# FORMULATION OPTIMIZATION AND EVALUATION OF PREGABALIN FLOATING CONTROLLED-RELEASE TABLETS

**Dr. N. Deepa[1]*, Dr. Sangeetha Mani[2], Dr. P. Balaji[3], Dr Shanmugasundaram Palani[4]**

[1] *Dean & Professor, Department of Pharmacognosy, Faculty of Pharmacy, Sree Balaji Medical College and Hospital (SBMCH), Bharath Institute of Higher Education and Research (BIHER), Chennai – 600073, Tamil Nadu, India.*

[2] *Professor, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research (SRIHER), Porur, Chennai – 600116, Tamil Nadu, India.*

[3] *Professor, Department of Pharmacology, School of Pharmaceutical Sciences, VELS Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai – 600117, India.*

[4] *Department of Pharmaceutical Chemistry & Analysis, School of Pharmaceutical Sciences, VELS Institute of Science, Technology & Advanced Studies (VISTAS), Pallavaram, Chennai – 600117, Tamil Nadu, India.*

**Corresponding Author**
***Dr. N. Deepa***
Dean & Professor
Department of Pharmacognosy
Faculty of Pharmacy, SBMCH, BIHER
Chennai – 600073, Tamil Nadu, India
Email : deepanatarajan@yahoo.com

**Abstract:**
In the current study, controlled-release floating bilayer tablets of pregabalin and (X1–X9) were developed with different rates of polymeric materials by a direct compression method. During the formulation, Fourier-transform infrared spectroscopy (FTIR) analysis was performed for possible interactions between drugs and excipients. No interactions between drugs and excipients were noted. the tablets containing HPMC K4M with HPMC K100 LV (X7) had a short buoyancy lag time, a total floating time of more than 10 h and sustained release up to 12 h. This novel gastro retentive dosage form could be fascinating for enhancement of bioavailability and the stomach specific delivery of pregabalin. From the above study it could be concluded that floating gastroretentive drug delivery system is most stable system.
The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of Pregabalin tablets.

**Keywords:** pregabalin, controlled-release floating, Fourier-transform infrared spectroscopy.
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## Introduction

Oral delivery of drugs is the most preferable route among all the drug delivery due to the ease of administration, patient compliance and flexibility in formulation. From immediate release to site specific delivery, oral dosage forms have really progressed. The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration (Garg *et. al.,* 2008).

Technological attempts have been made in the pharmaceutical research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Dosage forms that can be retained in the stomach are called Gastro retentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability (Chien, 1992).

Invariably, conventional dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period. To achieve the same, a drug may be administered repeatedly using a fixed dosing interval. This causes several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration-time curve (Fig.1).

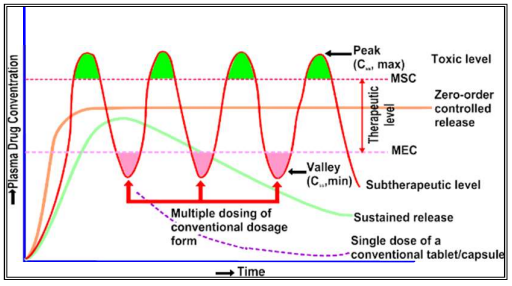



Fig. 1: Plasma level profiles following conventional and controlled release dosing.

Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. An important requisite for the successful performance of oral CRDDS is that the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion, to ensure continuous absorption of the released drug. The average time required for a dosage unit to traverse the GIT is 3-4 hrs., although slight variations exist among various dosage forms (Arora, *et. al.,* 2005).

Orally administered drugs are absorbed by passive diffusion processes and by nonpassive means. Drugs absorbed by active and facilitated transport mechanisms show higher regional specificity because of the prevalence of these mechanisms in only certain regions of the GIT (fig.2). Many drugs show poor BA because of the presence of enzymes and efflux pumps. Intestinal metabolic enzymes primarily, Phase I metabolizers such as cytochrome P450 (CYP3A) are abundantly present in the intestinal epithelium. Their activity decreases longitudinally along the small intestine, with levels rising slightly from the duodenum to the jejunum and declining in the ileum and colon.

In addition, carriers like secretary transporter are P-glycoprotein (P-gp) may affect drug absorption. An example of such a, which is present in the villus tip of enterocytes and has the capacity to interact with a vast variety of drugs. P-gp sends the absorbed drug from the cytoplasm of the enterocytes back to the intestinal lumen, thus reducing the drug's bioavailability.

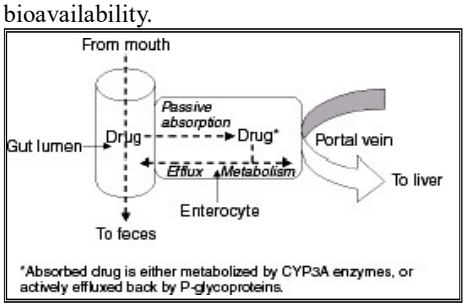



Fig. 2: Depicts the mechanism involved in the interaction between drug efflux and metabolism.

The enzyme metabolizes the drug molecule absorbed into the enterocytes. Then that portion of the drug is transported from the enterocytes back into the intestinal lumen by the action of P-gp, following which it is reabsorbed and again subjected to metabolism and efflux. Therefore, the drug is continually cycled between the enterocytes and the gut lumen, which allows the enzyme to have repeated access to the drug molecule, thus reducing absorption.

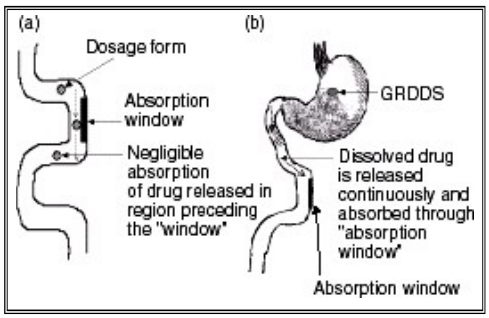



Fig. 3: Drug absorption in the case of (a) Conventional dosage forms and (b) gastroretentive drug delivery systems.

A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular portion of the GIT only or are absorbed to a different extent in various segments of the GIT. Such drugs are said to have an absorption window, which identifies the drug's primary region of absorption in the GIT (Singh *et al*., 2000). An absorption window exists because of physiological, physicochemical, or biochemical factors. The pH-dependent solubility and stability level of a drug plays an important role in its absorption. A drug must be in a solubilized and stable form to successfully cross the biological membrane, and it will experience a pH range from 1 to 8 as it travels through the GIT.

Because most drugs are absorbed by passive diffusion of the un-ionized form, the extent of ionization at various pH levels can lead to non uniform absorption or an absorption window. After crossing the absorption window, the released drug goes to waste with negligible or no absorption (Fig. 3a and 3b).

Gastric Retention Platform

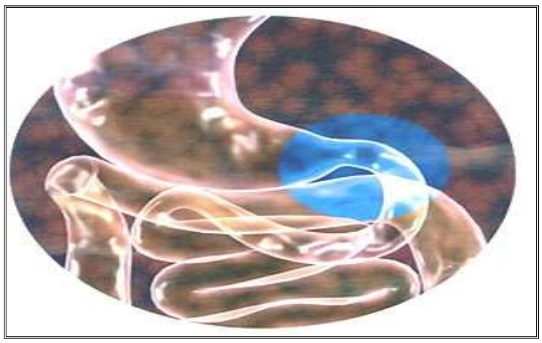


Fig. 4: Gastroretentive drug delivery systems.

There are many drugs that are not absorbed to the same extent once they pass the upper small intestine and thus, once-daily formulations are exclusive for these drugs (Fig.4). One method to overcome the fast GI transit is to maintain the dosage form in the stomach for extended periods of time, and therefore, research efforts have been focused on development of gastric retention platforms. Several drugs are absorbed to the most extent in the upper part of the small intestine (Rouge et al., 1996).

One of the major scientific challenges in the development of gastric retention devices is overcoming the housekeeping waves that consist of strong gastric contractions that occur every few hours, particularly in the fasted state.

Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site specific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bioadhesive drug delivery are widely used techniques for gastro retention (Singh and Kim, 2000).

We will elaborate the most important features of the core research persued on the above mentioned subject. The following chapter gives the review of literature in the light of subject discussed here.

**Pharmacokinetic Advantages**

Any solute released in the stomach will empty together with fluids and have the whole surface of small intestine available for absorption. This should particularly be useful when an absorption window exists in proximal small intestine. In addition, with the total GI transit duration is increased, a greater amount of drug may be delivered and thus the relative bioavailability will consequently be increased. For instance, a significant increase in bioavailability of furosemide has been obtained (42.90%) when administered as a floating dosage form, compared to the commercially available tablet (Lasix®, 33.40%). Other drugs with poor bioavailability like verapamil hydrochloride were also formulated into FDDS apparently due to the analogous reasons.

**MATERIALS AND METHODS**

**Materials**

The following drug, excipients and chemicals were used for the formulation and evaluation of Gastroretentive drug delivery system.

Table 3: List of drugs, polymers, excipients, chemical and reagent used for study

| **Drug** | **Name of Manufacturer** |
|---|---|
| Pregabalin | Drugs India, Hyd |
| Polymers and Excipients | |
| HPMC (K4M, K100 LV) | Colorcon Asia Pvt. Ltd., Goa, India |
| Microcrystalline cellulose (MCC KG 100) | S.D. Fine Chemicals., Mumbai, India |
| Sodium bicarbonate | Lubrizol., Mumbai, India |
| Anhydrous citric acid, | S.D. Fine Chemicals., Mumbai, India |
| Magnesium stearate | S.D. Fine Chemicals., Mumbai, India |
| Talc | S.D. Fine Chemicals., Mumbai, India |
| Reagents | |
| (1) Acetonitrile (HPLC grade) | Merck Specialties Pvt. Ltd. |
| (2) Disodium dihydrogen orthophosphate | Loba chem. |
| (3) Orthophosphoric acid (AR grade) | Merck Specialties Pvt. Ltd. |
| (4) Tetrabutylammonium hydroxide | Loba chem. |
| (5) Water (HPLC grade or equivalent) | Milli Q. |

Table 4: List of Equipment's, make and model used for the study

| **Equipment's Name** | **Name of Manufacturer and Model** |
|---|---|

| | |
|---|---|
| Digital Balance | AUX 120, Shimadzu, Japan. |
| Differential scanning calorimeter | METTLER DSC 30 S, Mettler Toledo India Pvt. Ltd. |
| Infra Red Spectrophotometer | 8400S, Shimadzu, Kyoto Japan. KBr press, TSI, Mumbai |
| KBr Press | Electrolab ETD 1020, Mumbai, India. Electrolab TDT 08 L Plus. |
| Tap density tester | Electrolab, disintegration tester (USP) ED-2L LAB-HOSP, Mumbai |
| USP II Dissolution Test Apparatus | Elico Model- LI 612 |
| Disintegration apparatus | CHM-10S Remi Lab, Mumbai. |
| Sonicator | Rimek minipress-1, Ahmedabad, India. Agilent technologies. |
| Digital pH meter | Monsanto hardness tester. Mitutoyo, Absolute, USA. Wipro GE DX-300, Pune, India. |
| Stability chamber | Electrolab, EF-2, Friabilator (USP). Shimadzu 1700, Japan |
| Tablet compression machine HPLC | Remi Instruments, Mumbai, India. Fabricated in lab. |
| Hardness tester | |
| Vernier caliper X-ray machine Roche friabilator | |
| Ultraviolet Spectrophotometer | |
| Mechanical stirrer | |
| Mucoadhesive strength determination Apparatus | |

**Methodology**

**1. Preformulation study**

**A) Identification of drug**

Identification of drug was carried out by infrared spectroscopy and differential scanning calorimetry (DSC).

**Infrared spectroscopy**

The potassium bromide disk method was used for the preparation of sample. IR spectrum of drug was measured in the solid state as potassium bromide dispersion. The bands ($cm^{-1}$) have been assigned.

**Differential scanning calorimetry study**

Melting point of drug was determined by using DSC. The drug was hermetically sealed in perforated aluminum pans and heated at constant rate of 10 $^0$C / min over the temperature ranges of 50-300 $^0$C.

**B) Melting point determination**

The melting point of Pregabalin were determined by using melting point apparatus.

**C) Solubility study of Pregabalin in different solvents**:

The solubility of drug to be determined by taking 10 ml of various medium and then cumulative addition of drug was carried out in order to make saturated drug solution, maintained at 37 °C ± 0.5 °C in a water bath and continually shaken in to mechanical shaker (Remi mechanical shaker, Mumbai) up to 24 h. Samples were withdrawn, filtered through a filter paper (pore size 0.45 µm), suitably diluted and assayed by UV spectrophotometer.

**D) Standard calibration curve**

**Standard calibration curve of Pregabalin in pH 3 buffer**

Stock standard solution was prepared by dissolving accurately weighed 100 mg Pregabalin in volumetric flasks, dissolved in methanol and diluted to 100 ml with freshly prepared in glycine buffer (pH 3.0). The stock solution was filtered through a 0.45 µm membrane filter. A standard curve was prepared by withdrawing appropriate aliquots from stock solution into a series of 10 ml of volumetric flasks. The volume was made upto the mark with mobile phase to obtain concentration range 10-20 µg/ml of Pregabalin. Detection of Pregabalin was performed with the UV spectrophotometry set at 226 nm. The peak area was recorded and calibration curves were plotted with peak area verses the respective concentration of Pregabalin.

**A)** Evaluation of precompression parameters of drug, polymer and excipients Drug, polymers and excipients were characterized for their physical properties such as angle of repose, density, compressibility, and Hausner's ratio. Pregabalin and Pregabalin were evaluated for particle size determination by Malvern technique.

**Angle of Repose**

The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surfaces of a pile of powder or granules and the horizontal plane. Different ranges of flow ability in terms of angle of repose shown in Table 5. The angle of repose was determined by the funnel method (Lachman et al., 1990, V. Bhavani et al., 2012). The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured by scale. The angle of repose was calculated using the following equation.

$\tan(\Theta) = h / r$ (1)

Where 'h' and 'r' are the height and radius respectively of the powder cone

Table 5: Different ranges of flow ability in terms of angle of repose

| Angle of repose, (Θ) | Predicted flow property |
|---|---|
| < 25 | Excellent |
| 25-30 | Good |

| | |
|---|---|
| 30-40 | Passable |
| >40 | Very poor |

**Determination of bulk density**

Weigh accurately 25 gm of material (W), which was previously passed through 20 # sieve and transfer in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume ($V_0$) (USP., 2010). Calculate the apparent bulk density in gm/ml by the following formula.

Bulk density = Weight of powder / Bulk volume (2)

**Determination of tapped bulk density**

Tapped bulk density is the ratio of weight of the powder sample to its tapped volume. Weigh accurately 25 gm of material, which was previously passed through 20 # sieve and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume ($V_1$) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume ($V_2$) to the nearest graduated units. If the difference between the two volume is less than 2 % then final the volume ($V_2$) (USP., 2010).

Tapped Density = Weight of powder / Tapped Volume (3)

**Compressibility index**

The compressibility index of material was determined by following equation (Reddy *et al.* 2003).

Carr's Index = [(Tapped bulk density- Loosed bulk density) X 100 / Tapped bulk density] (4)

**Hausner's ratio**

Hausner's ratio was determined by following equation (Lachman et al., 1990) Hausner's ration = Tapped bulk density / Loosed bulk density (5)

Table 6: Standard values of Carr's index and Hausner's ratio

| Carr's index | Type of flow | 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 |
| 32-38 | Very poor | 1.46-1.59 |
| >38 | Very, Very poor | >1.60 |

**A) Particle size determination**

Particle size determination of Pregabalin was determined using dry method by Malvern technique.

**B) Drug excipients compatibility study**

The drug excipients interaction study was carried out by using Fourier transform infrared spectroscopy and Differential scanning calorimetry.

**Differential scanning calorimetry study:**

Physical mixtures of drug and drug with excipients were filled in dried vial. The sealed vials were stored at 40 ºC/ 75 % RH for four weeks in stability chamber. At the end of four weeks vials were removed from stability chamber and subjected for interaction study. Drug polymer interaction study was carried out by using DSC. In this study thermogram of pure drug, drug with polymer and mixtures of drug with excipients were taken. Heating was done at a scan rate of 10 °C / min. over a temperature range of 30 to 340 °C in a dynamic Nitrogen atmosphere. An empty sealed Aluminum pan was used as a reference.

**FTIR spectroscopy study**

IR spectroscopy was used to determine the molecular interaction between drug and excipients. The above (as per DSC study) all physical mixtures and drug sample were mixed with dried KBr in ratio 1:100. The mixture was compressed to a 12 mm semi transparent disk by applying a pressure of 10 tons for 2 min. The FTIR spectra over the wavelength range 4000-400 $cm^{-1}$ were recorded using a FTIR spectrometer (8400S, Shimadzu, Japan).

**Pregabalin GRDDS**

**Pregabalin Gastroretentive drug delivery system**

In the present study, statistical experimental design was used in order to get more information about the effect of formulation components on drug release and to obtain the optimum formulation through minimum time and expenses. The levels of the two factors were selected on the basis of preliminary studies carried out before implementing the experimental design. The experimental design was generated using state-of-art computerized optimization software Design Expert Version 8.0.3.1 (Design Expert, 2010).

Experimental Design (For Floating Gastroretentive drug delivery system) In $3^2$ full factorial design, 2 independent variables Polymer 1 are Concentration of HPMC K4M / HPMC K4M (P1) and Polymer 2 are Concentration of HPMC K100LV (P2) were selected at 3 different levels for, Percentage drug release at 12 h (Q 12), Total floating time (TFT), Buoyancy lag time, as dependent variables (Table 7). Experimental trials were performed using all 9 possible combinations were shown in Table 10-11(Design Expert Version 8.0.3..1).

Table 7: The variables used in Gastroretentive Floating tablets of Pregabalin

| Independent variables | Symbols | Dependent variables |
|---|---|---|
| Concentration of HPMC K4M / HPMC K4M | P1 | % Drug released (Q 12) Total floating time (TFT) Buoyancy lag time (BLT) |
| Concentration of HPMC K100 LV | P2 | |

**Preparation of Gastroretentive tablets of Pregabalin**

Pregabalin tablets were prepared by the direct compression method. Each tablet contained about 330 mg of the drug. All the ingredients were sifted through sieve no. 40 and magnesium stearate was passed through sieve no 60. The required quantities of the materials were mixed thoroughly for 15 minutes in polybag and lubricated with magnesium stearate for 3 minutes.

Compositions of all the formulation were given in Table 8.

Table 8: Composition of Pregabalin Floating tablets (X1-X9)

| Ingredients (in mg) | X1 | X2 | X3 | X4 | X5 | X6 | X7 | X8 | X9 |
|---|---|---|---|---|---|---|---|---|---|
| Pregabalin | 330 | 330 | 330 | 330 | 330 | 330 | 330 | 330 | 330 |
| HPMC K4M | 16.5 | 21.45 | 26.40 | 16.5 | 21.45 | 26.40 | 16.50 | 21.45 | 26.40 |
| HPMC K100 LV | 26.40 | 26.40 | 26.40 | 33.0 | 33.0 | 33.0 | 39.60 | 39.60 | 39.60 |
| MCC KG-100 | 21.55 | 16.60 | 11.65 | 14.95 | 10.0 | 5.05 | 8.35 | 3.40 | 3.45 |
| Sodium lauryl sulphate | 4.90 | 4.90 | 4.90 | 4.90 | 4.90 | 4.90 | 4.90 | 4.90 | 4.90 |
| Citric acid | 14.70 | 14.70 | 14.70 | 14.70 | 14.70 | 14.70 | 14.70 | 14.70 | 14.70 |
| Sodium bicarbonate | 73.50 | 73.50 | 73.50 | 73.50 | 73.50 | 73.50 | 73.50 | 73.50 | 73.50 |
| Magnesium stearate | 2.45 | 2.45 | 2.45 | 2.45 | 2.45 | 2.45 | 2.45 | 2.45 | 2.45 |
| Total weight | 490 | 490 | 490 | 490 | 490 | 490 | 490 | 490 | 495 |

**Pre-compression parameter of powder blend**

Powder blend were evaluated for various pre-compression parameters such as Angle of repose, Loosed bulk density (LBD), Tapped bulk density (TBD), Compressibility index and Hausner's ratio. The blends were compressed using a single-punch tablet compression machine using 8.0 mm standard concave punch, and their physical parameters were evaluated, such as the average weight, thickness, hardness and friability (Lachman L and Hebert A et al., 1987).

**Evaluation parameters of tablets**

Evaluation parameters for Floating drug delivery system of Pregabalin are shown in Table 09. (Indian Pharmacopoeia 2007)

Table 9: Evaluation parameters applicable for Mucoadhesive and Floating drug delivery system of Pregabalin

**a) Weight Variation test**

Twenty tablets were taken from each formulation and weighed individually to check for weight variation (Table 10). Calculated average weight and compared the individual tablet weight to the average.

Table 10: Weight variation tolerances for tablets

| Average weight of tablets (mg) | Maximum % difference allowed |
|---|---|
| **80 or less** | **10** |
| 80 – 250 | 7.5 |
| More than 250 | 5 |

**b) Thickness:** Thickness of tablets was measured by using digital Vernier caliper.

**c) Hardness:** Tablets were selected at random from individual formulations and hardness was measured and expressed in Kg/cm$^2$ or Newton's (N).

**d) Friability**: Twenty tablets were randomly selected and placed in the drum of a tablet friability test apparatus. The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated. Results are expressed as mean values ± SD.

Friability (%) = Initial weight-Final weight / Initial weight X 100 (6)

### I. *In vitro* study

#### a) Drug content

Accurately weighed and powdered 20 tablets, weighed accurate quantity of the powder equivalent to 330 mg of Pregabalin into 100 ml of volumetric flask, add 30 ml of Acetonitrile, mix and sonicate for 5 minutes to dissolve and dilute to volume with pH 6.5, buffer solution. Filter through 0.45 µl filter. Dilute 5 ml to 50 ml with mobile phase (Acetonitrile: pH 6.5 buffer). Record the chromatogram and measure the peak responses at 226 nm and calculate the content of Pregabalin in the sample.

#### b) Swelling study

The tablets were weighed individually (as W1), placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37 ± 1 °C. The mucoadhesive tablets were removed from the beakers at 1-hour intervals (over a total of 12 h), and the liquid was removed carefully from the surface using paper. The swollen tablets were then weighed (W2). The swelling index (SI) was calculated using the following formula.

% Swelling Index = $(W_2 - W_1) / W_1 X 100$

Where W1- Initial weight of tablet, W2- Weight of the swollen tablet.

#### c) *In vitro* buoyancy studies

The *in vitro* buoyancy was determined by buoyancy lag time. The time taken for the tablet to rise to the surface and float was taken as floating lag time. The test was performed by placing each of the tablets in a 250 ml beaker containing 200 ml of 0.1 N HCl, pH 1.2 maintained at 37 ± 0.5 °C in a water bath.

#### d) *In vitro* drug released study

The drug release of various formulations (X1-X9) was studied *in vitro* using USP type II apparatus set at 100 rpm. A buffer medium with pH 3.0 (900 ml) at 37.5 ± 0.5 °C was used. A 10 ml sample was withdrawn at 1, 2, 4, 6, 8, 10 h time intervals over a period of 12 h and replaced with the same dissolution media. The withdrawn samples were analyzed using UV Spectrophotometry at 226 nm. Kinetic modeling of drug release. The drug released profile of all the batches was analyzed using the zero order, first order, Higuchi, Hixon-crowell, Korsmeyer's Peppas model was selected to perform kinetic modeling of the drug release. A criterion for selecting the most appropriate model was based on high regression coefficient value.

## RESULTS AND DISCUSSION

### A) Preformulation Study

**Confirmation of drug:**

Confirmation of drug was carried out by following methods.

**FTIR Spectroscopy**

The IR spectrum was obtained in the solid state as potassium bromide dispersion. The IR spectrum of Pregabalin is presented in Fig 12. Observed peaks are shown in Table 11.

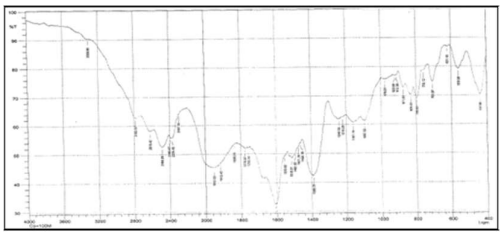


Fig: 12. IR spectrum of Pregabalin

Table 11: Principal peak and functional group present in IR spectrum of Pregabalin

| Sr. No | Peak observed ($cm^{-1}$) | Functional group |
|---|---|---|
| 1. | 2937.04 | C-H Stretching (Aliphatic) |
| 2. | 2984.39 | C-H Stretching (Aromatic) |
| 3. | 3330.81 | N-H Stretching |
| 4. | 1618.01 | N-H Bending |
| 5. | 1638.04 | C=N Stretching |
| 6. | 1074.15,1099.46 | C-O Stretching |
| 7. | 1761.84 | C= O Stretching |
| 8. | 674.20 | C-S-C Stretching |
| 9. | 1274.25 | C-N Stretching |
| 10. | 1375.64 | C-H Bending |

**DSC study**

Pregabalin was confirmed by differential scanning calorimetry (DSC) at scan rate of 10 ºC / min. The DSC thermogram of Pregabalin (Fig. 13) exhibited a single sharp endothermic peak at 98.79 $^0$C and 102.99 $^0$C respectively, related to its melting transition temperature. Okonogi and Puttipipatkhachorn., 2006)

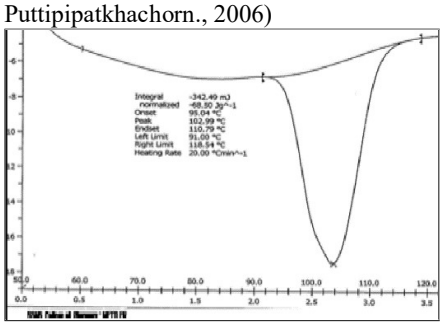


Fig. 13: DSC thermogram of Pregabalin

**Melting point determination**

The melting point of Pregabalin was confirmed by using melting point apparatus. The melting point of Pregabalin was found to be in the range of 98.04 - 102.99 ºC

**Solubility Study**

Results of solubility studies are shown in Table 24.

Table 12: Solubility study of Pregabalin and Pregabalin in different solvent

| Sr. No | Solvent | Solubility (mg/ml) |
|---|---|---|
| 1. | 0.1N HCl (pH 1.2) | 5.60 |
| 2. | Glycine buffer (pH 3.0) | 6.10 |
| 3. | pH 4.5 | 0.40 |
| 4. | pH 6.8 | 0.37 |

**Standard calibration curve**

**Standard calibration curve of Pregabalin in pH 3.0**

Calibration curve of Pregabalin in glycine buffer pH 3.0 was studied; plots of area verses concentration was found to be linear between the range of 10 to 60 µg/ml. The $r^2$ value of the calibration curve was found to be 0.999. Results of standard calibration curve of Pregabalin in glycine buffer (pH 3) are shown in Fig. 14 and Table 13.

Table 13: Calibration Curve of Pregabalin

| S.No | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | 10 | 0.24 |
| 2 | 20 | 0.48 |
| 3 | 30 | 0.68 |
| 4 | 40 | 0.91 |
| 5 | 50 | 1.12 |
| 6 | 60 | 1.38 |

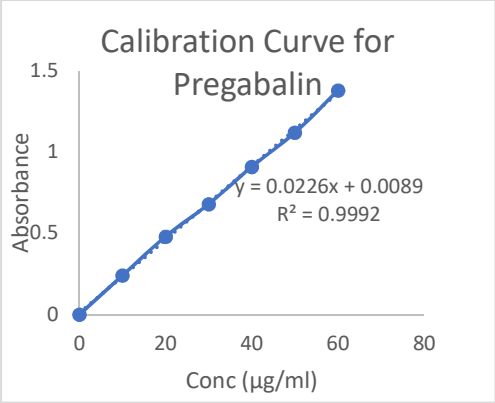



Fig 14: Calibration Curve of Pregabalin

**B) Evaluation of precompression parameters of drug, polymers, and excipients**

Drug, polymers and excipient were characterized for their physical properties such as angle of repose, density, compressibility, Hausner's ratio and given in Table 14.

Table 14: Evaluation of precompression parameters of drug, polymers and excipients

| **Ingredients** | **Angle of repose (θ)** | **Bulk density gm/ml** | **Tapped density (gm/ml)** | **Hausner's ratio** | **Compressi-bility index (%)** |
|---|---|---|---|---|---|
| Pregabalin | 36.00 ±1.32 | 0.416 ±0.15 | 0.545 ±0.16 | 1.18 ±0.12 | 18.17 ±0.15 |
| HPMC K100 LV | 30.00 ±1.20 | 0.220 ±0.03 | 0.260 ±0.04 | 1.18 ±0.30 | 15.38 ±0.54 |
| HPMC K4M | 30.00 ±1.30 | 0.240 ±0.04 | 0.330 ±0.06 | 1.37 ± 0.26 | 27.27 ±1.16 |
| MCC KG 100 | 35.00 ±1.10 | 0.290 ±0.06 | 0.420 ±0.03 | 1.42 ±0.53 | 19.41 ±1.28 |
| Sodium lauryl sulphate | 28.00 ±1.30 | 1.500 ±0.06 | 2.350 ±0.28 | 1.56 ±0.25 | 36.59 ±1.25 |
| Sodium bicarbonate | 37.00 ±2.00 | 1.100 ±0.35 | 1.760 ±0.22 | 1.60 ±0.25 | 37.50 ±1.22 |
| Citric acid | 28.00 ±1.50 | 0.630 ±0.50 | 1.000 ±0.55 | 1.60 ±0.63 | 37.5± 1.30 |
| Magnesium stearate | 30.00 ±1.12 | 0.400 ±0.07 | 0.600 ±0.06 | 1.50 ±0.50 | 33.33 ±1.20 |

*All the values are mean ± SD of three determinations

**Particle size determination**

Particle size determination of Pregabalin was determined using dry method by Malvern technique and given in Fig 15.

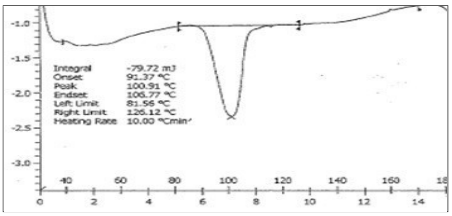


Fig. 15: Particle size distribution of Pregabalin by Malvern technique.

D (0.9):(90%oftheparticleswere53.438 µm or above) 53.438 µm

D (0.5) (50%oftheparticleswere2.494 µm or

: abov
2.49 e)
4 µm
D (0.1): 0.660 µm (10 % of the particles were 0.660 µm or above)

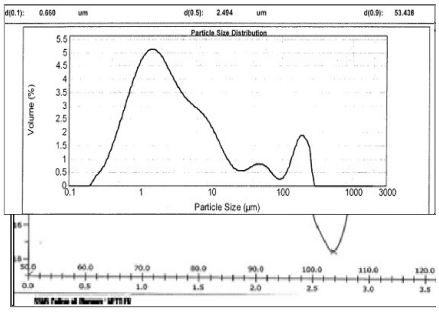
**Drug excipients compatibility study**

The drug excipients interaction study was carried out by using Fourier Transform Infrared spectroscopy and differential scanning calorimetry (DSC). In this study thermograms of pure drug, drug with polymer and mixtures of drug with excipients were taken and given in Fig16-18. The FTIR spectrum and DSC thermogram of alone drug is shown below.

**DSC study of Pregabalin physical mixture**

The drug, drug-excipients physical mixture studies reveal that there were no significant change in position of peak in thermogram of drug, drug-excipients was recorded. The DSC thermogram of Pregabalin exhibited a single sharp endothermic peak at 98.79 $^0$C related to its melting transition temperature shown in Fig. 18a and drug excipients physical mixture shows melting endothermic peak of Pregabalin at 100.92 $^0$C shown in Fig.18 b-h. From drug excipients compatibility study, it was concluded that the given drug was compatible with all the excipients and it was confirmed by DSC study.

Fig. 16: DSC thermogram of Pregabalin.



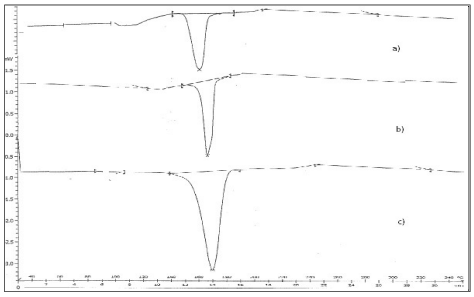



Fig. 17: DSC thermogram of Pregabalin with excipients mixture.

Fig. 18: DSC thermogram of a) Pregabalin (b) Pregabalin with HPMC K4M (c) Pregabalin with HPMC K100 LV.

**FTIR spectroscopy study of Pregabalin**

The drug excipients studies reveal that there were no physical changes in drug and excipients mixtures. The drug excipients studies reveal that there was no physical change in drug and excipients mixtures.

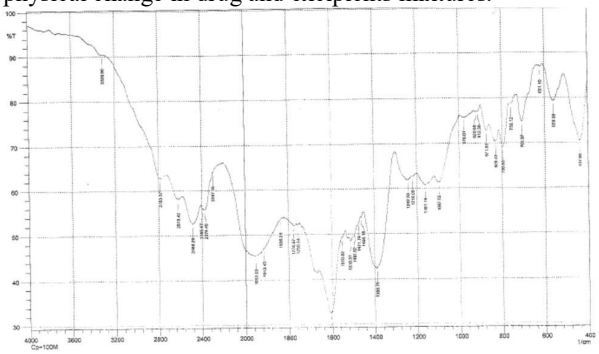


Fig. 19: FTIR spectrum of Pregabalin.

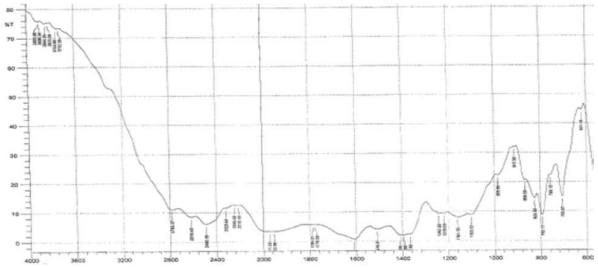


Fig. 20: FTIR spectrum of Pregabalin - excipients physical mixture.

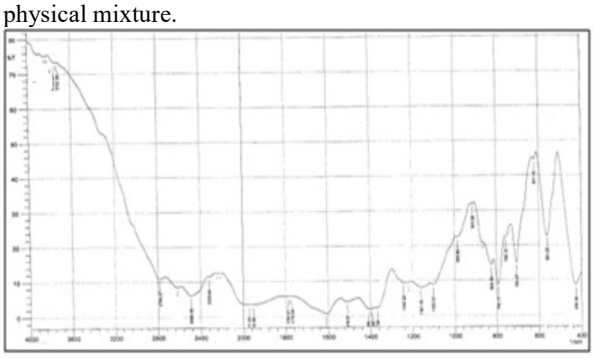


Fig. 21: FTIR spectrum of Pregabalin with HPMC K4M.

**C) Evaluation of precompression parameters of powder blend**

The powder blend of various formulations shows good flow property. Results are shown in Table 15. Results of various formulations revealed that the powder blend can be directly compressed into tablets.

Table 15: Evaluation of pre-compression parameters of Floating tablets of Pregabalin (X1-X9)

| Parameters | X1 | X2 | X3 | X4 | X5 | X6 | X7 | X8 | X9 |
|---|---|---|---|---|---|---|---|---|---|
| LOD (%)* | 1.68 □0 .67 | 1.72 □ 0.88 | 1.89 □ 0.94 | 1.69 □ 0.78 | 1.80 □ 0.88 | 1.91 □ 0.96 | 1.79 □0 .075 | 1.94 □ 0.57 | 1.83 □ 0.94 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Bulk density (gm/ml)* | 0.205□ 0.05 | 0.215 □0.08 | 0.202 □0.07 | 0.207 □0.06 | 0.210 □0.04 | 0.199 □0.08 | 0.215□ 0.08 | 0.198 □0.06 | 0.201 □0.03 |
| Tapped density (gm/ml)* | 0.249□ 0.04 | 0.250 □0.09 | 0.245 □0.08 | 0.239 □0.02 | 0.242 □0.08 | 0.237 □0.09 | 0.247□ 0.08 | 0.239 □0.09 | 0.237 □0.07 |
| Carr's compressi-bility index (%)* | 17.67□ 1.98 | 14.00 □2.15 | 17.55 □2.32 | 13.339 □2.11 | 13.22 □1.80 | 16.03 □1.98 | 12.95□ 2.11 | 17.15 □2.15 | 15.18 □2.50 |
| Hausner's ratio* | 1.214□ 0.24 | 1.162 □0.3 | 1.212 □0.35 | 1.150 □0.29 | 1.157 □0.27 | 1.190 □0.24 | 1.195□ 0.28 | 1.200 □0.45 | 1.179 □0.47 |
| Angle of repose(Ø) | 41.50□ 2.00 | 41.30 □2.50 | 36.61 □1.85 | 35.68 □1.54 | 38.32 □1.66 | 34.68 □1.68 | 42.69□ 2.50 | 42.51 □2.11 | 40.63 □2.31 |

**D) Evaluation of Post Compression Parameters for Pregabalin Tablets**

Physicochemical parameters of the formulations X1-X9 were within the acceptance limit. All the batches passed the Pharmacopoeial limits. The drug content was found to be within a narrow range as specified in pharmacopoeia (90-110 %) in all the formulations. Almost all the batches showed uniform thickness and drug content. All batches passed weight variation test and found to be within range (± 5 %) and friability was less than 1.0 %, it indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage, transportation and until they are consumed. post compression parameters, results are shown in Table 16.

Table 16: Physicochemical characterization of Floating tablets of Pregabalin (X1-X9)

| Parameters | X1 | X2 | X3 | X4 | X5 | X6 | X7 | X8 | X9 |
|---|---|---|---|---|---|---|---|---|---|
| Average weight (mg)* | 490 □ 3 | 490 □ 3 | 490 □ 3 | 490 □ 3 | 490 □ 3 | 490 □ 3 | 490 □ 3 | 490 □ 3 | 495 □ 3 |
| Thickness (mm)* | 5.83 | 5.82 | 5.82 | 5.83 | 5.84 | 5.84 | 5.83 | 5.8 | 5.86 |
| Hardness (kg/cm$^2$)* | 4-5 | 4-5 | 4-5 | 4-5 | 4-5 | 4-5 | 4-5 | 4-5 | 4-5 |
| Friability (%) | 0.25 | 0.43 | 0.33 | 0.46 | 0.56 | 0.49 | 0.51 | 0.46 | 0.52 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Buoyancy lag time (sec)* | 21 □ 3 | 23 □ 3 | 20 □ 3 | 25 □ 3 | 27 □ 3 | 26 □ 3 | 29 □ 3 | 30 □ 3 | 35 □ 3 |
| Total buoyancy time (h) | 12 | 12 | 12 | 8 | 12 | 10 | 12 | 12 | 12 |
| Drug content (%)* | 99.27 □ 1.58 | 98.64 □ 1.58 | 99.00 □ 1.58 | 99.71 □ 1.58 | 100.11 □ 1.58 | 99.51 □ 1.58 | 100.1 □ 1.58 | 100.34 □ 1.58 | 100.15 □ 1.58 |

*All values are mean ± SD of three determinations.

**Swelling study**

Swelling is also a very important factor to ensure drug dissolution of the formulation. The hydration ability of the formulation influences; (i) tablet buoyancy (ii) adhesion ability of swellable polymers and (iii) drug release kinetics. Pregabalin composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. The ability of hydrogel to absorb water is due to the presence of hydrophilic groups. The ability of hydrogel to absorb water is due to the presence of hydrophilic groups. The hydration of these functional groups results in water entry into the polymer network leading to expansion and consequently an ordering of the polymer chains. The hydration of these functional groups results in water entry into the polymer network leading to expansion and consequently an ordering of the polymer chains.

**a) Swelling study (for floating gastroretentive formulation)**

The floating tablets of Pregabalin composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug released from the matrix tablet. The floating tablets containing HPMC K4M with HPMC K100 LV (X7) showed less swelling index at the beginning but was found thick gel formation at the end of 8 h also maintains their matrix integrity up to 6 -7 h. These results suggest that the dried particles may swell in the stomach; the particles may begin to swell more and behave as matrices for controlled release of incorporated drug.

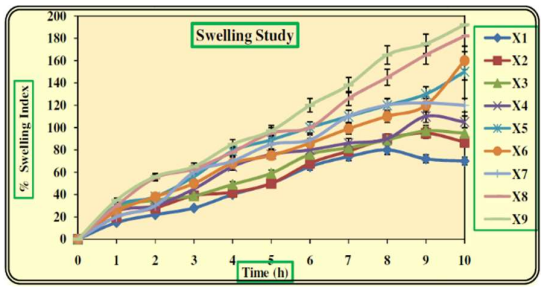



Fig. 22: Swelling index of Pregabalin floating tablets (X1 to X9)

***In vitro* buoyancy studies (For floating gastroretentive drug delivery system):**

This test was only performed to check the floating behavior of floating formulations. The buoyancy of floating tablet was studied at 37 ± 0.5 ºC in 200 ml of 1.2 pH buffer (Simulated gastric fluid without pepsin). The buoyancy lag time was measured by using stop watch and total floating time was observed visually until they are consumed. Floating lag time was observed less than 50 sec for all batches. Total floating time was observed more than 12 h.

***In vitro* drug released studies**

***In vitro* drug released for gastroretentive drug delivery system:**

In order to evaluate different hydrophilic matrixing polymers used to prepare Floating Gastroretentive tablets polymers like HPMC K4M, in combination with low viscosity polymer HPMC K100 LV were selected for floating tablets of Pregabalin and their individual drug released profile was evaluated. The gastroretentive tablets with formulations X1 to X9, containing combinations of HPMC K4M and HPMC K100 LV in different ratios exhibited cumulative percent drug release values of 71.52, 91.12, 83.43, 72.43, 79.38, 51.32, 95.06, 76.36 and 66.89, respectively. In the presence of HPMC K4M, HPMC K100 LV produces a firm gel that entraps the gas for a longer time and delays the release of the drug.

Table 17: *In-vitro* Drug Release of Pregabalin Floating tablets

| Time Hours | X1 | X2 | X3 | X4 | X5 | X6 | X7 | X8 | X9 |
|---|---|---|---|---|---|---|---|---|---|
| 0.15 | 12.71 | 16.2 | 8.288 | 6.337 | 7.177 | 3.333 | 14.13 | 11.29 | 7.177 |
| 0.45 | 16.2 | 23.56 | 10.25 | 7.778 | 8.667 | 4.311 | 20.4 | 13.38 | 8.667 |
| 1 | 27.59 | 32.45 | 16.36 | 9.666 | 12.62 | 7.552 | 28.3 | 18.35 | 12.62 |
| 2 | 30.75 | 47.68 | 22.52 | 15.05 | 19.22 | 10.38 | 39.22 | 26.97 | 19.22 |
| 3 | 39.63 | 59.62 | 34.37 | 27.79 | 31.52 | 19.19 | 51.48 | 42.46 | 31.52 |
| 4 | 49.52 | 67.52 | 40.19 | 33.47 | 38.78 | 22.33 | 69.38 | 53.43 | 38.78 |
| 5 | 53.52 | 74.35 | 55.58 | 48.07 | 53.64 | 37.67 | 78.4 | 61.36 | 53.64 |
| 6 | 64.35 | 81.52 | 62.54 | 54.35 | 59.4 | 43.3 | 85.65 | 69.29 | 59.4 |
| 9 | 71.52 | 87.41 | 71.42 | 61.42 | 66.89 | 51.32 | 89.41 | 76.36 | 66.89 |
| 10 | | 91.12 | 78.42 | 69.44 | 74.3 | | 93.25 | | |
| 12 | | | 83.43 | 72.43 | 79.38 | | 95.06 | | |

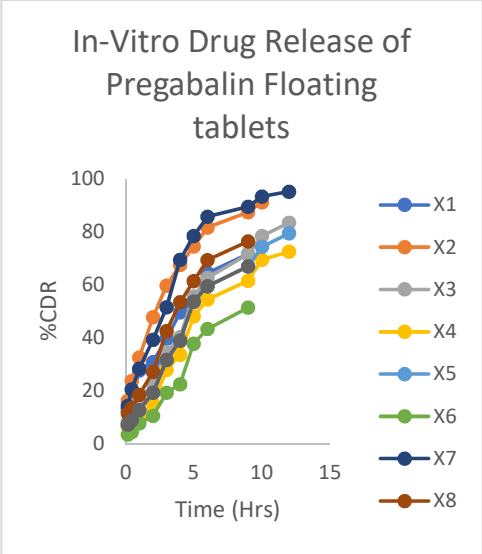



Fig: 23: *In vitro* Drug released of Pregabalin floating tablets (X1 to X9).

**Kinetic modeling of drug release for Floating Gastroretentive tablets**

The data obtained from the in vitro drug released studies of formulation X1-X9, were fitted to zero-order, first-order, Higuchi Korsmeyer Peppas equations, and the data were analyzed (Table 18). The r2 value of the optimized formulation X7 was found 0.98. The n values of the optimized formulation (X7) was found to be 0.547, which fall in the range 0.35<n<0.50 and k value was 17.61 with good floating properties. The value of the diffusion exponent indicates that the drug release follows non-Fickian release mechanism.

Table 18: Kinetic parameters of Pregabalin tablets (X1-X9)

| Batch Code | Zero order ($R^2$) | First order ($R^2$) | Higuchi ($R^2$) | Korsmeyer – Peppas ($R^2$) | n (Release exponent) | Hixon-Crowel |
|---|---|---|---|---|---|---|
| X1 | 0.908 | 0.973 | 0.982 | 0.989 | 0.511 | 0.848 |
| X2 | 0.940 | 0.949 | 0.980 | 0.989 | 0.548 | 0.733 |
| X3 | 0.908 | 0.89 | 0.952 | 0.989 | 0.525 | 0.876 |
| X4 | 0.905 | 0.878 | 0.887 | 0.989 | 0.446 | 0.705 |
| X5 | 0.938 | 0.926 | 0.951 | 0.989 | 0.467 | 0.893 |
| X6 | 0.952 | 0.910 | 0.971 | 0.989 | 0.529 | 0.730 |
| X7 | 0.982 | 0.977 | 0.976 | 0.989 | 0.547 | 0.850 |
| X8 | 0.919 | 0.927 | 0.946 | 0.989 | 0.562 | 0.890 |
| X9 | 0.959 | 0.895 | 0.987 | 0.989 | 0.458 | 0.843 |

**Optimized data analysis for the Floating Gastroretentive tablets of Pregabalin (X7)**

Responses observed for nine formulations (X1-X9) were fitted to various models using Design Expert Software (Design Expert version 8.0.1.). The dependent variables demonstrated that the model was significant for all the three response variables. Regression analysis of optimized formulation (X7) results for responses (Y1), (Y2), and (Y3) and analysis of variance for % CDR at 12 h, BLT and TBT of Pregabalin tablets were shown in Table. Comparison between the experimental and predicted values for the most probable optimal formulation X7 is reported in Table.19.

From above responses, it can be concluded that as predicted values agreed with the experimental values, demonstrating the feasibility of the model in development of Floating Gastroretentive drug delivery system.

Table 19: Comparison between the experimental and predicted values for the most probable optimal formulation X7 of Pregabalin floating tablet

| Optimized Formulation (X7) | | |
|---|---|---|
| Dependent variable | Experimental | Predicted |
| % CDR at 12 h (Y1) | 95.06 ± 1.50 | 87.59 |
| Buoyancy Lag Time (Y2) | 29± 3 | 25 |
| Total Buoyancy time (Y3) | 12 | 12 |

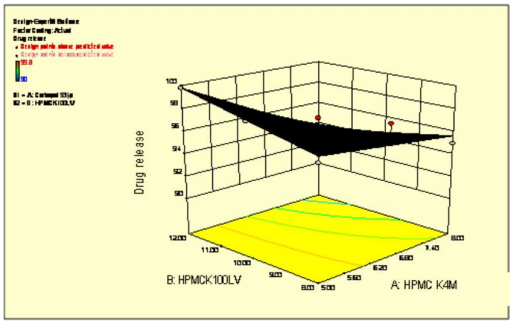



Fig. 24 : Response surface plot showing % CDR of formulation X7.

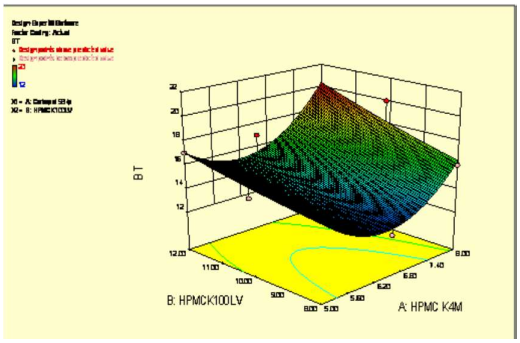



Fig. 25: Response surface plot showing % BLT of formulation X7.

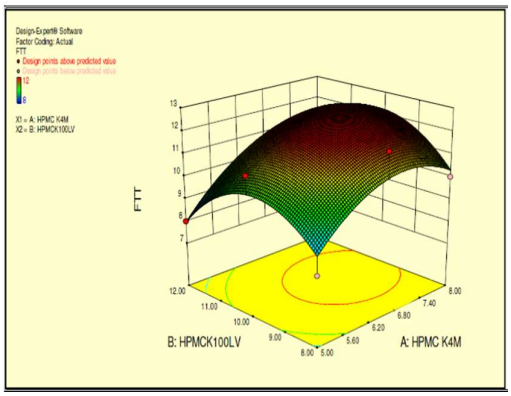



Fig. 26: Response surface plot showing % FTT of formulation X7.

**Conclusion:**

In conclusion, the tablets containing HPMC K4M with HPMC K100 LV (X7) had a short buoyancy lag time, a total floating time of more than 10 h and sustained release up to 12 h. This novel gastro retentive dosage form could be fascinating for enhancement of bioavailability and the stomach specific delivery of pregabalin. From the above study it could be concluded that floating

gastroretentive drug delivery system is most stable system.

The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of Pregabalin tablets.

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