | 37.06 | 0.381 | 0.451 | 15.52 | 1.18 |
| 9 | PNEGRT-9 | 39.08 | 0.339 | 0.447 | 24.16 | 1.32 |

**Physicochemical Characteristics of Tablets**

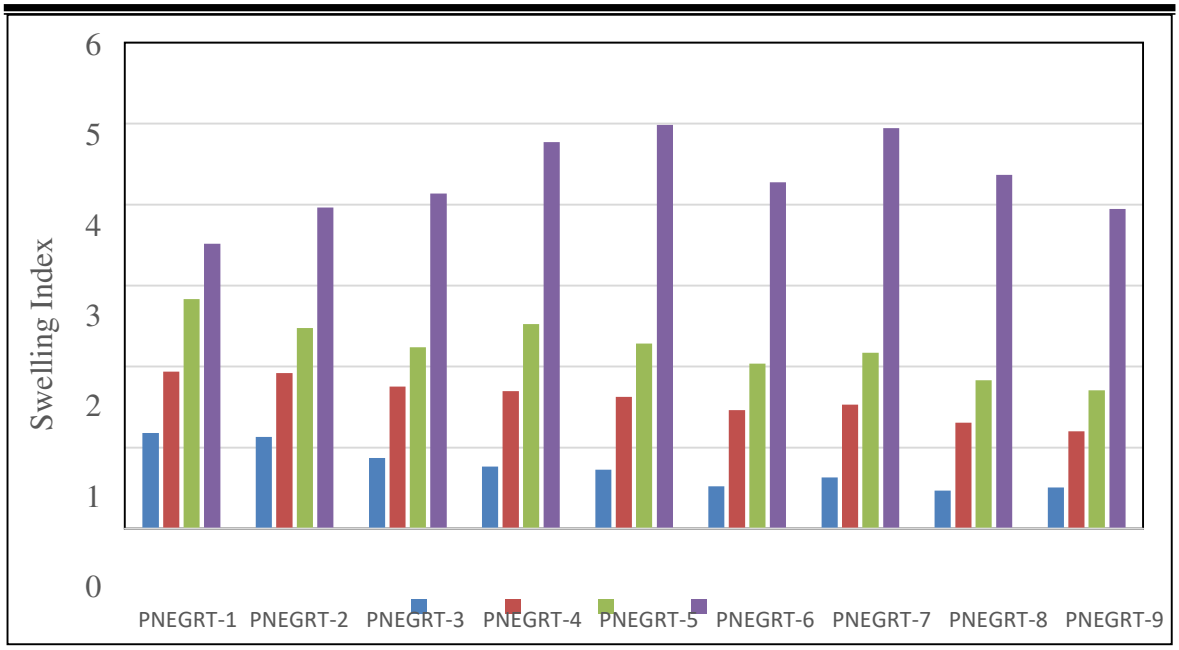
Release-retarding gel-forming polymer(s) such as HPMC K100M and Carbopol 971P were utilised in the development of controlled-release non-effervescent gastro-retentive tablets of PGB. Because it is water-soluble, mannitol was utilised as a filler. As a swelling agent, crospovidone was utilised. an agent that is insoluble in water and has the ability to increase water uptake in a matrix system that is hydrophilic. As can be observed in Table 7, each of the tablet formulations exhibited physicochemical features that were satisfactory and were in accordance with the pharmacopoeial standards regarding weight variation, friability, and drug content. There was a range of 669.0 to 677.2 milligrammes in the weight of the tablets. After being compressed to a thickness of around 6 millimetres, the tablets were measured to have a thickness that fell within the range of 5.90±0.03 to 6.13±0.06 millimetres. There was a range of 6.18±0.38 to 8.36±0.57 kilogrammes per square centimetre for the hardness of tablet formulations.

*Table 7 Result of post-compression evaluation of tablets*

| S. No. | Formulation | Average Weight (mg) | Weight Variation (%) | | Thickness (mm) | Hardness ($Kg/cm^2$) | Friability (%) | Drug Content (%) |
|---|---|---|---|---|---|---|---|---|
| | | | Min | Max | | | | |
| 1 | PNEGRT-1 | 674.3 | 1.08 | 1.44 | 5.93±0.04 | 7.15±0.46 | 0.01 | 99.52±0.54 |
| 2 | PNEGRT-2 | 671.4 | 1.25 | 0.83 | 5.91±0.03 | 7.52±0.37 | 0.06 | 99.70±0.41 |
| 3 | PNEGRT-3 | 669.4 | 1.10 | 0.99 | 6.04±0.05 | 8.36±0.57 | 0.00 | 99.65±0.50 |
| 4 | PNEGRT-4 | 670.8 | 1.01 | 0.78 | 5.90±0.03 | 6.37±0.46 | 0.02 | 99.99±0.13 |
| 5 | PNEGRT-5 | 672.8 | 1.16 | 0.62 | 6.05±0.02 | 7.63±0.53 | 0.11 | 100.13±0.36 |
| 6 | PNEGRT-6 | 673.3 | 1.08 | 1.44 | 5.93±0.03 | 8.20±0.54 | 0.06 | 100.22±0.34 |
| 7 | PNEGRT-7 | 669.0 | 0.90 | 1.05 | 6.08±0.03 | 6.18±0.38 | 0.09 | 99.38±0.58 |
| 8 | PNEGRT-8 | 677.2 | 1.95 | 2.19 | 6.10±0.04 | 6.33±0.60 | 0.01 | 99.43±0.49 |
| 9 | PNEGRT-9 | 676.1 | 1.20 | 1.46 | 6.13±0.06 | 6.93±0.47 | 0.07 | 98.95±0.35 |

*Table 8 Result of Swelling Ability of Pregabalin Gastro-retentive Tablets*

| S. No. | Formulation | Swelling Index | | | |
|---|---|---|---|---|---|
| | | 2 hour | 4hour | 8 hour | 24 hour |
| 1 | PNEGRT-1 | 1.18±0.07 | 1.94±0.16 | 2.83±0.09 | 3.52±0.13 |
| 2 | PNEGRT-2 | 1.13±0.09 | 1.92±0.13 | 2.48±0.20 | 3.96±0.19 |
| 3 | PNEGRT-3 | 0.87±0.08 | 1.75±0.12 | 2.24±0.11 | 4.14±0.16 |
| 4 | PNEGRT-4 | 0.76±0.06 | 1.70±0.08 | 2.52±0.15 | 4.77±0.11 |
| 5 | PNEGRT-5 | 0.73±0.08 | 1.63±0.13 | 2.29±0.14 | 4.98±0.06 |
| 6 | PNEGRT-6 | 0.52±0.05 | 1.46±0.13 | 2.04±0.07 | 4.28±0.21 |
| 7 | PNEGRT-7 | 0.63±0.04 | 1.53±0.09 | 2.17±0.11 | 4.94±0.10 |
| 8 | PNEGRT-8 | 0.47±0.04 | 1.31±0.03 | 1.83±0.08 | 4.37±0.10 |
| 9 | PNEGRT-9 | 0.51±0.07 | 1.20±0.06 | 1.71±0.11 | 3.95±0.12 |



In addition to Crospovidone, release retarding polymers such as HPMC K100M and Carbopol 971P also possess the ability to exert swelling activity. According to the findings of Bertram and Bodmeier (2006), the presence of hydrophilic groups in hydrogels is the reason for their capacity to absorb significant amounts of water. The hydration of these functional groups causes water to enter the polymer network, which in turn causes the network to expand and, as a result, the polymer chains to be ordered. It is possible to draw the conclusion that the amount of crospovidone, as well as the kind and ratio of swellable polymers, are factors that determine the amount of test medium that tablets take in in order to form a swellable matrix. It was noticed that formulations with a low amount of polymers exhibited a faster and larger swelling of the tablet over a period of time ranging from two hours to eight hours. Increases in polymer content were shown to result in a decrease in the amount of test medium that tablets absorbed up until eight hours, but after twenty-four hours, the swelling index was found to be increasing with an increase in polymer content.

**In vitro Drug Release Studies**

Two different polymers, namely Carbopol 971P and HPMC K100M, were utilised for the purpose of conducting this experiment. The purpose of this investigation was to investigate the controlled release capabilities of Crospovidone. The data that was plotted for the drug release from the Pregabalin floating gastro-retentive non-effervescent matrix tablet can be found in Figure 2.

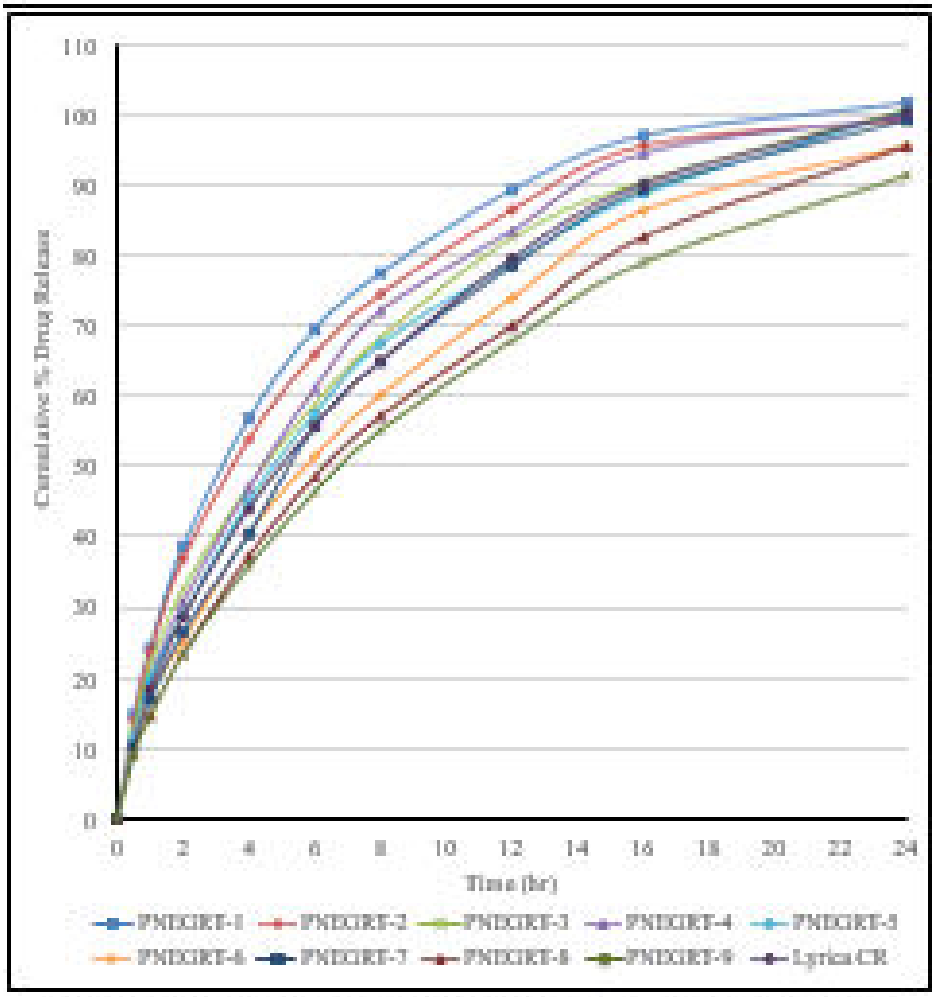



*Figure 3: Comparison of dissolution profiles of Pregabalin Non-effervescent Gastro-retentive Tablets with reference product Lyrica CR*

The in-vitro release of pregabalin from produced matrix tablet formulations was significantly impacted by the swelling behaviour of the formulations as well as the concentration of matrix-forming hydrophilic polymers. In every single one of the nine different PNEGRT formulations, the medication was progressively delivered over the course of time. Within the PNEGRT-1, pregabalin had the highest rate of dissolution, while within the PNEGRT-9, it exhibited the largest retardation of release. In general, the pregabalin release rate was shown to increase in proportion to the decrease in concentration of HPMC K100M and Carbopol 971P. In order to prevent the drug from diffusing from the core into the dissolving solution, a coating that is substantially hydrated is used. Furthermore, the increased concentration of release retarding polymers in the formulation supports a thicker diffusion barrier and a slower dissolving rate, which is in line with the findings that Garg and Gupta acquired in the past for both effervescent and non-effervescent floating dosage forms.[60] [60] The top side of the floating tablet is not suited for dissolving, so it is necessary to wet the bottom surface of the tablet in order to allow the drugs to spread out completely. In contrast to the situation in which sinkers are used to submerge tablets in the medium, the release of the medication from floating tablets is more gradual. Additionally, Hwang et al. observed the similar pattern of behaviour.[69] [69] A description of the drug release from PNEGRT is provided by the biphasic model. Due to the fact that they are in direct touch with the dissolving media, the drug molecules that are located on the periphery of the tablet experience a more rapid release beginning with the tablets. After that, the release is slowed down because the diffusion barrier, which is thickened by the swelling of matrix-forming release-retarding polymers, prevents the release from occurring.

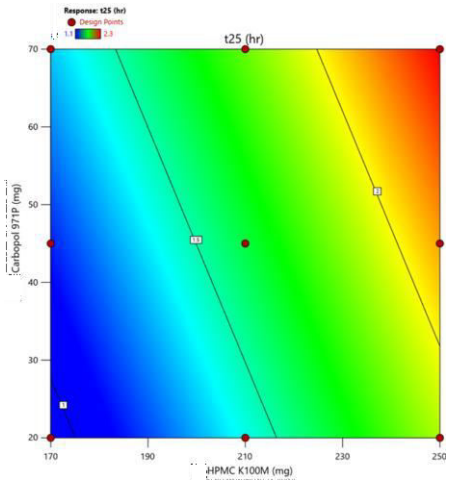
**Effect of Formulation Variables on t25 (*Y1),* t50 (*Y2) and* t80 (*Y3)***

The present study investigated the relationship between the quantities of HPMC K100M and Carbopol 971P polymers and the optimisation response parameters t25, t50, and t80. These factors were taken into consideration. Following the process of fitting the data of the observed responses, the programme generated appropriate polynomial model equations, which are presented in Table 8. These equations consider both the key components of the model individually as well as the interaction factors. The optimising model equations that relate Y1 (t25), Y2 (t50), and Y3 (t80) as answers are broken down into the following categories: From the previous equations, the X1 and X2 coefficients are positive for Y1 (t25), Y2 (t50), and Y3 (t80), and the X1X2 coefficient for Y3 (t80) is likewise positive. This indicates that the X1X2 coefficient is positive. This indicates that the dependent variables t25, t50, and t80 will also increase in value as the value of the independent factors, such as the quantity of HPMC K100M or Carbopol 971P, increases. Taking into consideration the equations that came before, it can be deduced that the amount of polymer present in the formulation has a relationship that is inverse to the rate at which the medication is released from the formulation. In contrast, a higher polymer amount leads in a slower release of the medication, while a lower polymer content causes the medication to be released more quickly.

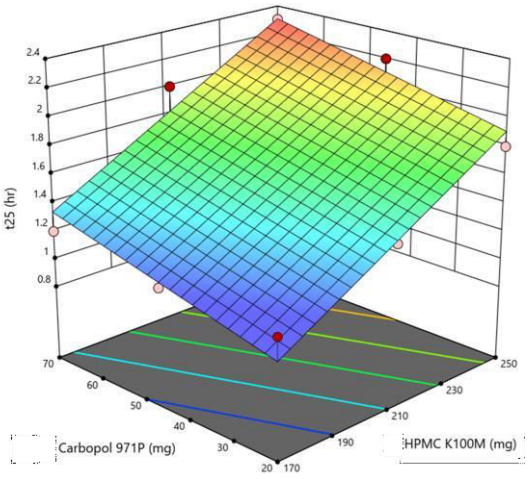
*Table 8 Analysis of variance table for dependent variables from full factorial Design*

| Source | Sum of Squares | df | Mean Square | F-value | p-value |
|---|---|---|---|---|---|
| Time required for 25% of drug release (*t25*) | | | | | |
| Model | 1.64 | 2 | 0.8208 | 43.24 | 0.0003 |
| *X1* | 1.40 | 1 | 1.40 | 73.84 | 0.0001 |
| *X2* | 0.24 | 1 | 0.24 | 12.64 | 0.0120 |
| Time required for 50% of drug release (*t50*) | | | | | |
| Model | 10.97 | 2 | 5.48 | 126.29 | <0.0001 |
| *X1* | 8.17 | 1 | 8.17 | 188.06 | <0.0001 |
| *X2* | 2.80 | 1 | 2.80 | 64.52 | 0.0002 |
| Time required for 80% of drug release (*t80*) | | | | | |
| Model | 48.66 | 3 | 16.22 | 367.72 | <0.0001 |
| *X1* | 33.61 | 1 | 33.61 | 761.86 | <0.0001 |
| *X2* | 14.41 | 1 | 14.41 | 326.79 | <0.0001 |
| *X1X2* | 0.64 | 1 | 0.64 | 14.51 | 0.0125 |

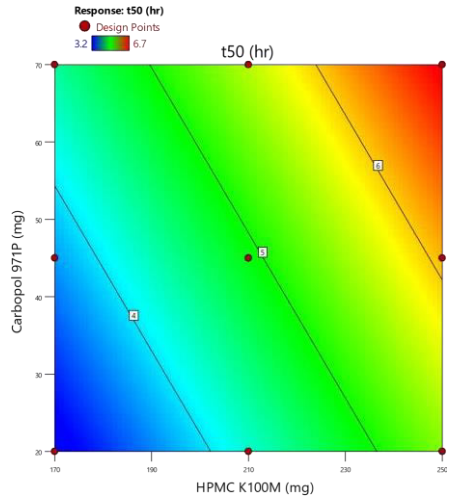
Figure 3 also displays three-dimensional response surface plots and contour plots created by Stat-Ease 360 software for Y1 (t25), Y2 (t50), and Y3 (t80). According to the 3D surface plots, the concentration of both HPMC K100M and Carbopol 971P showed an upward trend at a higher level (+1) and a downward trend of the wire mesh at a lower level (−1). We may infer that the concentrations of the HPMC K100M and Carbopol 971P polymers are directly proportional to the dependent variables t25, t50, and t80.


Response: t25 (hr)
Design Points
1.1
2.3
t25 (hr)
Carbopol 971P (mg)
HPMC K100M (mg)
70
60
50
40
30
20
170
190
210
230
250

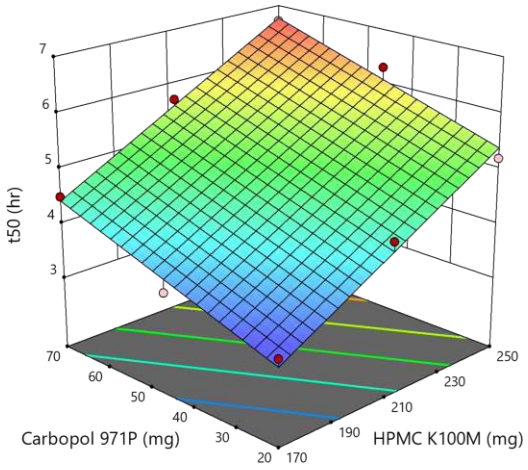
**(A1)**


t25 (hr)
2.4
2.2
2
1.8
1.6
1.4
1.2
1
0.8
Carbopol 971P (mg)
HPMC K100M (mg)
70
60
50
40
30
20
170
190
210
230
250

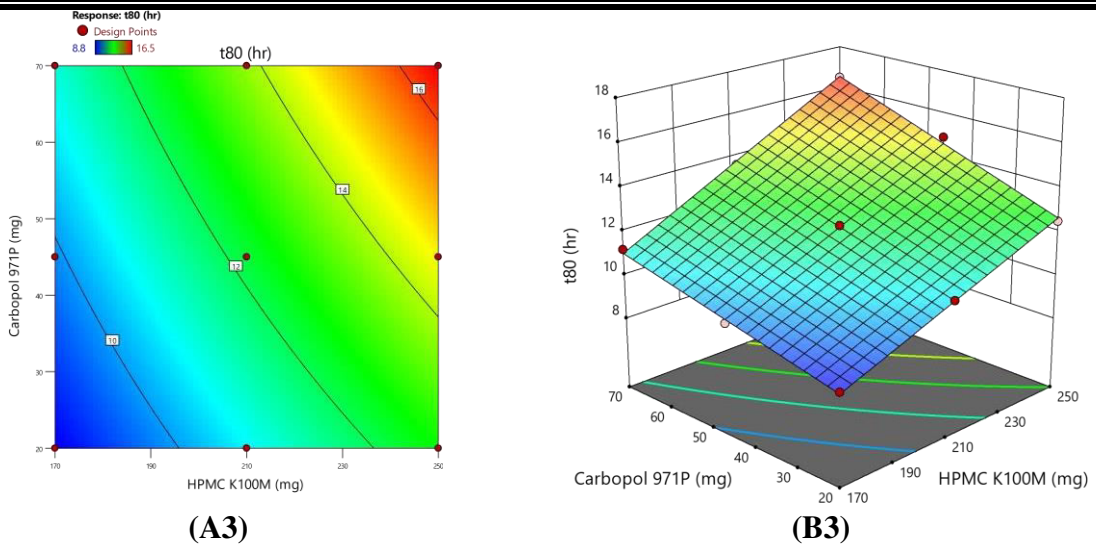
**(B1)**


Response: t50 (hr)
Design Points
3.2
6.7
t50 (hr)
Carbopol 971P (mg)
HPMC K100M (mg)

**(A2)**


t50 (hr)
7
6
5
4
3
Carbopol 971P (mg)
HPMC K100M (mg)
70
60
50
40
30
20
170
190
210
230
250

**(B2)**




**(A3)** **(B3)**

***Figure 3****: Contour plots (A) and Three-dimensional response surface plots (B) showing the effect of polymers on t25 (1), t50 (2) and t80 (3).*

**Optimization of PNEGRT by Response Surface Methodology**

A decision-making technique that takes into account many criteria was employed in order to optimise the PNEGRT formulation components that satisfied all of the responses with a variety of objectives. This method integrated graphical optimisation with numerical optimisation by utilising the desirability function. The overlay plot was used to complete the optimisation process. With the help of the models that were established during the analytical phase, numerical optimisation will investigate the design space in order to find factor configurations that are capable of meeting the objectives that have been stated. An overlay graph is formed through the process of graphical optimisation by comparing the predictions of the model to the criteria that have been established. This graph contains the contour plots from each answer placed on top of each other. A single graphic is produced by the overlay graph in order to demonstrate the "sweet spot" where the response requirements can be achieved. In order to accomplish the goal of producing the ideal formulation, we utilised restrictions on the responses of both the dependent variable and the independent variables. This table presents the criteria that should be considered when optimising the formulation of PNEGRT.

**Evaluation and Validation of Optimized Formulation**

The combo that is the most successful PNEGRT-O was able to fulfil all of the physicochemical requirements, as seen in Table 9. There were in vitro dissolving investigations carried out on the optimised formulation that had been produced in order to verify the theoretical prediction. It was determined how long it would take for 25% of the drug to be released (t25), 50% of the medication to be released (t50), and 80% of the drug to be released (t80). The experimental values of t25 (1.7 hours), t50 (5.0 hours), and t80 (12.5 hours) were in close agreement with the model predictions of 1.6 hours, 5.0 hours, and 12.4 hours, respectively. This fact substantiates the predictability and validity of the model.

*Table 9: Physicochemical evaluation of optimized formulation PNEGRT-O*

| S. No | Evaluation Parameter | Result | | | |
|---|---|---|---|---|---|
| 1 | Average Weight | 671.4 mg | | | |
| 2 | Weight Variation | Min: 1.25 % | Max: 1.04 % | | |
| 3 | Thickness | 5.97±0.03 mm | | | |
| 4 | Hardness | 8.11±0.43 Kgf | | | |
| 5 | Friability | 0.02 % | | | |
| 6 | Drug Content | 99.73 ± 0.26 % | | | |
| 7 | Swelling Index | 2 hr: 0.61±0.04 | 4 hr: 1.57±0.12 | 8 hr: 2.06±0.17 | 24 hr: 4.31±0.23 |
| 8 | Floating Lag Time | 1 min 35 sec – 2 min 18 sec | | | |
| 9 | Total Floating Time | > 24 hours | | | |
| 10 | Adhesion Retention Period | 41.74±4.12 min | | | |

The release profile of the reference product as well as the formulation that has been optimised With a similarity factor (f2) of 92.94 and a difference factor (f1) of 1.46, respectively, it was established that the release profile of PNEGRT-O was identical to that of the other. With an R2 value of 0.9944, the drug release from the optimised formulation was found to be consistent with the Higuchi model predictions. According to the Korsmeyer-Peppas plot, the release exponent 'n' was found to be 0.6184, which indicates that an anomalous diffusion mechanism is present.

**Stability Study**

The optimized formulation (PNEGRT-O) was evaluated for 2 months of storage at accelerated stability condition (40 ◦C ± 2 ◦C and 75% ± 5% RH) and real time stabilitycondition (30 ◦C ± 2 ◦C and 75% ± 5% RH). The tablets were evaluated for physical appearance, hardness, friability, floating characteristics, drug content and in vitro drugrelease. Stability studies showed the tablets complies with the physical properties and no any significant change was observed in drug content and dissolution profile indicating that the formulation is physically and chemically stable. The results of stability studies are depicted in Table12 and drug release profile is shown in Figure 5

*Table 10: Results of Stability study of Optimized Formulation (PNEGRT-O)*

| Parameters | Initial | 40°C/75%RH | | 30°C/75%RH | |
|---|---|---|---|---|---|
| | | 1 month | 2 month | 1 month | 2 month |
| Hardness (Kgf) | 8.11 ± 0.43 | 7.83 ± 0.36 | 8.04 ± 0.51 | 8.27 ± 0.58 | 8.11 ± 0.43 |
| Friability (%) | 0.02 % | 0.00 % | 0.03% | 0.02% | 0.01% |
| Drug Content (%) | 99.73 ± 0.26 | 99.41 ± 0.33 | 99.66 ± 0.19 | 100.02 ± 0.48 | 99.84 ± 0.34 |

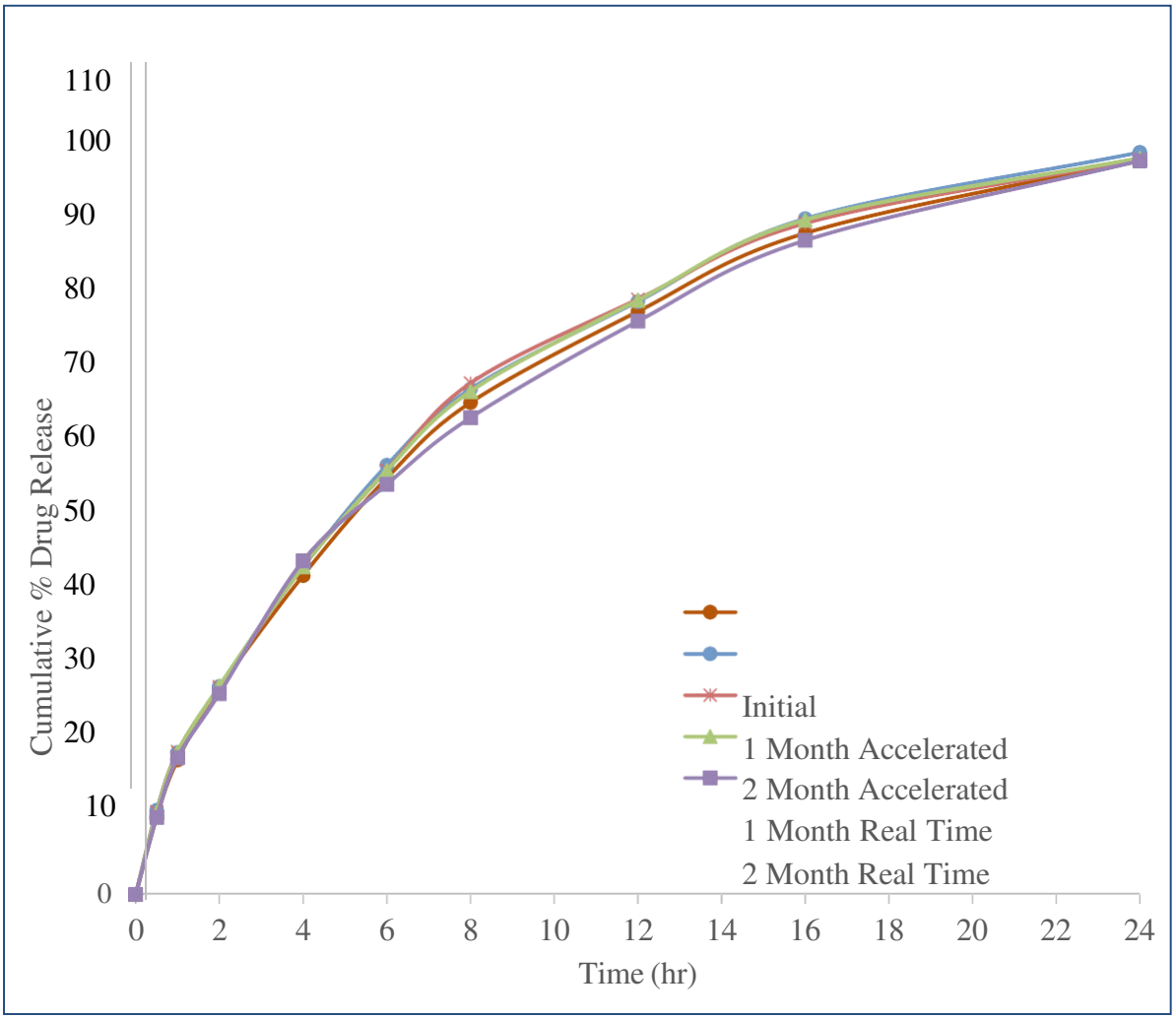



***Figure 4*** *Dissolution profiles of optimized Pregabalin Non-effervescent Gastro-retentive Tablet (PNEGRT-O) before and after stability*

## CONCLUSION

It was feasible to use polymers to create non-effervescent tablets with controlled release of pregabalin. With consistent weight, hardness, and thickness, the pre-compression results fulfilled all the desirable parameters. All nine formulations had the same amount of drug, which varied between 98.85±0.35% and 100.22±0.34%. Floating, swellable, extended-release tablets were prepared using crospovidone; other ingredients with swelling ability include HPMC K100M and carbopol 971P. As the tablet hardness increased, the floating lag time in carbopol 971P polymer also increased. The retention length of several formulations, measured in minutes, varied from 12.59 ± 1.46 to 55.02 ± 4.47, and the tablets stuck to the agar plates. While PNEGRT-9 exhibited the greatest retardation of release and the fastest rate of dissolution, pregabalin's release rate tended to rise when the carbopol and HPMC K100M content decreased. The physiochemical property criteria were the same for the optimised formulation PNEGRT-0. The optimised formulation PNEGRT-0 had a drug release profile that was found to be equivalent to the reference product's release. Over the course of two months, the PNEGRT-O formulation was tested under both accelerated stability (40 ◦C ± 2 ◦C and 75% ± 5% RH) and real time stability (30 ◦C ± 2 ◦C and 75% ± 5% RH) conditions. Tests included looking at the tablets' hardness, friability, floating qualities, drug content, and in vitro drug release, among other physical attributes. The tablets were found to meet the physical qualities in stability experiments, and there was no discernible change in the drug content or dissolving profile, suggesting that the formulation is physically and chemically stable. So, formulations worked, and patients may be more likely to take their medication as prescribed if that happens.

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