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Formulation and Evaluation of Comparative Study of Pregabalin Loaded Microbeads by Ionic Gelation Technique

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Abstract: *The present study aimed to formulate and evaluate Pregabalin loaded microbeads using ionic gelation technique for sustained drug release. Pregabalin is an anticonvulsant and neuropathic pain medication with short biological half-life requiring frequent administration. The formulation of microbeads can improve patient compliance and sustain drug release.*

Microbeads were prepared using sodium alginate alone and in combination with polymers such as chitosan and HPMC using calcium chloride as cross-linking agent. Different formulations were prepared by varying polymer concentrations. Prepared microbeads were evaluated for particle size, percentage yield, drug entrapment efficiency, swelling index, surface morphology, flow properties, and in-vitro drug release studies.

Results indicated that ionic gelation technique successfully produced spherical microbeads with satisfactory drug loading and sustained release characteristics. Formulations containing combination polymers exhibited better entrapment efficiency and prolonged drug release compared to alginate alone.

The study concluded that Pregabalin loaded microbeads prepared by ionic gelation technique are promising carriers for sustained drug delivery.

Keywords: Pregabalin, Microbeads, Ionic Gelation, Sustained Release, Sodium Alginate, Entrapment Efficiency..

I. INTRODUCTION

1.1 Novel Drug Delivery System (NDDS)

Novel Drug Delivery Systems (NDDS) are advanced formulations developed to improve the therapeutic efficacy and safety of drugs by controlling the rate, time, and site of drug release in the body. Conventional dosage forms often require repeated administration due to short halflife of drugs, resulting in fluctuating plasma drug concentration and poor patient compliance. NDDS are designed to overcome these limitations by delivering drugs in a controlled and sustained manner.

The major goals of NDDS include:

- Improvement of bioavailability
- Reduction in dosing frequency
- Enhancement of patient compliance
- Reduction of side effects
- Site specific drug delivery
- Controlled and sustained release of drugs

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Various NDDS include microspheres, nanoparticles, liposomes, microcapsules, transdermal patches, implants, and microbeads.

1.2 Microbeads

Microbeads are small spherical particles generally ranging from 1 µm to 1000 µm in diameter prepared using natural or synthetic polymers. These systems are widely used in controlled drug delivery because they can encapsulate drugs and release them over an extended period of time.

Microbeads can be prepared using different techniques such as:

- Ionic gelation
- Solvent evaporation
- Emulsification
- Spray drying
- Coacervation

Microbeads provide protection to encapsulated drugs from degradation and improve stability and bioavailability.

Advantages of Microbeads

- Sustained and controlled drug release
- Improved patient compliance
- Reduced dosing frequency
- Reduced gastrointestinal irritation
- Improved stability of drug
- Uniform distribution in gastrointestinal tract
- Reduced toxicity and adverse effects

1.3 Controlled Release Drug Delivery System

Controlled release drug delivery systems are designed to release drugs at predetermined rates for prolonged periods. These systems maintain constant therapeutic concentration of drug in plasma and reduce fluctuations associated with conventional dosage forms.

Advantages include:

- Maintenance of steady plasma concentration
- Reduction in dosing frequency
- Improved therapeutic efficacy
- Better patient adherence
- Reduced side effects

1.4 Sustained Release Drug Delivery System

Sustained release systems are dosage forms that release drugs slowly over an extended period. The purpose is to maintain therapeutic concentration for longer duration and minimize repeated administration.

Characteristics of sustained release systems:

- Slow release of drug
- Prolonged therapeutic effect
- Improved bioavailability
- Reduced frequency of administration

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1.5 Ionic Gelation Technique

Ionic gelation is one of the most commonly used techniques for preparation of microbeads. It involves interaction between oppositely charged polymers and cross-linking agents to form gel matrices.

Sodium alginate is widely used polymer in ionic gelation technique due to its biocompatibility, biodegradability, and non-toxic nature.

When sodium alginate solution containing drug is dropped into calcium chloride solution, calcium ions interact with alginate molecules and form calcium alginate beads.

Sodium Alginate + Ca^{2+} → Calcium Alginate Beads

1.5.1 Principle of Ionic Gelation

The principle of ionic gelation is based on cross-linking between negatively charged polymer and positively charged counter ions. Sodium alginate contains carboxyl groups which react with calcium ions and form three-dimensional gel network.

This process results in formation of spherical microbeads entrapping drug molecules inside polymer matrix.

1.5.2 Advantages of Ionic Gelation Technique

- Simple and economical process
- No use of organic solvents
- Suitable for heat sensitive drugs
- Mild processing conditions
- High drug entrapment efficiency
- Biocompatible and biodegradable polymers

1.6 Polymers Used in Microbeads

1.6.1 Sodium Alginate

Sodium alginate is a natural polysaccharide obtained from brown seaweed. It is widely used in pharmaceutical formulations due to its gel-forming property.

Properties

- Biodegradable
- Biocompatible
- Non-toxic
- Hydrophilic

Applications

- Controlled drug delivery
- Encapsulation
- Wound dressing
- Tissue engineering

1.6.2 Chitosan

Chitosan is a natural polymer obtained from chitin. It possesses mucoadhesive and biocompatible properties.

Advantages

- Biodegradable
- Mucoadhesive
- Enhances drug absorption
- Sustains drug release

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1.6.3 HPMC

Hydroxy Propyl Methyl Cellulose (HPMC) is a semi-synthetic polymer commonly used as release retardant in sustained release formulations.

Functions

- Controls drug release
- Improves matrix integrity
- Enhances swelling behavior

1.7 Drug Profile Overview Pregabalin

Pregabalin is an anticonvulsant and neuropathic pain relieving agent used in treatment of epilepsy, diabetic neuropathy, fibromyalgia, and anxiety disorders.

Pregabalin has short biological half-life and requires frequent dosing, making it suitable candidate for sustained release drug delivery system.

1.8 Need for Present Study

Pregabalin requires multiple daily dosing due to its short half-life, which may reduce patient compliance. Development of sustained release Pregabalin microbeads can:

- Prolong drug release
- Reduce dosing frequency
- Improve patient compliance
- Maintain steady plasma concentration
- Reduce adverse effects

Ionic gelation technique provides an effective method for formulation of Pregabalin loaded microbeads using biodegradable polymers.

II. REVIEW OF LITERATURE

2.1 Overview

Literature review is an important part of research work which provides information regarding previous studies related to formulation and evaluation of microbeads, ionic gelation technique, sustained release systems, and Pregabalin delivery systems. Various researchers have

developed polymeric microbeads using natural and synthetic polymers for controlled drug delivery applications.

2.2 Review of Reported Research Work Study 1

Patel et al. developed alginate microbeads using ionic gelation technique for sustained drug delivery. The study demonstrated that increase in polymer concentration improved drug entrapment efficiency and prolonged drug release. Calcium chloride was used as cross-linking agent for bead formation.

Conclusion

Alginate microbeads effectively sustained drug release and improved formulation stability.

Study 2

Kulkarni et al. prepared chitosan coated microbeads by ionic gelation method and evaluated their controlled release properties. The researchers observed that chitosan coating enhanced mucoadhesion and reduced burst drug release.

Conclusion

Combination polymer systems improved sustained release behavior compared to single polymer formulations.

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Study 3
Sriamornsak studied the application of pectin and alginate polymers in microencapsulation technology. The research revealed that ionic cross-linking produced spherical and stable microbeads with good encapsulation efficiency.

Conclusion
Natural polymers are highly suitable for controlled drug delivery systems.

Study 4
Anal and Stevens prepared chitosan-alginate multilayer microcapsules for controlled release of drugs. Their study showed improved drug retention and prolonged release profile due to polymer interaction.

Conclusion
Multilayer polymer systems are effective in sustained release applications.

Study 5
Rajinikanth et al. formulated floating alginate beads using calcium chloride cross-linking method. The formulation exhibited controlled release and prolonged gastric retention.

Conclusion
Ionic gelation technique is economical and suitable for sustained drug delivery formulations.

Study 6
Hariharan et al. developed sustained release microspheres using sodium alginate and HPMC polymers. The formulation demonstrated excellent swelling characteristics and controlled release pattern.

Conclusion
HPMC effectively retarded drug release and improved matrix stability.

2.3 Summary of Literature Review
From the literature survey, the following observations were made:

- Ionic gelation is a simple and effective method for preparation of microbeads.
- Sodium alginate is the most widely used polymer due to its biocompatibility and gel forming ability.
- Combination of polymers such as alginate, chitosan, and HPMC improves sustained release properties.
- Cross-linking concentration affects bead formation and drug release profile.
- Sustained release formulations improve therapeutic efficacy and patient compliance.
- Pregabalin is a suitable drug candidate for sustained release microbead formulation because of its short half-life.

2.4 Research Gap
Although many studies have been carried out on sustained release microbeads, limited research is available on comparative evaluation of Pregabalin loaded microbeads prepared using different polymer combinations by ionic gelation technique.

Therefore, the present study aims to formulate and comparatively evaluate Pregabalin loaded microbeads using sodium alginate, chitosan, and HPMC polymers for sustained drug delivery.

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III. AIM, OBJECTIVES AND PLAN OF WORK

3.1 Aim

To formulate and evaluate comparative Pregabalin loaded microbeads using ionic gelation technique for sustained and controlled drug delivery.

3.2 Objectives

1. To prepare Pregabalin loaded microbeads by ionic gelation technique

The primary objective of the study is to formulate Pregabalin loaded microbeads using ionic gelation technique. This method involves interaction between sodium alginate and calcium ions to produce spherical microbeads capable of entrapping the drug within polymer matrix. The technique is simple, economical, and suitable for sustained drug delivery systems.

2. To compare formulations prepared using different polymer combinations

Different formulations containing sodium alginate alone and in combination with polymers such as chitosan and HPMC are prepared to compare their effect on formulation characteristics. Comparative evaluation helps in selecting the best polymer combination for sustained drug release and improved entrapment efficiency.

3. To use sodium alginate, chitosan, and HPMC polymers for formulation development

Natural and semi-synthetic polymers are selected due to their biocompatibility, biodegradability, and controlled release properties. Sodium alginate forms gel matrix, chitosan enhances mucoadhesion and matrix strength, while HPMC acts as release retardant polymer.

4. To evaluate physicochemical properties of prepared microbeads

Prepared microbeads are evaluated for parameters such as shape, particle size, surface morphology, flow properties, and stability. These evaluations ensure quality, uniformity, and suitability of formulation for pharmaceutical application.

5. To determine percentage yield and drug entrapment efficiency

Percentage yield indicates efficiency of preparation process, while entrapment efficiency determines amount of drug successfully incorporated into microbeads. High entrapment efficiency indicates better drug retention within polymer matrix.

6. To study swelling behavior and particle size distribution of microbeads

Swelling behavior affects penetration of dissolution medium and drug release rate from microbeads. Particle size distribution influences drug release pattern, stability, and uniformity of dosage form.

7. To perform in-vitro drug release studies

In-vitro drug release studies are conducted to evaluate sustained release behavior of prepared formulations. These studies help determine release pattern and duration of drug release from microbeads in simulated physiological conditions.

8. To optimize the best formulation based on sustained release characteristics

The final objective is to identify optimized formulation showing:

- Maximum entrapment efficiency
- Desired particle size
- Good physicochemical properties
- Controlled and prolonged drug release

3.3 Expected Outcome

The present study is expected to develop stable and effective Pregabalin loaded microbeads with sustained release properties using ionic gelation technique. The optimized formulation may improve patient compliance, reduce dosing frequency, and enhance therapeutic efficacy of Pregabalin.

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3.3 Plan of Work

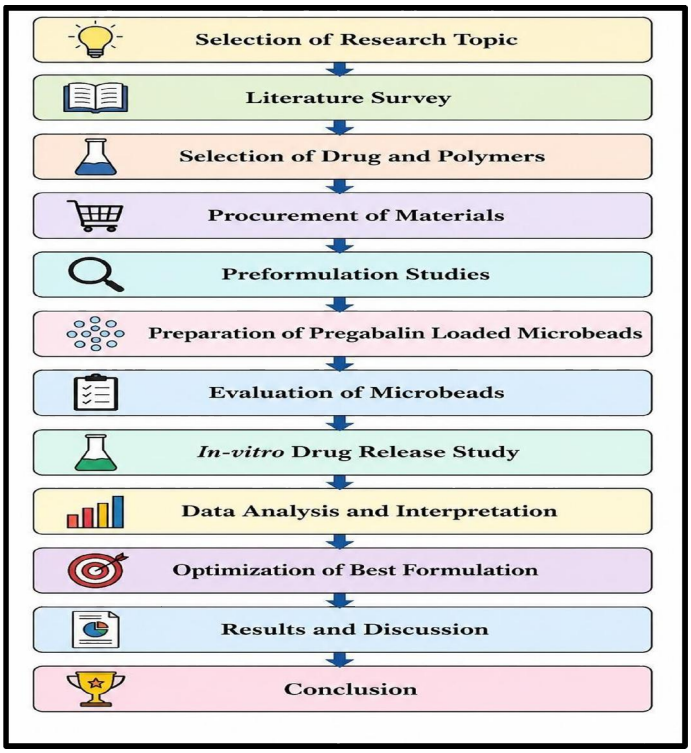

Fig. 1: Flowchart of Plan of Work

IV. DRUG PROFILE

4.1 Introduction

Drug profiling is an important step in formulation development which provides detailed information regarding physicochemical, pharmacological, and biological properties of the drug. These properties help in selection of suitable formulation technique and excipients for development of effective dosage forms.

The present study involves formulation of Pregabalin loaded microbeads for sustained drug delivery using ionic gelation technique.

4.2 Drug Profile of Pregabalin

Parameter	Description
Drug Name	Pregabalin
Category	Anticonvulsant
Therapeutic Class	Neuropathic Pain Reliever
Official Status	IP / USP
Dosage Form Available	Capsules, Tablets, Oral Solution
Route of Administration	Oral

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4.2.2 Chemical Information

Pregabalin

Parameter	Description
Chemical Name	(S)-3-(aminomethyl)-5-methylhexanoic acid
Molecular Formula	$C_8H_{17}NO_2$
Molecular Weight	159.23 g/mol
Structure	Gamma amino butyric acid analogue
IUPAC Name	(3S)-3-(aminomethyl)-5-methylhexanoic acid

4.2.3 Molecular Formula

C8H17NO2C_8H_{17}NO_2C8H17NO2

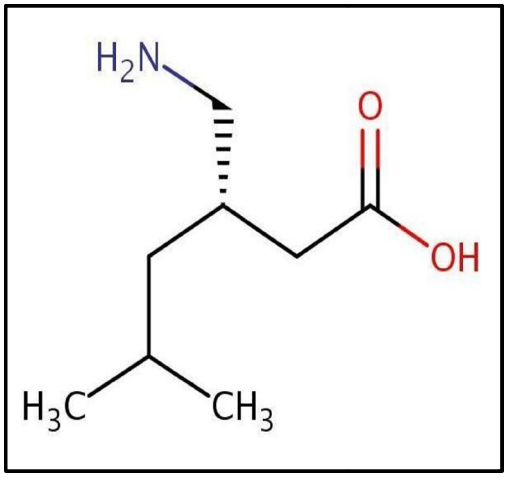

Fig. 2: Pregabalin Drug and Chemical Structure

4.2.4 Molecular Weight

159.23 g/mol

4.3 Physical Properties

Property	Description
Appearance	White crystalline powder
Color	White
Odor	Odorless
Taste	Slightly bitter
Melting Point	194–196°C
Solubility	Freely soluble in water
pH	Neutral

4.4 Pharmacological Properties

Parameter	Description
Mechanism of Action	Binds to α2-δ subunit of voltage gated calcium channels
Biological Half-life	Approximately 6 hours
Protein Binding	Negligible

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Bioavailability	Greater than 90%
Metabolism	Negligible hepatic metabolism
Excretion	Renal

4.5 Mechanism of Action

Pregabalin acts by binding to the alpha-2-delta subunit of voltage gated calcium channels in the central nervous system. This action decreases calcium influx into nerve terminals and reduces release of excitatory neurotransmitters such as glutamate, norepinephrine, and substance P.

4.6 Therapeutic Uses

Pregabalin is widely used for treatment of:

- Neuropathic pain
- Epilepsy
- Fibromyalgia
- Generalized anxiety disorder
- Diabetic neuropathy
- Post-herpetic neuralgia

4.7 Adverse Effects

Common side effects of Pregabalin include:

- Dizziness
- Drowsiness
- Dry mouth
- Blurred vision Weight gain
- Fatigue

4.8 Drug Interaction

Pregabalin may interact with:

- CNS depressants
- Alcohol
- Opioid analgesics
- Antidiabetic agents

Combination with CNS depressants may increase sedation and dizziness.

4.9 Storage Conditions

Pregabalin should be stored:

- In a cool and dry place
- Protected from moisture
- Away from direct sunlight
- At controlled room temperature

4.10 Rationale for Selection of Drug

Pregabalin was selected for the present study because:

- It has short biological half-life.
- It requires frequent dosing.
- It is highly water soluble.

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- Sustained release formulation can improve patient compliance.
- Controlled release may reduce dose related side effects.

These properties make Pregabalin a suitable candidate for sustained release microbead formulation using ionic gelation technique.

V. MATERIALS AND METHODS

5.1 Introduction to Materials and methods

Materials and methods play an important role in formulation development and evaluation of pharmaceutical dosage forms. The present study involves preparation of Pregabalin loaded microbeads using ionic gelation technique with different polymer combinations for sustained drug delivery.

5.2 Materials

5.2.1 List of Materials

Sr. No.	Material	Category	Function
1	Pregabalin	Drug	Active Pharmaceutical Ingredient
2	Sodium Alginate	Polymer	Gel forming polymer
3	Chitosan	Polymer	Release retardant
4	HPMC	Polymer	Sustained release polymer
5	Calcium Chloride	Cross-linking Agent	Bead formation
6	Distilled Water	Solvent	Preparation medium
7	Phosphate Buffer pH 6.8	Dissolution Medium	Drug release study

5.3 Instruments and Equipment

Sr. No.	Instrument	Purpose
1	Digital Balance	Accurate weighing
2	Magnetic Stirrer	Mixing
3	Hot Air Oven	Drying
4	UV Spectrophotometer	Drug analysis
5	Optical Microscope	Particle size analysis
6	FTIR Spectrophotometer	Compatibility study
7	Dissolution Apparatus USP Type II	In-vitro drug release
8	pH Meter	pH determination

5.4 Method of Preparation of Pregabalin Loaded Microbeads Ionic Gelation Technique

Pregabalin loaded microbeads were prepared by ionic gelation technique using sodium alginate alone and in combination with chitosan and HPMC polymers.

5.4.1 Principle

The ionic gelation method is based on interaction between negatively charged sodium alginate and positively charged calcium ions, resulting in formation of calcium alginate gel beads.

Sodium Alginate +Ca2 + → Calcium Alginate Microbeads

5.4.2 Procedure

Step-by-Step Procedure

1. Required quantity of sodium alginate was dissolved in distilled water with continuous stirring.
2. Pregabalin was accurately weighed and dispersed uniformly in polymer solution.

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3. Chitosan and HPMC were added according to formulation design.
4. The dispersion was stirred continuously until homogeneous solution was obtained.
5. Calcium chloride solution was prepared separately as cross-linking solution.
6. The prepared polymer-drug dispersion was transferred into syringe fitted with needle.
7. The solution was added dropwise into calcium chloride solution under continuous stirring.
8. Formation of spherical microbeads occurred immediately due to ionic cross-linking.
9. The formed microbeads were allowed to cure for 30 minutes.
10. Microbeads were filtered and washed with distilled water to remove excess calcium chloride.
11. Prepared microbeads were dried at room temperature or in hot air oven.
12. Dried microbeads were stored in airtight container for further evaluation.

5.5 Flowchart of Preparation Method

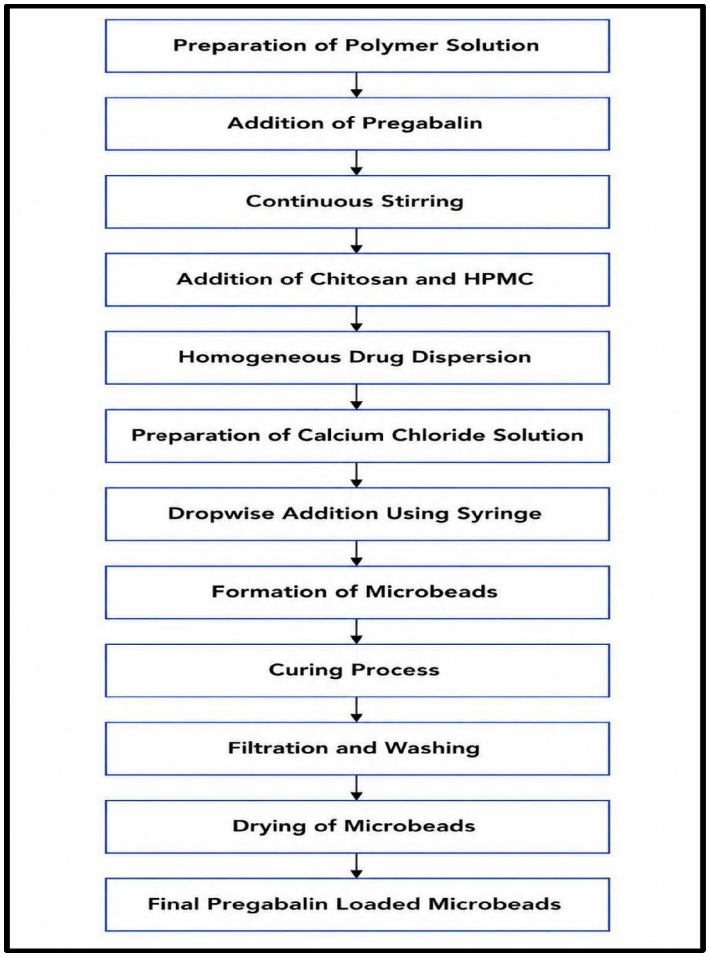

Fig. 3: Flowchart of Preparation Method

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5.6 Formulation Design

Composition of Pregabalin Microbeads

Ingredients	F1	F2	F3	F4
Pregabalin (mg)	100	100	100	100
Sodium Alginate (%)	2	3	2	3
Chitosan (%)	-	-	1	1
HPMC (%)	1	1	1	2
Calcium Chloride (%)	5	5	5	5

5.7 Evaluation Parameters

Prepared Pregabalin microbeads were evaluated for:

- Percentage yield
- Drug entrapment efficiency
- Particle size analysis
- Swelling index
- Surface morphology
- Flow properties
- In-vitro drug release study

5.8 Statistical Analysis

All experiments were carried out in triplicate and results were expressed as mean ± standard deviation.

VI. PREFORMULATION STUDIES

6.1 Preformulation studies

Preformulation studies are the initial phase of formulation development in which physical, chemical, and analytical properties of drug substances are evaluated. These studies help in selection of suitable excipients, formulation method, and storage conditions.

Preformulation parameters such as organoleptic properties, solubility, melting point, compatibility studies, and analytical methods were carried out for Pregabalin before formulation of microbeads.

6.2 Organoleptic Properties

Organoleptic evaluation includes study of color, odor, appearance, and texture of drug. Table

6.1: Organoleptic Properties of Pregabalin

Parameter	Observation
Color	White
Odor	Odorless
Appearance	Crystalline powder
Taste	Slightly bitter

6.3 Solubility Study

Solubility study was performed in different solvents to determine solubility characteristics of Pregabalin.

Procedure

An excess amount of Pregabalin was added separately into different solvents and shaken continuously. The solutions were observed visually for solubility.

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Table 6.2: Solubility Study of Pregabalin

Solvent	Solubility
Water	Freely soluble
Methanol	Slightly soluble
Ethanol	Slightly soluble
Chloroform	Insoluble
Phosphate Buffer pH 6.8	Soluble

6.4 Determination of Melting Point

Procedure

Melting point of Pregabalin was determined using capillary method. Small quantity of drug was filled into capillary tube and placed in melting point apparatus. Temperature at which drug melted completely was noted.

Observation

Melting point observed: 194–196°C

6.5 Determination of λmax

The absorption maximum (λmax) of Pregabalin was determined using UV spectrophotometer. Procedure

1. Pregabalin solution was prepared in phosphate buffer pH 6.8.
2. The solution was scanned between 200–400 nm using UV spectrophotometer.
3. Wavelength showing maximum absorbance was recorded.

Observation

Pregabalin showed maximum absorbance at 210 nm.

6.6 Preparation of Standard Calibration Curve

Procedure

1. Standard stock solution of Pregabalin was prepared.
2. Different concentrations were prepared by suitable dilution.
3. Absorbance was measured at 210 nm using UV spectrophotometer.
4. Calibration curve was plotted between concentration and absorbance.

Table 6.3: Calibration Data of Pregabalin

Concentration (µg/ml)	Absorbance
2	0.112
4	0.224
6	0.331
8	0.447
10	0.558

6.7 Calibration Curve Equation

$$Y = mx + c$$

Where:

- y = Absorbance
- x = Concentration
- m = Slope
- c = Intercept

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The calibration curve showed good linearity within selected concentration range.

6.8 Drug-Excipient Compatibility Study

Compatibility study was performed to evaluate possible interaction between Pregabalin and selected polymers.

6.8.1 FTIR Study

Fourier Transform Infrared Spectroscopy (FTIR) was used to identify compatibility between drug and excipients.

Procedure

1. Samples of pure drug and physical mixtures were prepared.
2. Samples were mixed with potassium bromide.
3. FTIR spectra were recorded over range of 4000–400 cm^{-1}.

Observation

Characteristic peaks of Pregabalin were retained in physical mixture indicating absence of significant interaction between drug and polymers.

Table 6.4: FTIR Peaks of Pregabalin

Functional Group	Observed Peak (cm^{-1})
N–H Stretching	3300
C=O Stretching	1645
C–N Stretching	1280
C–H Stretching	2950

6.8.2 Differential Scanning Calorimetry (DSC)

DSC study was performed to evaluate thermal behavior and compatibility of drug with polymers.

Observation

The characteristic endothermic peak of Pregabalin was retained in formulation mixture indicating compatibility with selected excipients.

VII. FORMULATION DEVELOPMENT

7.1 Rationale for Selection of Excipients

7.1.1 Sodium Alginate

Sodium alginate was selected due to:

- Excellent gel forming property
- Biocompatibility
- Biodegradability
- Non-toxic nature
- Easy cross-linking with calcium ions

7.1.2 Chitosan

Chitosan was selected because:

- It provides mucoadhesive property
- Improves sustained drug release
- Enhances matrix strength
- Increases entrapment efficiency

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7.1.3 HPMC

HPMC was incorporated for:

- Retarding drug release
- Improving swelling behavior
- Increasing viscosity
- Maintaining matrix integrity

7.1.4 Calcium Chloride

Calcium chloride acts as cross-linking agent and reacts with sodium alginate to form calcium alginate microbeads.

Alginate− + Ca2 + → Cross-linked Alginate Beads

7.2 Method of Formulation Development

Pregabalin loaded microbeads were developed using ionic gelation technique by varying concentration of polymers.

Different formulations were prepared to compare:

- Effect of polymer concentration
- Effect of polymer combination
- Drug release behavior
- Entrapment efficiency

7.3 Preparation of Pregabalin Loaded Microbeads

Procedure

1. Sodium alginate solution was prepared in distilled water under continuous stirring.
2. Required quantity of Pregabalin was added into polymer solution.
3. Chitosan and HPMC were added according to formulation design.
4. Homogeneous dispersion was prepared using magnetic stirrer.
5. Calcium chloride solution was prepared separately.
6. Drug polymer dispersion was added dropwise into calcium chloride solution using syringe.
7. Microbeads were formed due to ionic cross-linking reaction.
8. Formed microbeads were cured for 30 minutes.
9. Beads were filtered and washed with distilled water.
10. Prepared microbeads were dried and stored in airtight container.

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7.4 Flowchart of Formulation Process

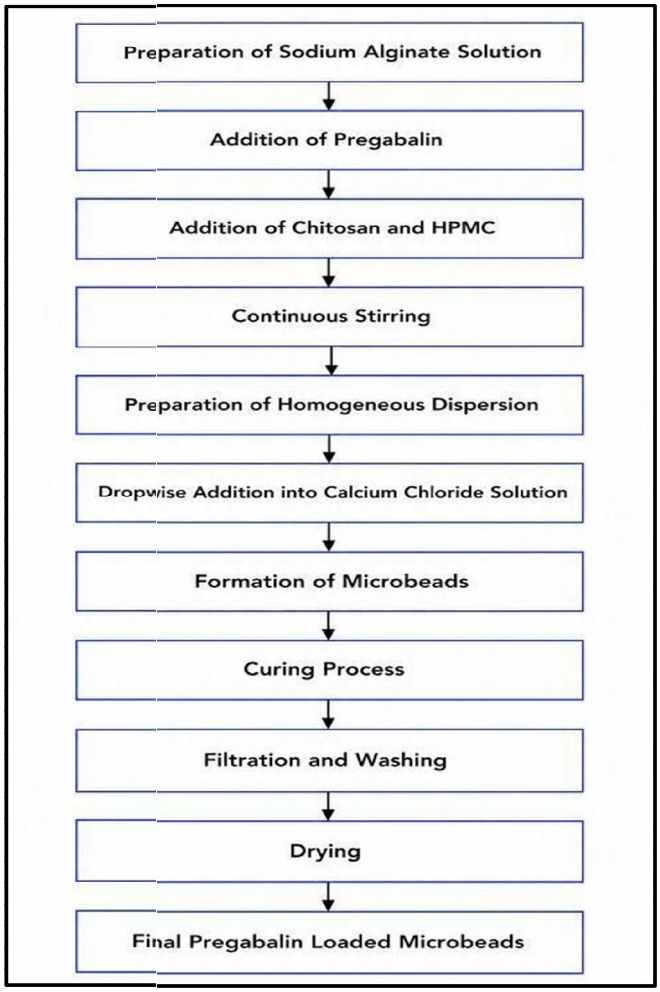

Fig. 4: Flowchart of Formulation Process

7.5 Formulation Composition

Table 7.1: Composition of Pregabalin Loaded Microbeads

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Calcium Chloride (%)	5	5	5	5

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7.6 Optimization Parameters

Formulations were optimized based on:

- Percentage yield
- Entrapment efficiency
- Particle size
- Swelling behavior
- Sustained drug release
- Surface morphology

7.7 Mechanism of Drug Release from Microbeads Drug release from microbeads occurs by:

- Diffusion of drug through polymer matrix
- Swelling of polymer
- Erosion of polymer network

Initially, surface drug dissolves rapidly followed by sustained release from inner polymeric matrix.

7.8 Factors Affecting Microbead Formation

7.8.1 Polymer Concentration

Increase in polymer concentration:

- Increases viscosity
- Produces larger beads
- Enhances entrapment efficiency
- Retards drug release

7.8.2 Cross-linking Agent Concentration Higher

calcium chloride concentration:

- Produces rigid beads
- Increases cross-linking density
- Decreases drug release rate

7.8.3 Stirring Speed

Stirring speed affects:

- Particle size
- Shape of beads
- Uniformity of formulation

7.10 Advantages of Prepared Microbeads

- Sustained drug release
- Reduced dosing frequency
- Improved patient compliance
- Better therapeutic efficacy
- Reduced side effects

Pregabalin loaded microbeads were successfully formulated using ionic gelation technique with sodium alginate, chitosan, and HPMC polymers. Variation in polymer concentration influenced bead formation, entrapment efficiency, and drug release behavior. Prepared formulations were suitable for further evaluation studies.

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VIII. EVALUATION OF MICROBEADS

Evaluation of pharmaceutical formulations is essential to determine quality, stability, and performance of dosage forms. Prepared Pregabalin loaded microbeads were evaluated for various physicochemical parameters to assess their suitability for sustained drug delivery.

The evaluation parameters included:

- Percentage yield
- Particle size analysis
- Drug entrapment efficiency
- Swelling index
- Surface morphology
- Flow properties
- In-vitro drug release study

8.1 Percentage Yield

Percentage yield indicates efficiency of preparation process.

$$\% \, Yield = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

Formula

Procedure

1. Prepared microbeads were collected and dried.
2. The final weight of microbeads was recorded.
3. Percentage yield was calculated using above formula.

Table 8.1: Percentage Yield of Formulations

Formulation	Percentage Yield (%)
F1	78.4 ± 0.4
F2	82.5 ± 0.5
F3	85.7 ± 0.6
F4	88.2 ± 0.3

8.2 Particle Size Analysis

Particle size analysis was performed using optical microscopy. Procedure

1. Small quantity of microbeads was placed on glass slide.
2. Diameter of beads was measured using optical microscope.
3. Average particle size was calculated.

Table 8.2: Particle Size of Formulations

Formulation	Particle Size (µm)
F1	610 ± 12
F2	685 ± 10
F3	720 ± 15
F4	810 ± 11

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8.4 Drug Entrapment Efficiency

Entrapment efficiency indicates amount of drug encapsulated within microbeads.

Formula

$$\%EE = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Procedure

1. Accurately weighed microbeads were crushed.
2. Drug was extracted using phosphate buffer pH 6.8.
3. Solution was filtered and analyzed using UV spectrophotometer at 210 nm.
4. Entrapment efficiency was calculated.

Table 8.3: Entrapment Efficiency of Formulations

Formulation	Entrapment Efficiency (%)
F1	70.2 ± 0.5
F2	76.5 ± 0.7
F3	82.1 ± 0.6
F4	87.3 ± 0.4

8.5 Swelling Index

Swelling behavior influences drug release characteristics of microbeads.

Formula

$$\text{Swelling Index} = \frac{W_t - W_0}{W_0} \times 100$$

Where:

- Wt = Weight of swollen beads
- W_0 = Initial weight of beads

Procedure

1. Dried microbeads were weighed accurately.
2. Microbeads were immersed in phosphate buffer pH 6.8.
3. Swollen beads were removed at predetermined intervals and weighed.
4. Swelling index was calculated.

Table 8.4: Swelling Index of Formulations

Formulation	Swelling Index (%)
F1	58
F2	65
F3	72
F4	80

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8.6 Surface Morphology

Surface morphology was evaluated using scanning electron microscopy (SEM).

Observation

SEM analysis showed:

- Spherical shape of microbeads
- Smooth surface morphology
- Uniform distribution of drug within polymer matrix

8.7 Flow Properties

8.7.1 Bulk Density

$$\text{Bulk Density} = \frac{\text{Mass}}{\text{Bulk Volume}}$$

8.7.2 Tapped Density

$$\text{Tapped Density} = \frac{\text{Mass}}{\text{Tapped Volume}}$$

8.7.3 Carr's Index

$$\text{Carr's Index} = \frac{TD-BD}{TD} \times 100$$

8.7.4 Hausner Ratio

$$\text{Hausner Ratio} = \frac{TD}{BD}$$

Table 8.5: Flow Property Results

Parameter	Result
Bulk Density	0.48 g/cm³
Tapped Density	0.56 g/cm³
Carr's Index	14.2%
Hausner Ratio	1.16

8.8 In-vitro Drug Release Study

In-vitro drug release study was performed using USP dissolution apparatus Type II.

8.8.1 Dissolution Conditions

Parameter	Condition
Apparatus	USP Type II
Dissolution Medium	Phosphate Buffer pH 6.8
Temperature	37 ± 0.5°C
Speed	50 RPM
Duration	8 Hours

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Procedure

1. Accurately weighed microbeads were placed in dissolution medium.
2. Samples were withdrawn at predetermined time intervals.
3. Fresh medium was replaced after each withdrawal.
4. Samples were analyzed using UV spectrophotometer at 210 nm.

Table 8.6: In-vitro Drug Release Study

Time (hr)	F1	F2	F3	F4
1	20	18	15	12
2	35	30	26	22
4	60	52	45	38
6	82	75	68	60
8	96	90	84	78

8.9 Drug Release Kinetics

Drug release data may be fitted into different kinetic models:

- Zero order kinetics
- First order kinetics
- Higuchi model
- Korsmeyer-Peppas model

These models help determine mechanism of drug release from microbeads.

XI. RESULTS AND DISCUSSION

The study was carried out to formulate and evaluate comparative Pregabalin loaded microbeads using ionic gelation technique for sustained drug delivery. Different formulations were prepared using sodium alginate, chitosan, and HPMC polymers.

Prepared microbeads were evaluated for percentage yield, particle size, entrapment efficiency, swelling behavior, flow properties, and in-vitro drug release study. The obtained results are discussed in this chapter.

9.1 Percentage Yield

Percentage yield of all formulations was found to be satisfactory.

Table 9.1: Percentage Yield of Formulations

Formulation	Percentage Yield (%)
F1	78.4 ± 0.4
F2	82.5 ± 0.5
F3	85.7 ± 0.6
F4	88.2 ± 0.3

Discussion

The percentage yield increased with increase in polymer concentration. Formulation F4 showed highest yield because higher concentration of sodium alginate and HPMC produced stronger cross-linked microbeads with less material loss during preparation.

9.3 Particle Size Analysis

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Table 9.2: Particle Size of Formulations

Formulation	Particle Size (µm)
F1	610 ± 12
F2	685 ± 10
F3	720 ± 15
F4	810 ± 11

Discussion

Particle size increased with increase in polymer concentration. Higher viscosity of polymer solution produced larger droplets during ionic gelation process leading to larger microbeads. Formulation F4 showed maximum particle size due to combined effect of sodium alginate and HPMC.

9.4 Drug Entrapment Efficiency

Table 9.3: Entrapment Efficiency of Formulations

Formulation	Entrapment Efficiency (%)
F1	70.2 ± 0.5
F2	76.5 ± 0.7
F3	82.1 ± 0.6
F4	87.3 ± 0.4

Discussion

Entrapment efficiency increased with increase in polymer concentration and cross-linking density.

Formulation F4 exhibited highest entrapment efficiency due to:

- Increased viscosity of polymer solution
- Better matrix formation
- Reduced drug diffusion during bead formation

Combination polymers improved encapsulation of Pregabalin within polymer matrix.

9.5 Swelling Index

Table 9.4: Swelling Index of Formulations

Formulation	Swelling Index (%)
F1	58
F2	65
F3	72
F4	80

Discussion

Swelling index increased with increase in hydrophilic polymer concentration. HPMC and chitosan absorbed dissolution medium and formed swollen gel structure.

Higher swelling behavior contributed to sustained drug release by controlling diffusion of drug from polymer matrix.

9.6 Surface Morphology

SEM analysis revealed that prepared microbeads were:

- Spherical in shape
- Smooth surfaced
- Uniform in size distribution

No visible cracks were observed on surface of optimized formulation indicating proper crosslinking and matrix integrity.

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9.7 Flow Properties

Table 9.5: Flow Properties of Optimized Formulation

Parameter	Result
Bulk Density	0.48 g/cm³
Tapped Density	0.56 g/cm³
Carr's Index	14.2%
Hausner Ratio	1.16

Discussion

Flow property results indicated good flow characteristics of prepared microbeads. Carr's index and Hausner ratio values confirmed acceptable flowability which is important for handling and processing of formulation.

9.8 In-vitro Drug Release Study

Table 9.6: In-vitro Drug Release Profile

Time (hr)	F1	F2	F3	F4
1	20	18	15	12
2	35	30	26	22
4	60	52	45	38
6	82	75	68	60
8	96	90	84	78

Discussion

All formulations exhibited sustained drug release pattern.

- F1 showed rapid drug release due to lower polymer concentration.
- F2 and F3 demonstrated moderate sustained release behavior.
- F4 showed maximum sustained release effect because of higher concentration of sodium alginate and HPMC.

Increase in polymer concentration formed dense matrix structure which slowed penetration of dissolution medium and diffusion of drug.

9.9 Comparative Evaluation of Formulations

Table 9.7: Comparative Evaluation of Formulations

Parameter	F1	F2	F3	F4
% Yield	78.4	82.5	85.7	88.2
Entrapment Efficiency (%)	70.2	76.5	82.1	87.3
Particle Size (µm)	610	685	720	810
Drug Release at 8 hr (%)	96	90	84	78

Discussion

Comparative evaluation indicated that formulation F4 was optimized formulation because it exhibited:

- Highest entrapment efficiency
- Better swelling behavior
- Prolonged drug release
- Good surface morphology
- Acceptable flow properties

Thus, formulation F4 was considered most suitable for sustained release Pregabalin delivery.

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9.10 Mechanism of Drug Release

Drug release from prepared microbeads occurred through:

- Diffusion mechanism
- Polymer swelling
- Matrix erosion

Initially, small amount of surface drug was released rapidly followed by controlled diffusion through hydrated polymer matrix.

9.11 Overall Discussion

The present study demonstrated successful preparation of Pregabalin loaded microbeads using ionic gelation technique. Sodium alginate effectively formed calcium alginate beads in presence of calcium chloride.

Combination of chitosan and HPMC improved:

- Matrix strength
- Entrapment efficiency
- Sustained release characteristics

Among all formulations, F4 showed best sustained release behavior due to higher polymer concentration and stronger cross-linked network.

The obtained results confirmed suitability of ionic gelation technique for development of sustained release Pregabalin microbeads.

X. CONCLUSION AND FUTURE SCOPE

10.1 Conclusion

The present research work entitled “Formulation and Evaluation of Comparative Pregabalin Loaded Microbeads by Ionic Gelation Technique” was successfully carried out using sodium alginate, chitosan, and HPMC polymers for sustained drug delivery.

Pregabalin loaded microbeads were prepared successfully by ionic gelation technique using calcium chloride as cross-linking agent. Different formulations were developed by varying polymer concentration and polymer combinations to evaluate their effect on physicochemical properties and drug release behavior.

The major conclusions drawn from the study are as follows:

- Ionic gelation technique was found to be simple, economical, and suitable for preparation of Pregabalin loaded microbeads.
- Sodium alginate effectively formed stable calcium alginate microbeads in presence of calcium ions.
- Combination of polymers such as chitosan and HPMC improved matrix integrity and sustained drug release properties.
- Prepared microbeads showed satisfactory percentage yield, particle size distribution, and entrapment efficiency.
- Increase in polymer concentration increased particle size and entrapment efficiency while decreasing drug release rate.
- In-vitro drug release studies demonstrated sustained release profile for all formulations.
- Formulation F4 exhibited best performance among all formulations with:
- Highest entrapment efficiency
- Better swelling behavior
- Controlled and prolonged drug release
- Good physicochemical characteristics
- Drug release from microbeads occurred mainly through diffusion and polymer swelling mechanisms.

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The study confirmed that Pregabalin loaded microbeads prepared by ionic gelation technique can be successfully used as sustained release drug delivery systems for improving therapeutic efficacy and patient compliance.

10.2 Future Scope

The present study provides scope for further research and development in the following areas:

- Stability studies of optimized formulation under accelerated conditions.
- In-vivo pharmacokinetic and pharmacodynamic studies.
- Scale-up and industrial manufacturing studies.
- Development of targeted and site specific drug delivery systems.
- Evaluation of bioavailability and clinical efficacy.
- Use of advanced polymers for improved sustained release performance.
- Development of modified release capsule dosage form containing optimized microbeads.
- Investigation of mucoadhesive and gastro-retentive properties of formulation.
- Comparative studies with marketed sustained release formulations.
- Application of ionic gelation technique for other water soluble drugs.

10.3 Overall Summary of Research Work

The present work successfully demonstrated formulation and comparative evaluation of Pregabalin loaded microbeads using ionic gelation technique. The prepared formulations showed satisfactory sustained release characteristics and improved drug entrapment efficiency.

The optimized formulation may reduce dosing frequency, improve patient compliance, and enhance therapeutic effectiveness of Pregabalin in management of neuropathic disorders and epilepsy.

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