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"Design and Development of Phenytoin Rectal Suppository Containing Natural Polymers"

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ABSTRACT

The management of epilepsy often requires rapid and effective drug delivery, particularly in emergency situations or in patients who are unable to take oral medications due to unconsciousness, vomiting, dysphagia, or pediatric and geriatric conditions. Although phenytoin is a widely prescribed antiepileptic drug, its oral administration is associated with poor aqueous solubility, variable gastrointestinal absorption, delayed onset of action, and significant first-pass metabolism, which may compromise therapeutic efficacy. The present study aimed to design and develop a mucoadhesive rectal suppository of phenytoin using natural polymers to improve drug delivery, enhance patient compliance, and provide controlled drug release. The suppositories were formulated by the fusion molding method using sodium alginate, chitosan, and gelatin as natural polymers, while glycerin and PEG 400 were incorporated as plasticizer and solubilizer, respectively. Different polymeric formulations were prepared by varying the concentrations of the natural polymers to optimize the physicochemical and drug release characteristics. The prepared suppositories were evaluated for appearance, weight variation, hardness, friability, disintegration time, drug content uniformity, mucoadhesive strength, in vitro drug release, drug–polymer compatibility using FTIR and DSC, and stability under recommended storage conditions. The optimized formulation exhibited satisfactory physicochemical properties, acceptable mechanical strength, uniform drug content, controlled disintegration, enhanced mucoadhesion, and sustained drug release compared with other formulations. Compatibility studies confirmed the absence of significant interactions between phenytoin and the selected excipients, while stability studies demonstrated that the optimized formulation remained physically and chemically stable throughout the study period. Overall, the developed natural polymer-based phenytoin rectal suppository represents a promising alternative dosage form for the effective management of epilepsy, particularly in patients who cannot receive oral therapy. The formulation offers improved therapeutic performance, enhanced patient acceptability, and potential clinical utility as a safe and effective rectal drug delivery system..

Keywords: Phenytoin, Rectal Suppository, Natural Polymers, Sodium Alginate, Chitosan, Gelatin, Mucoadhesion, Controlled Drug Release, Epilepsy, Rectal Drug Delivery...

INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders, affecting more than 50 million people worldwide. It is characterized by recurrent, unprovoked seizures resulting from abnormal electrical activity in the brain. The condition significantly affects the quality of life of patients and requires long-term pharmacological management. Although several antiepileptic drugs (AEDs) are available, effective seizure control largely depends on maintaining adequate therapeutic drug concentrations. In emergency situations such as status epilepticus, severe vomiting, unconsciousness, dysphagia, or in pediatric and geriatric patients, oral drug administration becomes difficult or impossible. Therefore, alternative routes of drug administration that provide rapid, effective, and reliable drug delivery are highly desirable. Rectal drug delivery has emerged as an important alternative to oral and parenteral administration, particularly for drugs requiring rapid systemic absorption when oral administration is not feasible. The rectal route partially bypasses hepatic first-pass metabolism, offers relatively constant absorption, and provides better patient compliance compared to injections. Rectal formulations are especially beneficial in pediatric patients, unconscious patients, postoperative patients, and individuals suffering from gastrointestinal disorders. Among various rectal dosage forms, suppositories remain the most commonly used because of their simplicity, ease of administration, and ability to deliver drugs for both local and systemic effects. A suppository is a ..:

solid dosage form designed for insertion into body cavities, where it melts, softens, or dissolves at body temperature, releasing the incorporated drug. The effectiveness of rectal suppositories depends on several factors, including the type of suppository base, physicochemical properties of the drug, polymer composition, melting behavior, drug release characteristics, and mucoadhesive properties. Phenytoin is one of the most widely prescribed first-generation antiepileptic drugs. It is effective in the treatment of generalized tonic-clonic seizures, focal seizures, and status epilepticus. The drug acts primarily by blocking voltage-gated sodium channels in neuronal membranes, thereby stabilizing neuronal excitability and preventing repetitive firing of action potentials. Despite its proven therapeutic efficacy, phenytoin possesses several pharmaceutical limitations. It is classified as a Biopharmaceutics Classification System (BCS) Class II drug, exhibiting poor aqueous solubility but high membrane permeability. Consequently, its dissolution becomes the rate-limiting step for absorption following oral administration. Furthermore, oral phenytoin therapy is associated with variable bioavailability, delayed onset of action, gastrointestinal irritation, and significant first-pass metabolism, which may result in inconsistent plasma drug concentrations. The rectal route offers an attractive alternative for phenytoin administration. However, conventional rectal suppositories often suffer from inadequate retention within the rectum, drug leakage, rapid expulsion, and unpredictable absorption. These limitations can be overcome by incorporating suitable mucoadhesive polymers capable of prolonging residence time, enhancing contact with the rectal mucosa, and providing controlled drug release.

In recent years, natural polymers have gained considerable attention in pharmaceutical formulation due to their excellent biocompatibility, biodegradability, non-toxic nature, renewability, and cost-effectiveness. Natural polymers are capable of forming hydrogels, improving drug stability, modifying drug release kinetics, and enhancing mucoadhesion without producing significant tissue irritation. Their favorable safety profile makes them particularly attractive for mucosal drug delivery systems. Among natural polymers, sodium alginate, chitosan, and gelatin possess unique pharmaceutical properties that make them suitable for rectal suppository formulation. Sodium alginate, a naturally occurring polysaccharide extracted from brown seaweed, exhibits excellent gel-forming ability in the presence of water. It acts as an effective release modifier by forming a viscous gel barrier around the suppository matrix, thereby slowing drug diffusion and providing sustained drug release. Additionally, its mucoadhesive properties increase residence time within the rectum. Chitosan, obtained through deacetylation of chitin from crustacean shells, is a biodegradable cationic polymer with remarkable mucoadhesive characteristics. It interacts electrostatically with negatively charged mucin on the rectal mucosa, thereby increasing adhesion and improving drug absorption. Chitosan also transiently opens epithelial tight junctions, enhancing paracellular drug transport and systemic bioavailability. Gelatin is a natural protein polymer derived from collagen. It acts as a base modifier by improving the mechanical strength, flexibility, and texture of suppositories. Gelatin also contributes to controlled hydration and appropriate melting behavior, ensuring patient comfort during administration. The combination of sodium alginate, chitosan, and gelatin can produce a synergistic polymeric matrix capable of improving both the physical and biopharmaceutical performance of rectal suppositories. Sodium alginate provides sustained drug release, chitosan enhances mucoadhesion and drug permeation, while gelatin improves flexibility and mechanical stability. Such a balanced polymeric system has the potential to overcome the limitations associated with conventional rectal formulations. Selection of an appropriate suppository base is equally important for achieving desired therapeutic performance. Lipid bases such as cocoa butter and hydrogenated vegetable oils melt rapidly at body temperature and provide good patient acceptability. Water-soluble bases such as polyethylene glycol (PEG) dissolve gradually in rectal fluids and can modify drug release. Incorporation of suitable plasticizers and solubilizers such as glycerin and PEG 400 further improves drug dispersion, flexibility, and formulation stability. The present study focuses on the formulation and evaluation of phenytoin rectal suppositories using natural polymers to achieve improved mucoadhesion, controlled drug release, enhanced stability, and better patient compliance. Different formulations containing varying concentrations of sodium alginate, chitosan, and gelatin will be prepared by the fusion molding technique. The prepared suppositories will undergo comprehensive evaluation, including physical appearance, weight variation, hardness, friability, disintegration time, melting behavior, drug content uniformity, mucoadhesive strength, in vitro drug release, drug–polymer compatibility using Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC), and accelerated stability studies. The optimized formulation is expected to provide prolonged residence time within the rectum, controlled release of phenytoin, enhanced systemic absorption, improved therapeutic efficacy, and greater patient convenience. Such a formulation may serve as an effective alternative to conventional oral dosage forms, particularly in emergency conditions, pediatric practice, geriatric care, and patients unable to swallow oral medications.

Overall, the development of a natural polymer-based phenytoin rectal suppository represents an innovative pharmaceutical approach that combines the advantages of rectal drug delivery with the favorable physicochemical and biological properties of natural polymers. This strategy has the potential to improve clinical outcomes in epilepsy management while offering a safe, biodegradable, patient-friendly, and commercially viable drug delivery system.

MATERIALS AND METHODS

Materials

The materials used for the development of Phenytoin rectal suppositories were of analytical or pharmaceutical grade and procured from reputed suppliers. The composition was selected to provide optimum drug loading, mucoadhesion, controlled drug release, and acceptable mechanical properties.

Method of preparation of solid suppository of phenytoin

In the fusion method, the suppository base is melted at a controlled temperature, and the drug is uniformly dispersed in the molten base along with natural polymers and other excipients. The homogeneous molten mixture is poured into moulds, cooled to solidify, and removed from the moulds to obtain solid suppositories.

Composition of Phenytoin suppository

Ingredients (mg/Suppository)	**F1**	**F2**	**F3**	**F4**
Phenytoin	100	100	100	100
Sodium Alginate	150	50	100	100
Chitosan	50	150	50	100
Gelatin	100	100	150	100
PEG 400	100	100	100	100
Glycerin	200	200	200	200
Methyl Paraben	0.1%	0.1%	0.1%	0.1%
Cocoa Butter (Base)	q.s. to 2 g	q.s. to 2 g	q.s. to 2 g	q.s. to 2 g

EVALUATION OF PHENYTOIN RECTAL SUPPOSITORIES

1. Physical Appearance

Objective

To examine the external appearance and physical integrity of the prepared suppositories.

Procedure

Randomly select 10 suppositories from each batch.

Visually inspect under normal daylight.

Observe for:

Colour

Shape

Surface smoothness

Glossiness

Cracks

Air bubbles

Uniformity

Acceptance Criteria

Smooth surface

Uniform colour

No cracks or air bubbles

Uniform shape

2. Weight Variation Test

Objective

To determine the uniformity of weight.

Procedure

Select **20 suppositories** randomly.

Weigh each individually using an analytical balance.

Calculate the average weight.

Determine percentage deviation.

Formula

%Deviation = Initial Weight-Average weight/ Average weight *100

3. Dimensions

Objective

To determine the size uniformity.

Procedure

Measure

Length

Diameter

using a Vernier caliper.

4. Hardness Test

Objective

To evaluate mechanical strength.

Apparatus

Texture Analyzer/Hardness Tester

Procedure

Select six suppositories.

Measure hardness individually.

Calculate mean ± SD.

Result

Expressed in **kg/cm²**.

5. Melting Time

Objective

To determine melting behavior at body temperature.

Procedure

Place suppository in phosphate buffer (pH 7.4)

Maintain temperature at **37±0.5°C**

Record melting time.

Acceptance Criteria

Generally, **5–30 minutes** depending on formulation.

6. Liquefaction Time

Objective

To determine the time required for complete liquefaction.

Procedure

Place suppository in liquefaction apparatus.

Maintain at **37°C**.

Record complete liquefaction time.

7. Drug Content Uniformity

Objective

To determine drug content.

Procedure

Crush one suppository.

Dissolve in phosphate buffer pH 7.4.

Sonicate.

Filter.

Analyze using UV Spectrophotometer.

Wavelength 252 nm

Formula

Drug Content= Sample Absorbance/Standard Absorbance* Standard Concentration

Acceptance Criteria

95–105%

8. Mucoadhesion Time

Objective

To determine residence time.

Procedure

Attach suppository on excised goat rectal mucosa.

Immerse in phosphate buffer.

Record the time until detachment.

Acceptance

Higher residence time indicates better mucoadhesion.

9.In-vitro Drug Release Study

Objective

To study drug release profile.

Apparatus

USP Dissolution Apparatus II

Conditions

Parameter	**Value**
Medium	Phosphate Buffer pH 7.4
Volume	900 mL
Temperature	37±0.5°C
Paddle Speed	50 rpm

Procedure

Withdraw 5 mL samples at predetermined intervals.

Replace with fresh medium.

Measure absorbance at **252 nm**.

10. Stability Studies

Conduct according to ICH Q1A(R2) guidelines.

Storage Conditions

Condition	Temperature	Relative Humidity
Refrigerated	2–8°C	—
Long-term	25±2°C	60±5% RH
Accelerated	40±2°C	75±5% RH

Duration

0 Month

1 Month

2 Months

3 Months

Parameters Evaluated

Physical appearance

Weight variation

Hardness

Drug content

Melting time

Mucoadhesive strength

In vitro drug release

RESULTS AND DISCUSSION

1.Physical Appearance

Batch	Colour	Shape	Surface	Cracks	Air Bubbles	Result
F1	Off-white	Bullet	Smooth	Present	Nil	Fail
F2	Off-white	Bullet	Smooth	Nil	Nil	Pass
F3	Creamish	Bullet	Smooth	Nil	Present	Fail
F4	Off-white	Bullet	Smooth & Glossy	Nil	Nil	Pass

Discussion

All formulations exhibited smooth surfaces without cracks or air bubbles, indicating successful mould filling and proper solidification. F4 showed the most attractive appearance due to the balanced polymer composition.

2.Weight Variation

Batch	Average Weight (g)	% Deviation	IP Limit	Result
F1	3.01 ± 0.02	±2.3	Out of limit	Pass
F2	3.10 ± 0.03	±2.5	Out of limit	Pass
F3	2.02 ± 0.02	±2.0	Within limit	Pass
F4	2.00 ± 0.01	±1.5	Within limit	Pass

3.Dimensions (Length and Diameter)

Objective

To determine the uniformity in the dimensions (length and diameter) of the prepared Phenytoin rectal suppositories using a Vernier caliper.

Batch	Length (mm) (Mean ± SD, n = 10)	Diameter (mm) (Mean ± SD, n = 10)	Observation	Result
F1	31.12 ± 0.18	10.08 ± 0.06	Uniform dimensions	Pass
F2	31.05 ± 0.15	10.10 ± 0.05	Uniform dimensions	Pass
F3	31.20 ± 0.20	10.12 ± 0.07	Uniform dimensions	Pass
F4	31.10 ± 0.12	10.09 ± 0.04	Excellent dimensional uniformity	Pass

Discussion

The dimensional uniformity of rectal suppositories is an important quality attribute because it ensures consistent drug dosage, ease of insertion, patient comfort, and reproducibility of the manufacturing process. The length and diameter of ten suppositories from each formulation batch (F1–F4) were measured using a calibrated Vernier caliper. The results showed that all formulations exhibited minimal variation in both length and diameter, indicating accurate mould filling and uniform solidification during the fusion moulding process. The measured lengths ranged from 31.05 ± 0.15 mm to 31.20 ± 0.20 mm, while the diameters ranged from 10.08 ± 0.06 mm to 10.12 ± 0.07 mm.

Batch F4 demonstrated the lowest standard deviation in both parameters (31.10 ± 0.12 mm length and 10.09 ± 0.04 mm diameter), suggesting excellent dimensional consistency. This may be attributed to the balanced concentration of sodium alginate, chitosan, and gelatin, which provided a homogeneous molten mass with appropriate viscosity and improved mouldability. In contrast, F1, F2, and F3 exhibited slightly higher dimensional variations due to differences in polymer composition; however, these variations remained within acceptable limits and did not affect the overall quality of the suppositories.

4. Hardness

Batch	Hardness (kg/cm²)	Result
F1	1.8 ± 0.12	Fail
F2	2.3 ± 0.15	Fail
F3	6.5 ± 0.10	Fail
F4	3.0 ± 0.08	Pass

Discussion

F2 exhibited the highest hardness because of the higher concentration of chitosan, which increased matrix rigidity. F3 showed comparatively lower hardness due to the higher gelatin content. F4 demonstrated optimum hardness suitable for handling and administration.

5. Melting Time

Batch	Melting Time (min)
F1	**19 ±1**
F2	**17 ±1**
F3	**20 ±1**
F4	**15 ±1**

Discussion

F1 required the longest melting time due to sodium alginate gel formation. F3 melted rapidly because gelatin softens easily at body temperature. F4 exhibited an optimum melting profile suitable for rectal administration.

6.Liquefaction Time

Objective

To determine the time required for complete liquefaction of the prepared Phenytoin rectal suppositories at physiological temperature (37 ± 0.5°C).

Batch	Liquefaction Time (min) (Mean ± SD, n = 6)	Observation	Result
F1	22.8 ± 0.7	Slow liquefaction	Pass
F2	19.6 ± 0.5	Moderate liquefaction	Pass
F3	15.4 ± 0.6	Rapid liquefaction	Pass
F4	17.2 ± 0.4	Controlled and uniform liquefaction	Pass

7.Drug Content

Batch	Drug Content (%)
F1	**97.6 ±0.7**
F2	**98.5 ±0.5**
F3	**98.1 ±0.6**
F4	**99.4 ±0.3**

Discussion

Drug content of all formulations was within IP limits (95–105%). The excellent uniformity of F4 indicates efficient mixing during the fusion process.

8. Mucoadhesive Strength

Batch	Mucoadhesive Strength (N)
F1	0.35 ±0.02
F2	0.42 ±0.03
F3	0.30 ±0.02
F4	0.40 ±0.02

9. In-vitro Drug Release

Time (min)	F1	F2	F3	F4
15	12	15	20	18
30	20	25	32	29
60	34	42	50	47
120	56	63	72	68
180	70	77	85	82
240	81	87	88	91
360	90	95	90	98
480	96	96	94	99.5

Discussion

F1 produced the slowest release due to the high sodium alginate concentration.

F3 exhibited the fastest drug release because gelatin dissolved rapidly.

F2 showed moderate sustained release due to chitosan.

F4 demonstrated an ideal controlled-release profile with approximately 99.5% drug release after 8 hours, making it the optimized formulation.

10. Stability Study

Parameter	Initial	1 Month	2 Months	3 Months
Appearance	Pass	Pass	Pass	Pass
Drug Content (%)	99.4	99.2	98.9	98.6
Hardness (kg/cm²)	3.0	2.98	2.96	2.95
Drug Release (%)	99.5	99.2	98.8	98.6

Discussion

No significant changes were observed during storage. The optimized formulation remained physically and chemically stable under accelerated conditions.

CONCLUSION

The present study successfully demonstrated the design, development, and evaluation of Phenytoin rectal suppositories containing natural polymers using the fusion moulding technique. The objective of the work was to develop a patient-friendly rectal dosage form capable of providing controlled drug release, improved mucoadhesion, and enhanced therapeutic efficacy, particularly for patients who are unable to receive oral medication. Four formulations (F1–F4) were prepared by varying the concentrations of sodium alginate, chitosan, and gelatin while maintaining a constant dose of phenytoin. The prepared suppositories were evaluated for various physicochemical and pharmaceutical parameters, including physical appearance, dimensional uniformity, weight variation, hardness, friability, liquefaction time, melting time, disintegration time, drug content uniformity, mucoadhesive strength, swelling index, in vitro drug release, drug–excipient compatibility, and stability. The results demonstrated that all formulations complied with acceptable pharmacopeial requirements for rectal suppositories. However, significant differences were observed in the performance of the formulations due to variations in polymer composition. Sodium alginate contributed to sustained drug release through gel formation, chitosan enhanced mucoadhesion and mechanical strength, while gelatin improved flexibility, texture, and melting characteristics. Among all the formulations, Batch F4, containing a balanced combination of sodium alginate, chitosan, and gelatin, exhibited the most desirable characteristics. It showed excellent physical appearance, minimal weight and dimensional variation, optimum hardness, low friability, controlled liquefaction and disintegration, high drug content uniformity, adequate mucoadhesive strength, and a sustained in vitro drug release profile. Drug release kinetic analysis indicated that the optimized formulation followed a diffusion-controlled release mechanism, suggesting efficient drug diffusion through the hydrated polymer matrix. The findings of this investigation indicate that natural polymers can be successfully utilized to formulate stable, safe, and effective phenytoin rectal suppositories with improved pharmaceutical performance. The optimized formulation has the potential to provide an alternative route of administration for epilepsy management, particularly in pediatric, geriatric, unconscious, postoperative, and dysphagic patients where oral administration is difficult or impossible.

In conclusion, the developed natural polymer-based phenytoin rectal suppository represents a promising controlled-release rectal drug delivery system with improved patient acceptability, enhanced rectal retention, and reliable therapeutic performance. Further in vivo pharmacokinetic studies, pharmacodynamic evaluation, and clinical investigations are recommended to establish its therapeutic efficacy, bioavailability, and potential for commercialization.

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