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Design, Development, and Evaluation of Gelucire-Based Gastric Floating Beads of Pregabalin

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Abstract:

Abstract: The objective of this research is to design, develop, and evaluate Gelucire-based gastric floating beads of Pregabalin. These beads are intended to provide a sustained release profile, enhance bioavailability, and improve patient compliance. The beads were prepared using the ionotropic gelation technique and characterized for their physicochemical properties, buoyancy, drug entrapment efficiency, and in vitro release profile. The results demonstrated that the optimized formulation exhibited a prolonged release of Pregabalin, enhanced floating ability, and improved bioavailability compared to conventional formulations.

An attempt is made to prepare bead of 210nm using various grades of gelucire such as Gelucire 50/13, Gelucire 48/01, Gelucire 43/01. Among which gelucire 43/01 gave spherical bead. The method of preparation of beads was found to be simple and reproducible. Percentage yield was found in a range of 70±1.5 to 89.25±0.28. Percentage drug entrapment of drug was obtained in all formulations in a range of 47.79±1.90 to 87.95±0.75. Due to higher Drug-lipid ratio beads the size of bead slightly increased produce. The average size of bead range was between 2.42±0.13 to 3.24±0.05µm. The in vitro data indicated that pure drug was 99% release with in 3hrs. The drug release from the bead prepared in formulation F8 achieved 60.93±0.56% in 6hrs and 80.06±0.28% in 12hrs.

Keywords: Pregabalin, Gelucire, Gastric floating beads, Sustained release, Bioavailability, Ionotropic gelation.

INTRODUCTION

Pregabalin is an antiepileptic drug used for neuropathic pain, fibromyalgia, and generalized anxiety disorder. Due to its short half-life and frequent dosing requirements, developing a sustained release formulation can improve patient compliance and therapeutic effectiveness.Gelucire is a family of lipid-based excipients that can be

used to enhance drug solubility and modify drug release profiles. Gelucire-based formulations are suitable for creating floating drug delivery systems that prolong gastric residence time, enhancing the bioavailability of drugs absorbed in the stomach or upper intestine.

Objective

The aim of this project is to design, develop, and evaluate Gelucire-based gastric floating beads containing Pregabalin. These beads are intended to provide a sustained release profile and improve the bioavailability of Pregabalin.Pregabalin, an antiepileptic drug, is widely used for neuropathic pain, fibromyalgia, and generalized anxiety disorder. Due to its short half-life, it requires frequent dosing, which can reduce patient compliance. To address this, we aimed to develop a sustained release formulation using Gelucire, a lipid-based excipient known for enhancing drug solubility and modifying release profiles. Gelucire-based floating drug delivery systems can prolong gastric residence time, potentially enhancing the bioavailability of drugs absorbed in the stomach or upper intestine.

Gastric floating beads represent a significant departure from traditional drug delivery methods. They are designed to float in the gastric fluid, continually releasing medications over an extended period. The fundamental concept underlying these beads lies in their composition, primarily comprised of a hydrophobic polymer matrix and a gas-generating agent.. Moreover, the simplified dosing schedules associated with these beads contribute to enhanced patient compliance, a pivotal factor in achieving successful treatment outcomes.

MATERIALS AND METHODS Materials Pregabalin was received gift sample from Triveni Chemicals Gujrat. All the excipients in analytical grade received from various reagent and chemical manufacturers.

Preparation of Beads:

Lipid (Gelucire 43/01/ Gelucire 54/02 Gelucire 50/13) was melted at 60°C and the finely powdered drug was gradually added with uniform mixing to form dispersion. The resultant dispersion was dropped via a 23-guage syringe needle (0.65 mm internal diameter) into 100 ml of pre-chilled (4°C) IPA at a rate of 5 ml/min. The distance from the needle tip to the IPA was 5 cm. The content was stirred at 100 rpm using magnetic stirrer for 15 min. The beads were collected after filtration through Whatman filter paper (# 41), washed three times with distilled water and subsequently dried to their constant weight in vacuum dessicator for 24 h to ensure complete removal of solvents. The vehicles such as isopropyl alcohol were used as dispersion medium.

Table No: 1 Composition of different bead formulations containing Pregabalin

S.No	Formulation Code	Drug (mg)	Gelucire 43/01 (mg)	Gelucire 54/02 (mg)	Gelucire 50/13 (mg)	Isopropyl alcohol (ml)
1	F1	75	-	100	-	100
2	F2	75	-	500	-	100
3	F3	75	-	1000		100
4	F4	75	-	1500	-	100
5	F5	75	100	-	-	100

6	F6	75	500	-	-	100
7	F7	75	1000	-	-	100
8	F8	75	1500	-	-	100
9	F9	75	-	-	100	100
10	F10	75	-	-	500	100
11	F11	75	-	-	1000	100
12	F12	75	-	-	1500	100

Evaluation of Gelucire floating bead
Percentage yield

The prepared beads were collected and weighed. The measured weight was divided by the total weight of all the excipients and drug. The % yield was calculated using following formula:

$$Percentage\ yield = \frac{Practical\ mass\ of\ Beads}{Theoretical\ mass\ (lipid + Drug)} X100$$

Floating Behavior of Beads

Floating beads (20 in numbers) were placed in 100 ml of the simulated gastric fluid (SGF; pH 2.0) at room temperature. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 h, the layer of buoyant beads was pipetted and separated by filtration. Beads in the sinking particulate layer were separated by filtration. Beads were dried in a vacuum desiccator until constant weight was achieved. Both the fractions of beads were counted and buoyancy was determined. The % buoyancy was calculated using the formula:

$$\%\ Buoyancy = \frac{Qf}{(Qf + Qs)} X100$$

Where;

Qf = Weight of floating beads

Qs = Weight of settled beads

Percentage Drug Entrapment

The Pregabalin content in Gelucire beads was determined by dispersing accurately weighed (20 mg) beads in 10 ml of 0.1N HCl after which the sample was centrifuged at 15000 rpm for 15 min in cooling centrifuge. The supernatant was collected and was analyzed by UV spectrophotometry at 294 nm using UV–visible spectrophotometer after suitable dilutions. The experiment was performed in triplicate.

Particle Size Analysis

The particle sizes of drug loaded formulations were measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. The model having resolution of 40 xs was used for this purpose. In all measurements at least 100 particles in five different fields were examined. Each experiment was carried out in triplicate.

In-Vitro Drug Release Study

The release of drug from floating beads was determined in a USP Type I basket dissolution apparatus.

A weighed amount of beads equivalent to 10 mg drug was placed in the dissolution rate apparatus. 900 ml of the simulated gastric fluid was added. The dissolution fluid was maintained at 37±0.5°C at a rotation speed of 50 rpm. Perfect sink conditions were prevailed during the drug release study. 5 ml of sample was withdrawn at specified intervals and passed through a 0.25-µm

membrane filter, and the initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. Samples were analyzed using a UV–visible spectrophotometer at 294 nm.

Drug release kinetics

Model dependent methods are based on different mathematical functions, which describe the release profile. Once a suitable function has been selected, the release profiles are evaluated depending on the derived model parameters. The data obtained from ex vivo permeation studies were plotted in different models of data treatment as follows;

- Zero Order model
- First Order model
- Higuchi's Model
- Korsmeyer-Peppas model

Zero order kinetics

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$Q_0 - Q_t = K_0 t$$

Where, Q_t is the amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from in vitro drug permeation studies were plotted as cumulative amount of drug released versus time.

It can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc.

First order kinetics

It can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

The release of the drug which followed first order kinetics can be expressed by the following equation:

$$\log C = \log C_0 - K.t / 2.303$$

Where, C_0 is the initial concentration of drug, k is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303.

Higuchi's Model

This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible), (iii) drug particles are much smaller than system thickness, (iv) matrix swelling and dissolution are negligible, (v) drug diffusivity is constant, and (vi) perfect sink conditions are always attained in the release environment.

Higuchi was the first to derive an equation to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.

Simplified Higuchi equation is following;

$$Q_t = K_H (t)^{0.5}$$

Where, Qt is the amount of drug released in time t and K_H is the Higuchi dissolution constant. The data obtained were plotted as cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

The slope is equal to 'K_H'.

Korsmeyer-Peppas Model

Korsmeyer derived a simple relationship which described drug release from a polymeric system.
The release rates from controlled release polymeric matrices can be described by the equation proposed by Korsmeyer et al.

$$\mathbf{M_t/M_\infty = K.t^n}$$

Where, M_t/M_∞ is fraction of drug released at time t, K is a release rate constant and 'n' is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices.

In this model, the value of n characterizes the release mechanism of drug as described in Table 7.

For Fickian release, n=0.45 while for anomalous (Non-Fickian) transport, n ranges between 0.45 and 0.89 and for case II (relaxational) transport n = 0.89, for super case II transport, n > 0.89. The Korsmeyer-Peppas model was plotted between log cumulative % drug releases versus log time.

Table 2: Interpretation of diffusional release mechanisms

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.45 < n = 0.89	Non-Fickian transport	t^{n-1}
0.89	Case II transport	Zero order release
Higher than 0.89	Super case II transport	t^{n-1}

Result and Discussion:

Organoleptic properties:

Organoleptic properties of drug Pregabalin was found to be as per USP monograph. The Organoleptic properties of Pregabalinare shown in **Table 3.**

Table 3: Organoleptic Properties of Pregabalin

Sr. No.	Properties	Inferences
1.	Colour	Off-white to Opaque White
2.	Form	Crystalline

Melting Point:

The melting point of a substance is the temperature at which the solid phase gets converted to liquid phase under the one atmosphere of pressure. The melting point determination implies the purity of drug. Melting point of Pregabalin was determined by capillary tube method and was found to be quite similar to the reported melting point as shown in **Table 4.**

Table 4: Melting Point of Pregabalin

Drug	Observed melting point	Reference melting point
Pregabalin	186°C±0.340°C	186-188 °C

Value is expressed as mean ± SD; n = 3

UV Spectroscopy

Determination of absorption maxima in 0.1N HCl

Absorption maxima of Pregabalinwas found to be at 210 nm similar to literature as shown in

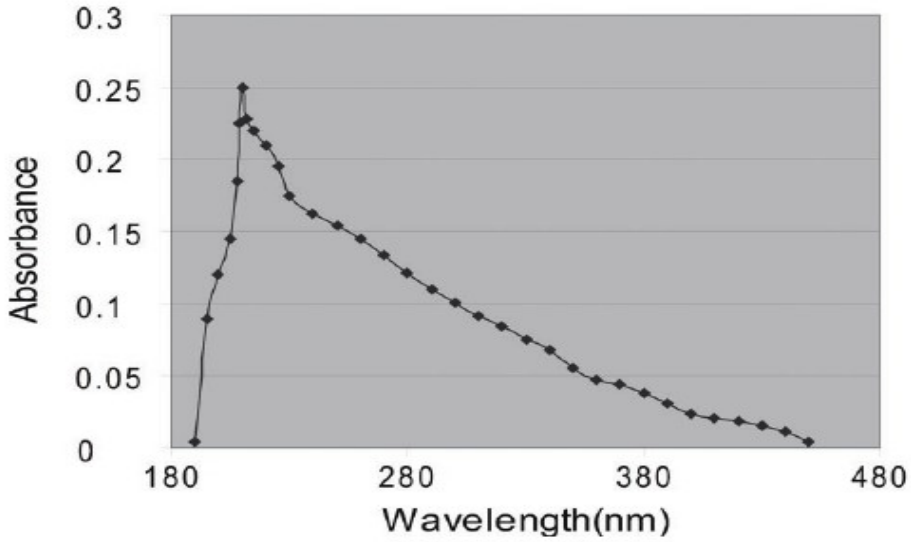

Figure 1: UV Spectrum of Pregabalin in 0.1N HCl

Preparation of standard curve of Pregabalin in 0.1N HCl

Table 5: Calibration curve of Pregabalin in 0.1N HCl (λ_{max}= 210nm)

S.No	Concentration (µg/ml)	Absorbance (mean±SD)
1	2	0.34 ± 0.001
2	4	0.47±0.001
3	6	0.65±0.001
4	8	0.83±0.002
5	10	0.98±0.007

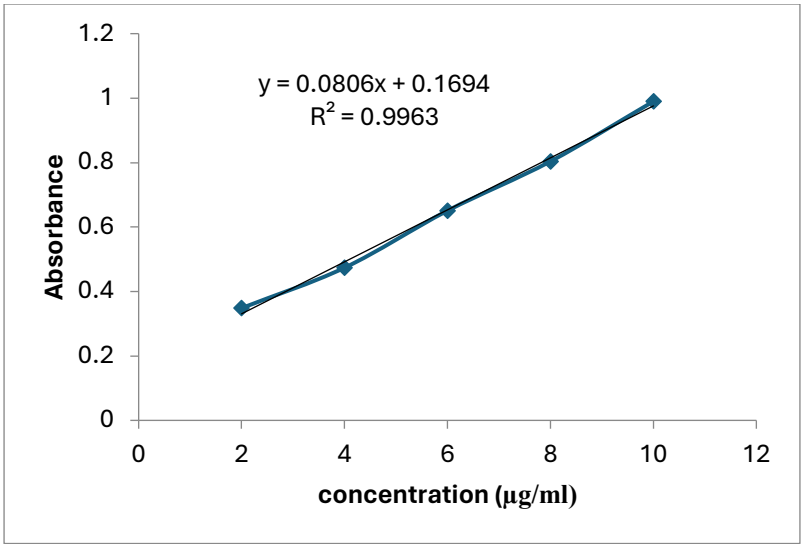

Figure 2: Graph of standard calibration curve of Pregabalin in 0.1N HCl

Table 6: Result of regression analysis of UV method for estimation of Pregabalin

Statistical parameters	Results
λ max	210 nm
Regression equation ** Y=mx+C	Y=0.080x+0.169
Slope (b)	0.080
Intercept (C)	0.169
Correlation coefficient (r^2)	0.996

Solubility studies

Solubility of drug in various solvents was carried out in order to screen for the components to be used for formulation development. Analysis of the drug was carried out on UV Spectrophotometer at 210nm.

Solubility Studies of Pregabalin in various Solvents:

Table 7: Solubility studies of Pregabalin for different solvents

S.No	Solvents	Solubility (mg/ml)
1	Methanol	0.10±0.003
2	Ethanol	0.019±0.0002
3	Water	0.015±0.018
4	pH6.8	0.006±0.0007
5	0.1N NaOH	5.54±0.29
6	0.1N HCL	7.24±0.05

Value is expressed as mean ± SD; n = 3

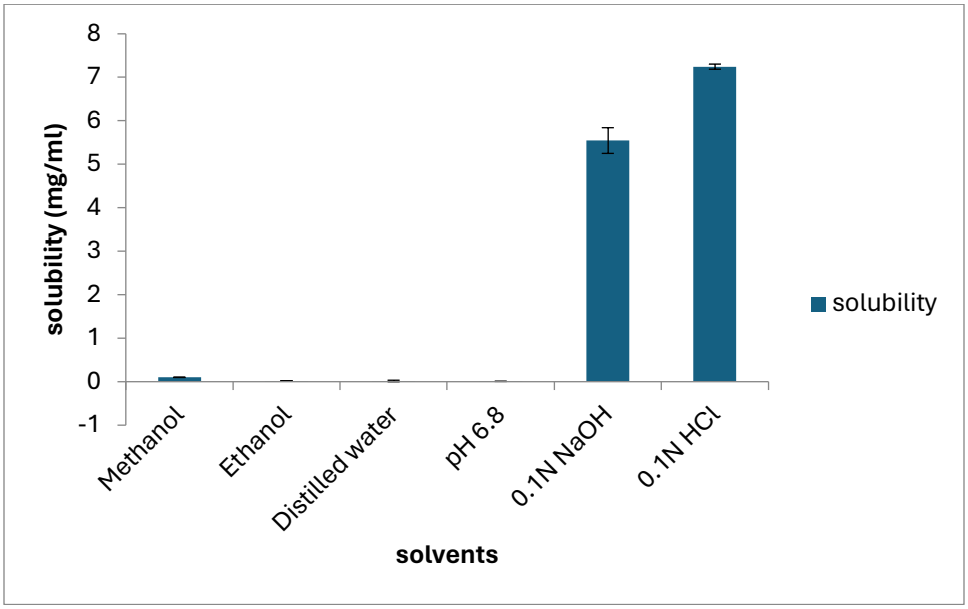

Figure 3: Solubility study of Pregabalin in different solvents

Partition coefficient determination

Partition coefficient of the Pregabalin was determined using n-octanol and water. Log P greater than one indicates that the drug is lipophilic in nature, whereas those with partition coefficients less than one are indicative of a hydrophilic drug.

Table 8: Partition coefficient determination of Pregabalin

Drug	Solvent System	Log P Value
Pregabalin	Water:n-octanol	1.98 ± 0.030

Value is expressed as mean ± SD; n = 3

Result: The log P value was found to be 1.96 ± 0.030 which indicates the hydrophilicity and purity of drug.

FTIR studies

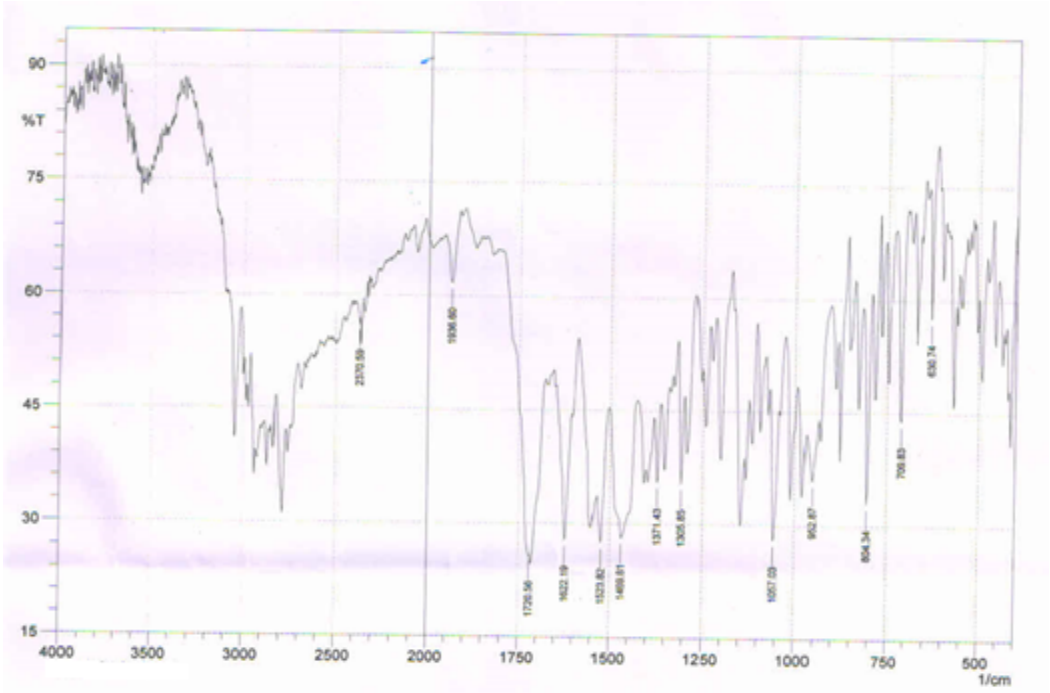

Figure 4: FTIR Spectra of Pregabalin

Table 9: FTIR interpretation of Pregabalin

Reference peak (cm^{-1})	Observed peak (cm^{-1})	Characteristic peaks
3300-2500	2370.59	Carboxylic acid OH band
1400	1469.81	Protonation of N_4 in piperazinyl group
1715	1720.56	C=O stretching
1621	1622.19	C=C stretching or carbonyl stretch
1530	1523.82	C=O aromatic stretching
1055	1057.03	C-O-C stretch of ether group

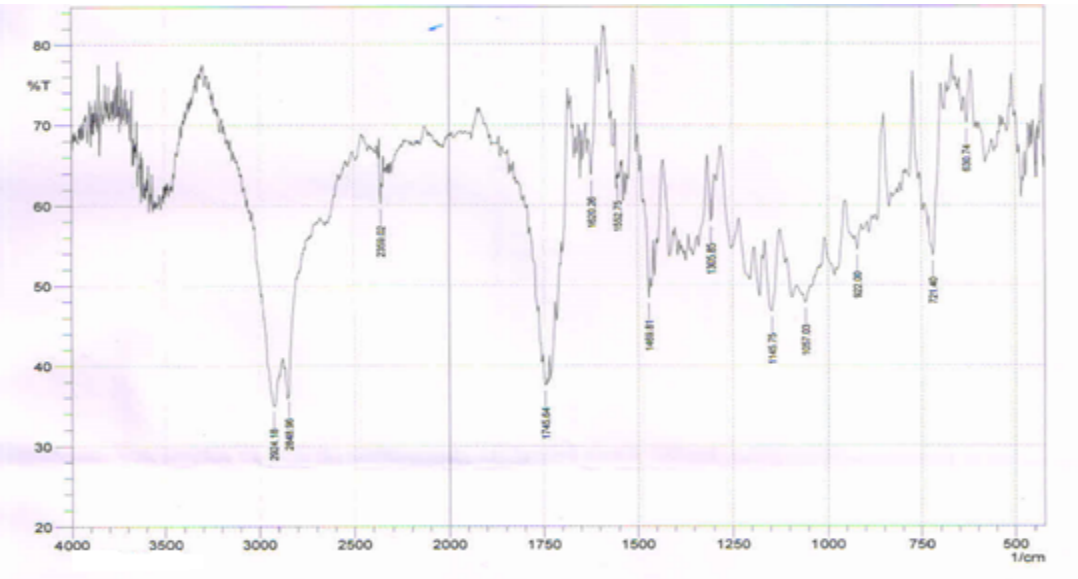

Figure 5: FTIR Spectra of Gelucire 43/01

Table 10: FTIR interpretation of Gelucire 43/01

Reference peak (cm^{-1})	Observed peak (cm^{-1})	Characteristic peaks
1741, 1735	1745.64	C=O stretch of ester group
1,17,21,100	1145.75, 1057.03	C-O stretch of alcohols

Table 11: FTIR interpretation of physical mixture

Reference peak (cm^{-1})	Observed peak (cm^{-1})	Characteristic peaks
1469.81	1465.95	Protonation of N_4 in piperazinyl group
1720.56	1749.49	C=O stretching
1622.19	1653.05	C=C stretching or carbonyl stretch
1523.82	1558.54	C=O aromatic stretching
1057.03	1057.03	C-O-C stretch of ether group
1745.64	1749.49	C=O stretch of ester group
1145.75	1095.6	C-O stretch of alcohols

FTIR of Pure drug and physical mixture studies **(Figure 4, 5, 6Table 9, 10, 11)** were carried out to eliminate the possibility of interaction between drug and excipients. All the spectrum peaks revealed that the corresponding peaks of drug are present in the above spectra along with the peak of lipid used. Hence no interaction was observed in this mixture.

Preparation of Bead

In the present investigation, a multiparticulate delivery system of Pregabalin capable of providing controlled release was prepared using Gelucire 43/01. The method of preparation of beads was found to be simple and reproducible.

Table 12: Appearance of different Gelucire based bead containing Pregabalin

S.No	Formulation Code	Drug (mg)	Gelucire 43/01 (mg)	Gelucire 54/02 (mg)	Gelucire 50/13 (mg)	Isopropyl alcohol (ml)
1	F1	75	-	100	-	100
2	F2	75	-	500	-	100
3	F3	75	-	1000		100
4	F4	75	-	1500	-	100
5	F5	75	100	-	-	100
6	F6	75	500	-	-	100
7	F7	75	1000	-	-	100
8	F8	75	1500	-	-	100
9	F9	75	-	-	100	100
10	F10	75	-	-	500	100
11	F11	75	-	-	1000	100
12	F12	75	-	-	1500	100

Evaluation of bead
Appearance of bead

Table 13: Appearance of different Gelucire based bead containing Pregabalin

S. No	Formulation Code	Appearance
1	F1	Bead Not formed
2	F2	Bead Not formed
3	F3	Irregular shape formed
4	F4	Irregular shape formed
5	F5	Spherical Bead formed
6	F6	Spherical Bead formed
7	F7	Spherical Bead formed
8	F8	Spherical Bead formed
9	F9	Irregular shape formed
10	F10	Irregular shape formed
11	F11	Bead Not formed
12	F12	Irregular shape formed

Percentage yield
Percentage yield of all formulation was given in **Table 14**.

Table 14: Percentage yield of different Gelucire based bead containing Pregabalin

S.No.	Formulation Code	Percentage Yield
1	F5	70±1.5
2	F6	77.5±0.76
3	F7	80.78±0.59
4	F8	89.25±0.28

Percentage Drug Entrapment

PercentageDrug Entrapment of all formulation was given in **Table 15**.

Table 15: Percentage Drug Entrapment of different Gelucire based bead containing Pregabalin

S.No.	Formulation Code	Percentage drug entrapment
1	F5	47.79±1.90
2	F6	69.68±0.57
3	F7	73.43±0.781
4	F8	87.95±0.75

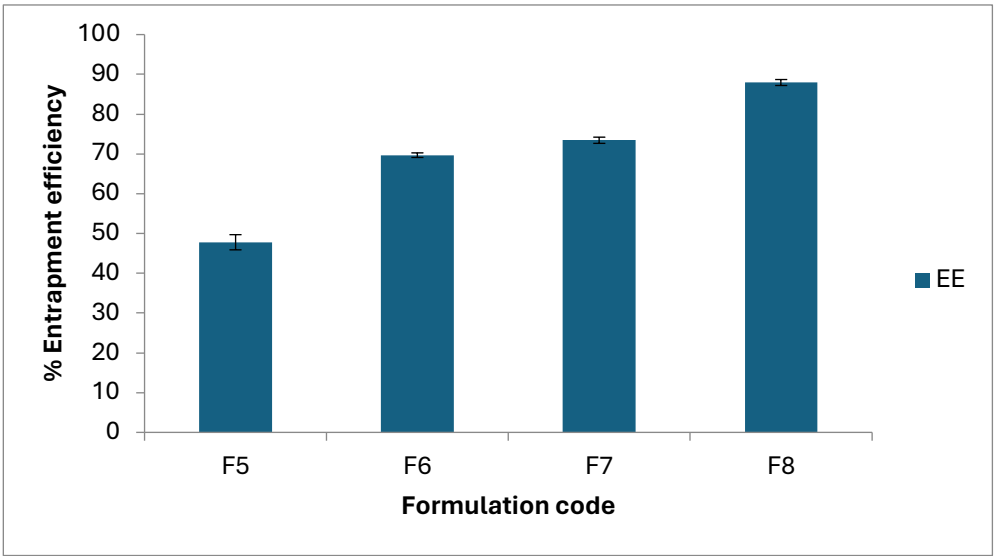

Figure 7: Percentage drug entrapment of Pregabalin loaded Gelucire floating beads

Particle Size analysis

Particle size of formulations was given in **Table 16**.

Table 16: Particle size of different Gelucire based bead containing Pregabalin

S.no.	Formulation Code	Particle Size (µm)
1	F5	2.42±0.13
2	F6	3.00±0.08
3	F7	3.04±0.05
4	F8	3.24±0.05

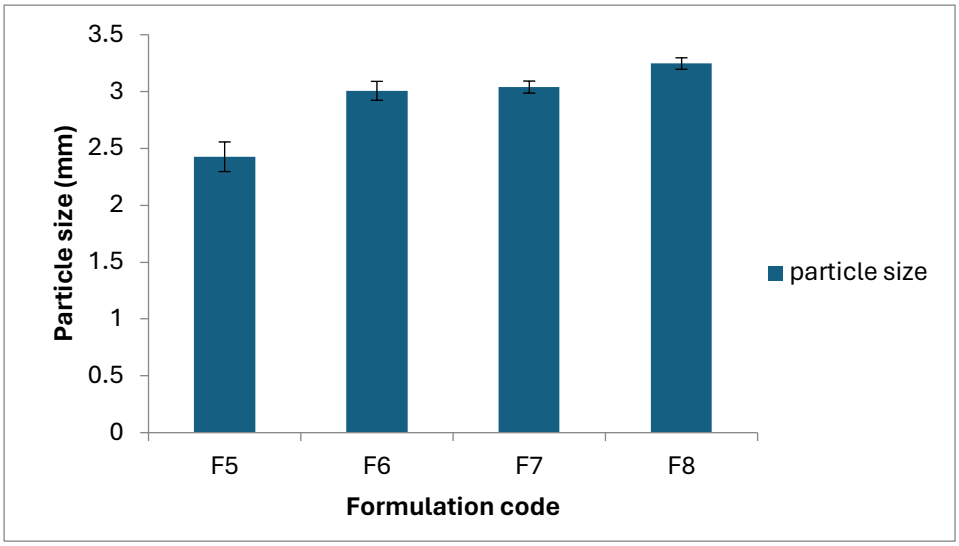

Figure 8: Particle Size of Pregabalin loaded Gelucire floating beads

In vitro Floating study

In-vitro percentage floating of all formulation was given in a **Table 17**.

Table 17: Percentage floating of different Gelucire based bead containing Pregabalin

S.No.	Formulation Code	Percentage Floating
1	F5	90% floating
2	F6	80% floating
3	F7	100 % floating
4	F8	100 % floating

In-vitro Drug release study

The in-vitro drug release of Formulation F8 and Pure drug was given in a **Table 18**.

Table 18: Percentage drug release of Formulation F8 and Pure drug

Time (h)	% Drug release of pure drug	% Drug release of F8 formulation
0	0	0
0.25	33.48±0.17	8.21±0.02
0.5	58.42±0.45	12.82±0.11
1	80.17±0.25	23.58±0.28
2	96.75±1.94	31.91±0.34
3	99±1.12	39.78±0.17
4		47.17±0.23
5		55.42±0.06
6		60.93±0.56
7		64.8±0.19
8		69.6±0.17
9		74.92±0.40
10		76.23±0.34
12		80.06±0.28

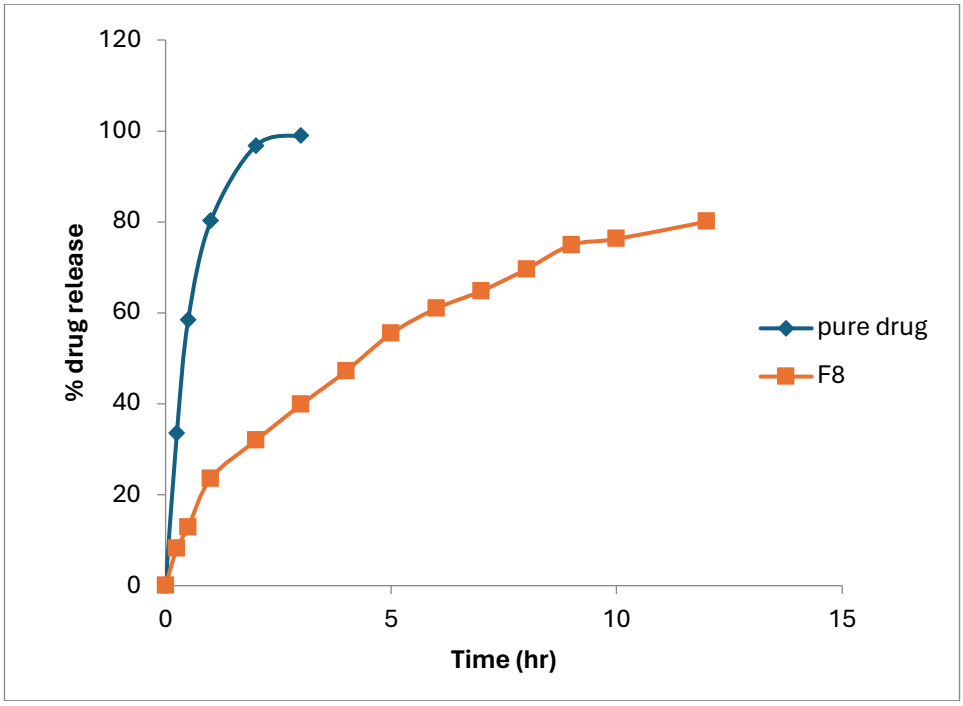

Figure 9: In-Vitro Drug release of Pregabalin loaded Gelucire 43/01 floating bead and pure drug.

The in-vitro release of drug from the lipid based floating bead was found to be lower as compare to pure drug that showed the effect of lipid matrix of Gelucire in drug release property. The fast effect, namely the amount of encapsulated compound released at short times, is normally related to the drug embedded into or near the beads surface.

Drug was dispersed into the molten Gelucire 43/01 as a micronized powder and the resulting beads were formed by a dispersion of drug particles through the waxy matrix. **Table 18** indicated that in vitro release of pure drug show 100% release within 3 hr. Formulations displayed a biphasic sustained release pattern and an initial burst release viz. 12.82 % of Pregabalin was obtained from F8 in 15mins. A possible reason that may be accounted is the fast release of drug adsorbed on the surface of the bead or entrapped in the outermost stratum. Furthermore, the release profiles of Pregabalin from beads made from Gelucire 43/01 showed that Gelucire 43/01 employed yielded a sustained Pregabalin release. These behaviours can be explained in terms of release mechanism of the entrapped compound from the lipid beads. It has been suggested that, because of the high hydrophobicity of lipid materials, the release medium is not able to diffuse through the matrix and can progress in the dosage form by dissolving the grains of drug in contact with it. The dissolution of the drug particles on the surface of the matrix allows the formation of channels, from which the drug is slowly released. From the in-vitro drug release study it was found that F8 formulation showed lower drug release as compare to pure drug.

In-vitro drug release kinetic

In-vitro drug release kinetic study data of formulation F8 is given below.

Zero order

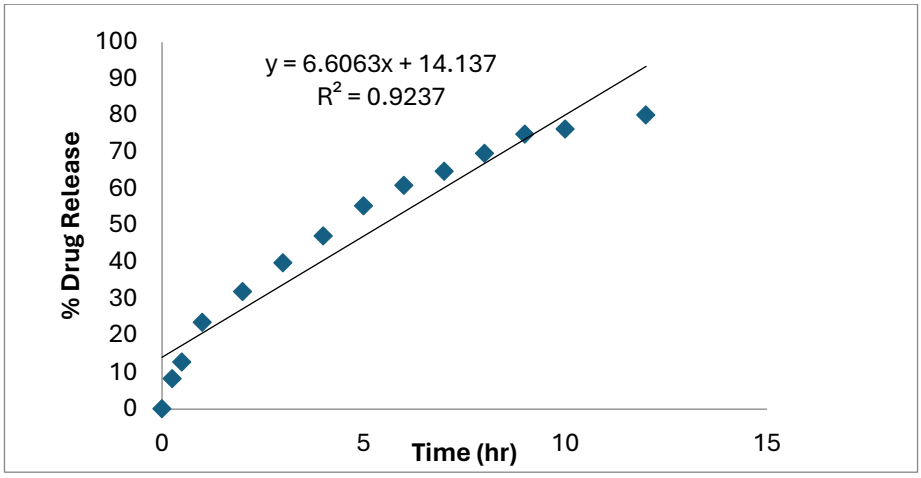

Figure 10: Zero order graph of formulation F8

First Order

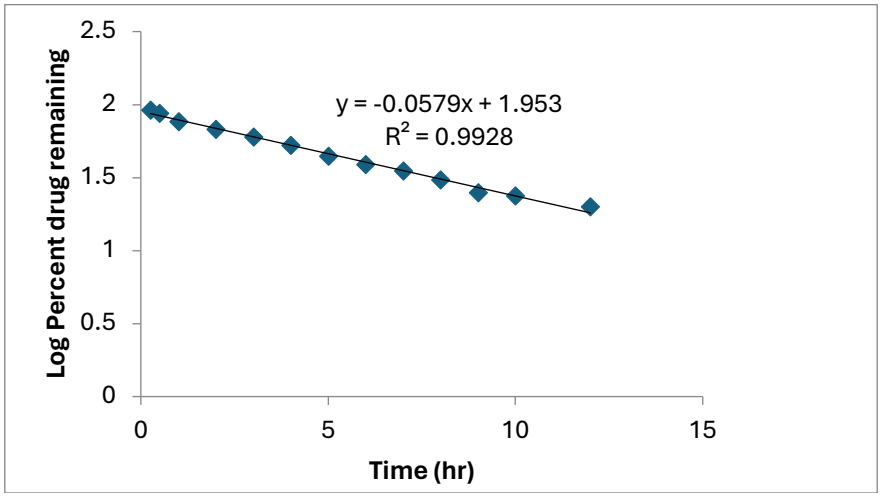

Figure 11: First order graph of formulation F8

Higuchi

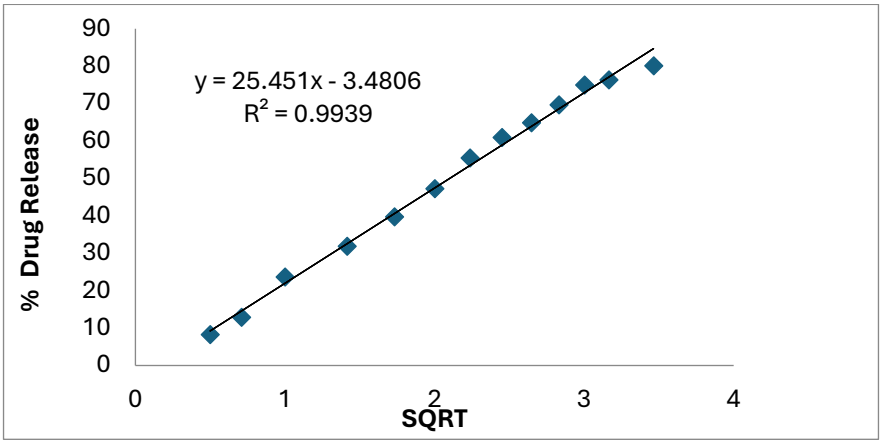

Figure 12: Higuchi order graph of formulation F8

Korsmeyer peppas

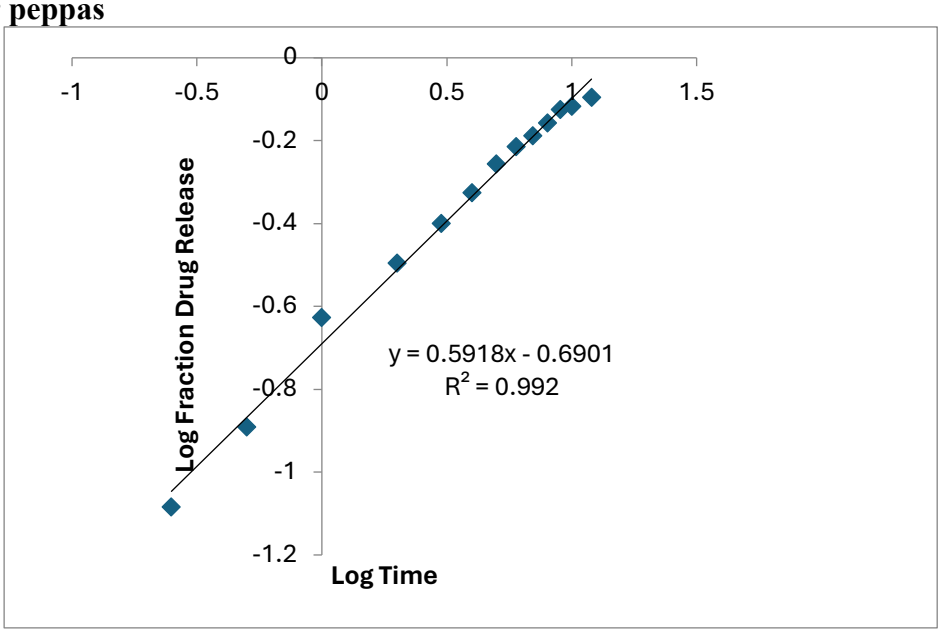

Figure 13: Korsmeyer peppas order graph of formulation F8

Table 19: Kinetic equation parameter of formulation F8

Formulation name	Zeroorder		Firstorder		Higuchi		Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F8	**0.923**	**6.606**	**0.992**	**-0.057**	**0.993**	**25.45**	**0.992**	**0.591**

Mathematical models are commonly used to predict the release mechanism and compare release profile. For all the optimized formulations, the % drug release vs time (zero order), log percent drug remaining vs time (first order), log per cent drug release vs square root of time (Higuchi plot), and log fraction drug release vs. log time (Korsmeyer and PeppasExponential Equation) were plotted. In each case, R^2 value was calculated from the graph and reported in **Table 19**and **Figure 10 to Figure 13.** Considering the determination coefficients, Higuchi model was found (R^2=0.993)to fit the release data best. This demonstrates that Pregabalin molecules were loaded in the bead and there was no interaction between the drug and formulation material. It could be concluded from the results that the drug was released from bead by a diffusion-controlled mechanism.

Conclusion:

The melting point of Pregabalin was found to be in range 186°C±0.340ºC which is of the pure drug. Hence drug sample was free from any type of impurities.The calibration curve for Pregabalin was obtained by using the 2 to 10 µg/ml concentration of Pregabalin in 0.1N HCl. The absorbance was measured at 210 nm. The calibration curve of Pregabalin as shown in graph indicated the regression equation Y=0.080x+0.169 and R^2 value 0.996, which shows good linearity as shown in Table 6 and Figure 2.From the above data, it is clearly seen that Pregabalin is highly soluble in aqueous acid & base. (Figure 3 and Table

7). From the Table 13, it was found that Gelucire 43/01 and isopropanol has formed spherical shape beads. Beads were not formed when the high ratio of lipid as well as low ratio of lipid was used. Uniform and compact beads were formed with IPA when we used Gelucire 43/01 and IPA was used as surface active agent and cross-linking agent. So these properties might play an important role in uniform bead formation. Percentage yield was found in a range of 70±1.5 to 89.25±0.28. From the Table 15, it was found that Percentage drug entrapment of all formulation was found to be in a range 47.79±1.90 to 87.95±0.75. These results explain that there is a significant effect on percent entrapment efficiency of beads with lipid concentration. Particle size of all beads found to be in the range from 2.42±0.13 to 3.24±0.05µm. From the result it was found that on increasing lipid concentration particle size slightly increase. The formed beads were sufficiently hard and spherical in shape. The results show that all formulations remain floating up to 8 h, reflects excellent floating ability of beads (Table 17). Apart from hydrophobicity, density of Gelucire 43/01 (true density 0.0856 g/cm^3) also plays an important role in floating ability of beads.

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