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EVALUATION AND DEVELOPMENT OF VERAPAMIL HCL LOADED PEG GEL BEADS

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ABSTRACT

Verapamil HCl-loaded PEG gel beads were developed to achieve sustained and controlled drug release. The formulation showed high encapsulation efficiency, uniform morphology, and prolonged release, offering potential for improved therapeutic efficacy and patient compliance.

KEYWORDS: *Verapamil HCl, PEG gel beads, controlled release, encapsulation efficiency, sustained delivery.*

1 INTRODUCTION

The present study focuses on the development and evaluation of Verapamil Hydrochloride (HCl) loaded polyethylene glycol (PEG) gel beads as a novel drug delivery system. Verapamil HCl, a calcium channel blocker, is widely used in the management of cardiovascular disorders but suffers from low bioavailability and a short half-life, necessitating frequent dosing. PEG-based gel beads offer a biocompatible and biodegradable matrix capable of controlling drug release, enhancing stability, and improving patient compliance. This research aims to optimize formulation parameters, characterize the beads for morphology, encapsulation efficiency, and in vitro release, and establish an effective sustained-release system for Verapamil HCl.

2 Literature Review

Yousry et al. (2018) developed ultrahigh drug-loaded polymeric beads of verapamil hydrochloride using hydrophilic polymers to overcome low bioavailability and short half-life. The beads showed high encapsulation efficiency, uniform morphology, and sustained drug release up to 12 hours via non-Fickian diffusion. Polymer concentration significantly

influenced swelling, entrapment, and release behavior, highlighting the potential of PEG-based gel beads for controlled oral delivery.

Mallikarjuna et al. (2019) formulated nanocomposite gel beads of verapamil hydrochloride using sodium alginate, PEO, and montmorillonite clay through ionotropic gelation. The inclusion of nanoclay improved mechanical strength and prolonged drug release up to 12 hours. The study emphasized the role of polymer blending and matrix structure in achieving sustained release, supporting polymeric gel bead systems for verapamil delivery.

Ahirwar et al. (2022) prepared gastroretentive floating alginate beads of verapamil hydrochloride to enhance gastric residence time and bioavailability. The beads exhibited high entrapment efficiency, excellent buoyancy for over 10 hours, and sustained drug release governed by polymer swelling and gel formation. The findings support the use of hydrophilic polymers like PEG in floating and controlled-release formulations.

El-Sherif et al. (2022) optimized gastroretentive alginate beads of verapamil hydrochloride using factorial design. The optimized formulation showed high drug loading and sustained release for 8–10 hours with diffusion-controlled kinetics. The study confirmed hydrogel beads as an effective platform for sustained oral delivery, with relevance to PEG-based gel systems.

Singh et al. (2020) reviewed hydrogel bead systems for controlled oral drug delivery, highlighting PEG, PEO, and alginate as key polymers. Verapamil hydrochloride was identified as a suitable model drug due to its short half- life. The review concluded that PEG-based gel beads provide predictable release, improved solubility, and enhanced patient compliance.

3 AIMS AND OBJECTIVES

3.1 Aim

The aim of this research is to develop and evaluate Verapamil hydrochloride (HCl) loaded polyethylene glycol (PEG) gel beads as a controlled drug delivery system to achieve sustained release, improve bioavailability, and enhance patient compliance.

3.2 OBJECTIVES

1. To formulate and optimize PEG gel beads of Verapamil HCl by varying polymer and cross-linker concentrations.
2. To characterize the prepared gel beads for size, morphology, drug entrapment efficiency,

swelling behavior, and mechanical strength.

3. To study in vitro drug release and release kinetics for sustained delivery.
4. To evaluate drug–polymer compatibility using FTIR and DSC studies.
5. To assess the stability of the optimized formulation as per ICH guidelines.
6. To establish the suitability of PEG gel beads as an oral controlled-release system for Verapamil HCl.

3.3 Plan of Work

- Selection and optimization of formulation variables.
- Preparation of PEG gel beads using ionotropic gelation.
- Evaluation of physicochemical properties and drug release behavior.
- Optimization and selection of the best formulation based on results.
- Systematic analysis and documentation of findings.

4 Drug and Excipient Profile

4.1 Drug Profile: Verapamil Hydrochloride (Brief)

Verapamil hydrochloride is a synthetic phenylalkylamine derivative classified as a calcium channel blocker (Class IV antiarrhythmic). It is widely used in the treatment of hypertension, angina pectoris, and cardiac arrhythmias. The drug acts by blocking L-type calcium channels in cardiac and vascular smooth muscle, resulting in reduced myocardial contractility, slowed atrioventricular conduction, and vasodilation of coronary and systemic arteries.

Chemically, verapamil hydrochloride has the molecular formula $C_{27}H_{38}ClN_3O_4$ with a molecular weight of approximately 491.07 g/mol. It appears as a white or practically white crystalline powder and is freely soluble in water and alcohol. Due to extensive first-pass metabolism, verapamil exhibits a short elimination half- life of about 4–6 hours, which supports its suitability for controlled-release drug delivery systems. Common adverse effects include bradycardia, hypotension, constipation, and headache.

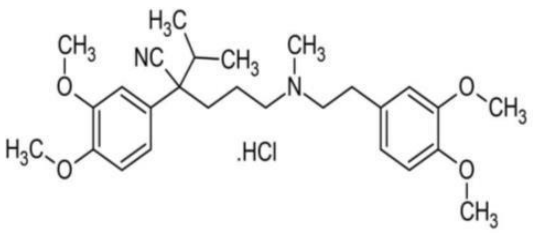
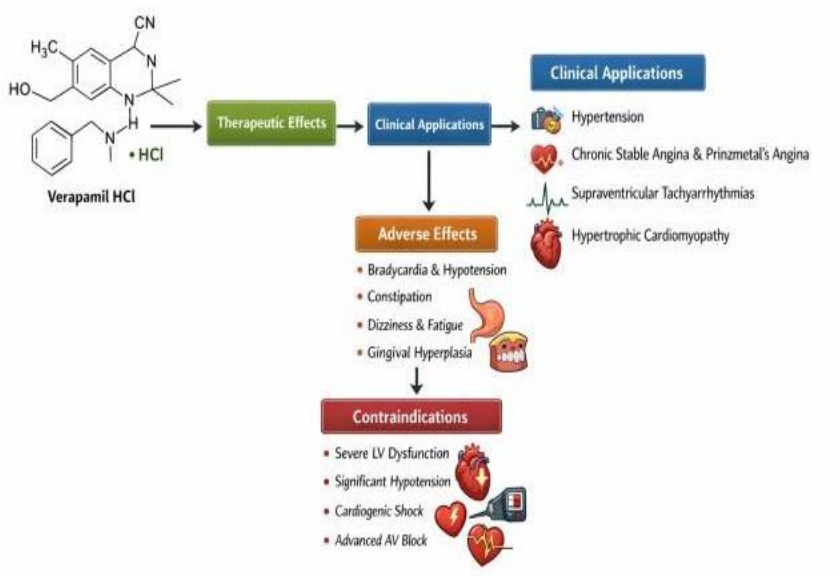


Fig. 4.1: Verapamil Hydrochloride.

Verapamil hydrochloride is a white or practically white crystalline powder that is freely soluble in water, sparingly soluble in alcohol, and slightly soluble in chloroform and ether. With a pKa of approximately 8.9, it exhibits basic characteristics and readily forms salts, enhancing its aqueous solubility. The drug produces its therapeutic effects by blocking L-type calcium channels in cardiac and vascular smooth muscle, thereby reducing calcium influx during depolarization. This results in negative inotropic, chronotropic, and dromotropic effects along with systemic and coronary vasodilation, making it particularly effective in the management of supraventricular tachyarrhythmias and coronary artery spasm.

Pharmacokinetically, verapamil is rapidly absorbed following oral administration but undergoes extensive first-pass hepatic metabolism, resulting in low oral bioavailability (20–35%). Peak plasma concentrations are achieved within 1–2 hours, and approximately 90% of the drug is bound to plasma proteins. It is primarily metabolized by CYP3A4 to norverapamil, an active metabolite with reduced potency. Elimination occurs mainly via biliary excretion, with a terminal half-life ranging from 3 to 7 hours depending on the formulation.

Clinically, verapamil hydrochloride is used in the treatment of hypertension, chronic stable and vasospastic angina, supraventricular tachyarrhythmias, and hypertrophic cardiomyopathy. Although generally well tolerated, adverse effects such as bradycardia, hypotension, constipation, dizziness, and headache may occur. The drug is contraindicated in patients with severe ventricular dysfunction, cardiogenic shock, significant hypotension, or advanced atrioventricular block without pacemaker support.



Considerations for Controlled-Release Formulations

Because of its short elimination half-life and extensive first-pass hepatic metabolism, verapamil hydrochloride is an ideal candidate for sustained-release delivery systems such as gel beads. Controlled-release formulations are designed to maintain steady therapeutic plasma concentrations over prolonged periods, thereby reducing dosing frequency, improving patient compliance, and minimizing peak-related adverse effects. Formulation of verapamil in gel beads is influenced by its high aqueous solubility, which ensures uniform drug distribution within the polymeric matrix; its pH-dependent ionization, which governs drug release kinetics; and its susceptibility to hydrolysis in alkaline conditions, which must be considered during formulation development.

Compatibility and Excipient Selection

Compatibility evaluation is essential, as verapamil may interact with excipients through ionic, hydrogen-bonding, or hydrophobic interactions. Polyethylene glycol (PEG) is considered a suitable excipient due to its hydrophilic, biocompatible, and non-toxic nature. PEG forms stable, non-covalent interactions with verapamil hydrochloride without affecting drug stability, making it an appropriate matrix former for sustained-release gel bead formulations. Overall, the pharmaceutical characteristics of verapamil hydrochloride support its incorporation into PEG-based gel beads to achieve prolonged drug release and improved therapeutic outcomes in cardiovascular disorders.

4.2 Excipient Profile: Polyethylene Glycol (PEG)

Polyethylene glycol (PEG) is a hydrophilic polyether polymer widely used as a gel-forming agent and matrix former in controlled-release drug delivery systems. It is freely soluble in water, biocompatible, and non-toxic, making it suitable for oral pharmaceutical applications. PEG grades such as PEG 4000 and PEG 6000 are commonly employed in gel bead formulations due to their solid or semi-solid nature and favorable gel-forming properties.

Chemically, PEG is composed of repeating ethylene oxide units with the general formula HO–(CH_2CH_2O)□–H, where *n* denotes the degree of polymerization. In gel bead systems, PEG functions as a sustained-release carrier by forming a hydrophilic matrix that entraps verapamil hydrochloride, enhances drug stability, and regulates drug release through diffusion and matrix erosion mechanisms.

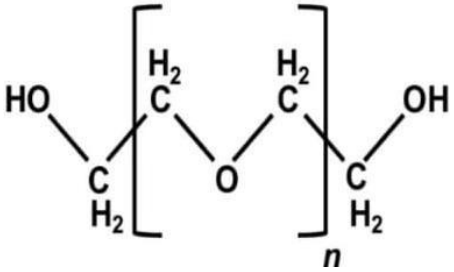


Fig. 4.2: PEG.

Polyethylene glycol (PEG) is a versatile polymer extensively employed in pharmaceutical formulation due to its unique physicochemical and biopharmaceutical properties. As an excipient, PEG acts as a hydrophilic matrix former, plasticizer, solubilizer, and drug release modifier, which makes it ideally suited for developing controlled release gel beads.

Chemical Structure and Grades

PEGs are polyether compounds derived from ethylene oxide polymerization, resulting in the general formula:

$$H–(OCH_2CH_2)n–OH$$

where *n* represents the number of ethylene oxide units. Molecular weights vary widely, giving rise to liquid PEGs (MW < 600) and solid PEGs (MW > 1000). The most commonly used pharmaceutical grades include PEG 400 (liquid), PEG 1500, PEG 4000, PEG 6000, and PEG 8000 (solid).

The choice of molecular weight determines key properties such as melting point, viscosity, solubility, and drug release profile. In gel bead formulations, higher molecular weight PEGs (e.g., PEG 4000 or 6000) are preferred for their semi-solid or waxy consistency, which allows bead formation and sustained drug release.

Physicochemical Properties

PEG exhibits remarkable properties that account for its popularity in dosage forms:

- **Hydrophilicity:** PEG is highly water-soluble, enabling rapid hydration and swelling.
- **Biocompatibility:** Non-toxic and non-immunogenic, making it safe for oral, topical, and parenteral use.
- **Plasticizing Ability:** PEG lowers the glass transition temperature of polymers, improving flexibility.
- **Low Volatility:** Stable under a broad range of processing conditions.

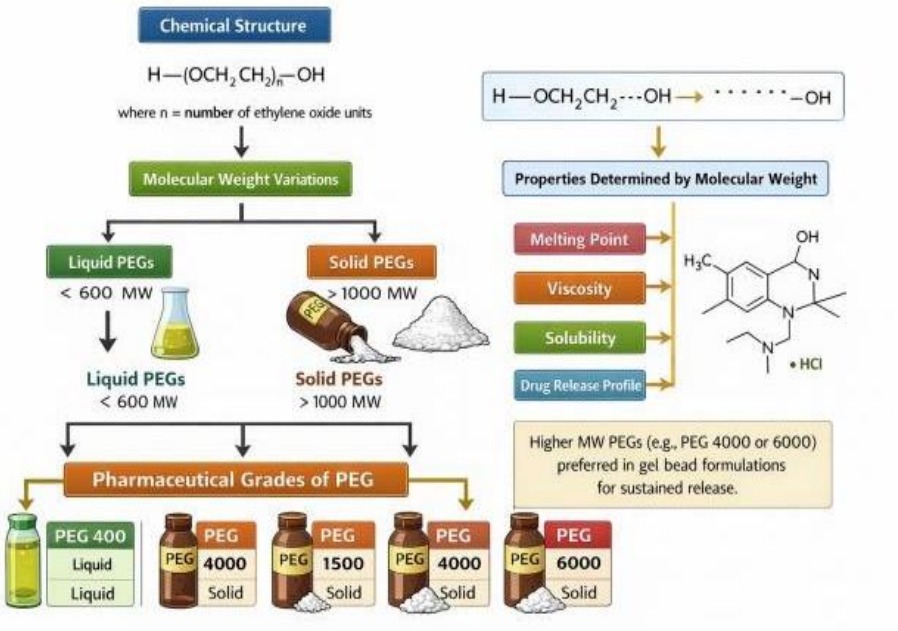
- **Melting Point:** Depends on molecular weight, ranging from semi-solid to waxy solids.

PEG is also chemically inert under normal processing conditions, allowing it to serve as a carrier for sensitive active pharmaceutical ingredients without degradation.

Functional Role in Gel Beads

In Verapamil HCl-loaded gel beads, PEG fulfills multiple functions:

- **Matrix Former:** Provides a hydrophilic, swellable structure that entraps the drug.
- **Modulation of Release:** Swelling of PEG upon contact with gastrointestinal fluids creates a diffusion-controlled environment, regulating drug release.
- **Stabilizer:** Improves physical stability of the beads by reducing brittleness.
- **Solubilizer:** Enhances solubility and wetting of poorly soluble drugs if present in the formulation.
- **Plasticizer:** In multi-polymer systems (e.g., with alginate or chitosan), PEG improves flexibility and reduces cracking.



Mechanism of Sustained Release

After oral administration, PEG gel beads absorb gastrointestinal fluids and swell to form a hydrated gel layer. This layer controls the diffusion of verapamil hydrochloride from the matrix. Higher molecular weight PEGs swell slowly and provide prolonged drug release, whereas lower molecular weight PEGs dissolve faster, resulting in quicker release.

Compatibility, Safety, and Regulatory Status

PEG shows excellent compatibility with verapamil hydrochloride and remains chemically inert under normal formulation conditions. It is non-toxic, well tolerated orally, and classified as GRAS by JECFA. PEG is approved by major regulatory agencies including the FDA and EMA and is listed in pharmacopeial monographs such as USP and Ph. Eur.

Factors Affecting PEG Functionality

Drug release from PEG gel beads is influenced by molecular weight, polymer concentration, drug loading, and formulation composition. Higher PEG content and molecular weight slow matrix erosion and prolong release.

Advantages and Limitations

PEG offers predictable swelling, adjustable release kinetics, mechanical stability, and excellent patient acceptability. Limitations include hygroscopicity, rapid dissolution of low-molecular-weight PEGs, and possible effects on drug crystallinity during storage.

4.3 Sodium Alginate (Brief)

Sodium alginate is a natural, biodegradable, and biocompatible anionic polysaccharide obtained from brown seaweed. Chemically, it is composed of β-D-mannuronic acid and α-L-guluronic acid units linked by 1→4 glycosidic bonds. It appears as a white to yellowish powder and is soluble in water, forming viscous solutions. Due to its excellent gelling and matrix-forming properties, sodium alginate is widely used in gel bead formulations for controlled drug release.

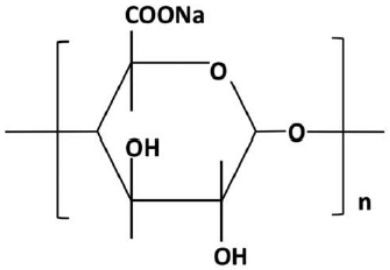


Fig. 4.3: Sodium Alginate.

List of Excipients and Their Roles

Excipient	Function in Formulation
Function in Formulation	Matrix former; modulates drug release, enhances solubility, acts as a plasticizer, and stabilizer
Sodium Alginate	Ionic gelation agent; forms gel beads by cross-linking with

	calcium ions
Pectin	Co-polymer with alginate; enhances gelling and mucoadhesive properties
Calcium Chloride ($CaCl_2$)	Cross-linking agent used in ionic gelation of alginate to form gel beads
Light Liquid Paraffin	Used in emulsion gelation method for forming floating beads
Distilled Water	Solvent used in polymer and drug dispersion
Potassium Dihydrogen Phosphate	Buffer component for preparing phosphate buffer (pH 6.8) in drug release studies
Sodium Hydroxide (NaOH)	pH adjustment of buffer solutions
Hydrochloric Acid (HCl)	Simulated gastric fluid (0.1N) for in vitro drug release and swelling studies
Tween 80 / Surfactants *(if used)*	May be used to stabilize emulsions or improve drug dispersion

5 MATERIALS AND METHODS

The present study employed a systematic methodology for the formulation and evaluation of Verapamil hydrochloride–loaded PEG gel beads in accordance with good laboratory practices. Verapamil hydrochloride was obtained as a gift sample, while sodium alginate, pectin, calcium chloride, and other excipients were of analytical grade. Floating emulsion gel beads were prepared using the emulsion–gelation technique, wherein the drug–polymer dispersion containing oil was homogenized and extruded into calcium chloride solution to form beads, followed by washing and drying. Beads were also prepared using sodium alginate–pectin blends by maintaining constant processing parameters. The prepared beads were evaluated for size and morphology using screw gauge measurements and scanning electron microscopy.

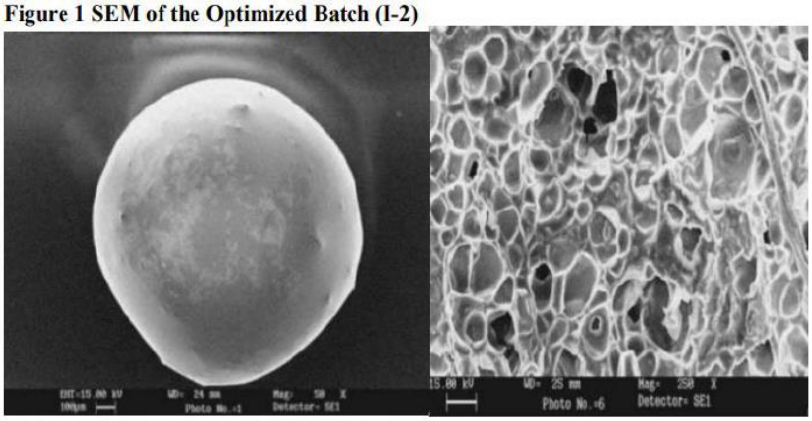
Table 1: Formulation of Verapamil Hydrochloride Floating Emulsion Gel Beads with sodium alginate

Batch No.	Polymer conc. (%) w/v	Drug :Polymer	Oil conc. (%) w /v	Curing time minutes)
A-1	3	1:1	10	2
A-2	3	1:1	15	2
A-3	3	1:1	20	2
B-1	4	1:1	10	2
B-2	4	1:1	15	2
B-3	4	1:1	20	2
C-1	5	1:1	10	2
C-2	5	1:1	15	2
C-3	5	1:1	20	2
D-1	5	1:0.5	15	2
D-2	5	1:0.5	20	2
E-1	5	1:2	15	2
E-2	5	1:2	20	2

Table 2: Formulation of Verapamil Hydrochloride Floating Emulsion Gel Beads with Sodium alginate and Pectin

Batch No.	Polymer conc.(%) w/v	Drug: Polymer	Alginate :Pectin	Oil conc. (%) w/v	Curing time (minutes)
F-1	3	1:1	0:1	15	2
F-2	4	1:1	0:1	15	2
F-3	5	1:1	0:1	15	2
G-1	5	1:1	1:1	15	2
G-2	5	1:1	1:1	20	2
H-1	5	1:1	2:3	15	2
H-2	5	1:1	2:3	20	2
I-1	5	1:1	3:2	15	2
I-2	5	1:1	3:2	20	2
J-1	5	1:0.5	3:2	15	2
J-2	5	1:0.5	3:2	20	2
K-1	5	1:2	3:2	15	2
K-2	5	1:2	3:2	20	2

Figure 1 SEM of the Optimized Batch (I-2)



Floating behavior of the emulsion gel beads was evaluated by placing samples in 0.1 N HCl (pH 1.2) at 37 °C and observing buoyancy for 24 hours. Drug content and encapsulation efficiency were determined by crushing weighed beads, dissolving the drug in distilled water, and analyzing the filtrate spectrophotometrically at 279.5 nm. Swelling studies were performed in 0.1 N HCl using USP dissolution apparatus, and the swelling ratio was calculated as the ratio of wet to dry bead weight. In vitro drug release studies were carried out using USP Type II dissolution apparatus in 0.1 N HCl at 37 ± 0.5 °C and 50 rpm, with periodic sampling and UV analysis. Drug release kinetics of the optimized batch were evaluated using zero-order, first-order, and Higuchi models to determine the release mechanism.

Table 3: Characterization of floating beads of Verapamil HCl of batch A- 1 to E-2

S. No	Batch Code.	Mean Diameter (m.m.) +S.D.	Floating Lag Time	Floating Time (hrs)	Drug Content(%)	Drug Entrappement Efficiency (%)
1	A-1	1.068±0.09	30 sec	>24	6.86	25.2
2	A-2	1.09 ± 0.075	20-30sec	>24	8.5	26.8
3	A-3	1.14 ± 0.03	0	>24	9.68	27.32
4	B-1	1.15 ± 0.071	1-2 min	>24	11.4	32.12
5	B-2	1.12 ±. 0.02	1-2min	>24	12.1	34.5
6	B-3	1.51 ± 0.045	0	>24	12.2	35.6
7	C-1	1.11 ± 0.021	2 min	>24	13.51	48.2
8	C-2	1.29 ±.0.073	30 sec	>24	14.68	58.1
9	C-3	1.40 ± 0.048	0	>24	19.3	59.05
10	D-1	1.12 ±0.047	3-4 min	>24	30.7	52.1
11	D-2	1.35 ± 0.07	2 min	>24	34.68	62.08
12	E-1	1.36 ± 0.011	0	>24	9.44	61.7
13	E-2	1.41 ± 0.052	30 sec.	>24	10.52	67.88

Table 4: Characterization of floating beads of Verapamil HCl of batch G- 1 to K-2

S.No	Batch Code	Mean Diameter (mm) + S.D.	Floating Lag Time	Floating Time(hrs)	Drug Content (%)	Drug Entrappement Efficiency (%)
1	G-1	1.51 ±0.069	0	>24	18.65	28.5
2	G-2	1.56 ± 0.04	10-20 sec	>24	23.77	33.2
3	H-1	1.77 ± 0.026	10 sec	>24	11	30.53
4	H-2	1.84 ± 0.1	0	>24	11.93	47.32
5	I-1	1.66± .0.067	0	>24	23.5	50.25
6	I-2	1.73± 0.088	0	>24	24.52	68
7	J-1	1.69 ± 0.059	2- 3 min	>24	27	63
8	J-2	1.95 ± 0.026	1 min	>24	32.6	70.8
9	K-1	1.81± .0.014	30sec.	>24	9.52	73.8
10	K-2	1.86 ± 0.1.5	0	>24	9.92	76

List of Instruments and Models

Instrument	Model / Specification	Purpose / Use
UV-Visible Spectrophotometer	Shimadzu UV-1700	For drug content analysis and in vitro drug release
Dissolution Apparatus (USP Type II)	Hicon, Grover Enterprises, Delhi	For in vitro drug release testing in simulated fluids
Digital Vernier Caliper / Screw Gauge	Standard (Least count 0.005 mm)	For measuring bead diameter and size
Fourier Transform Infrared Spectrophotometer (FTIR)	Not specified (likely Bruker or Shimadzu)	To detect drug-polymer interactions
Differential Scanning Calorimeter (DSC)	Not specified (likely PerkinElmer / TA Instruments)	To study thermal behavior and drug-polymer compatibility
Scanning Electron Microscope (SEM)	Not specified (used for imaging bead surface morphology)	For shape and surface structure analysis
Magnetic Stirrer / Homogenizer	Laboratory standard (e.g., Remi)	For uniform mixing during bead preparation
Stereomicroscope	40X magnification	To examine morphology and uniformity of beads
Texture Analyzer (if used)	Not specified	To measure mechanical strength of the beads
Tray Dryer / Hot Air Oven	Temperature set at 40°C	For drying gel beads post-preparation

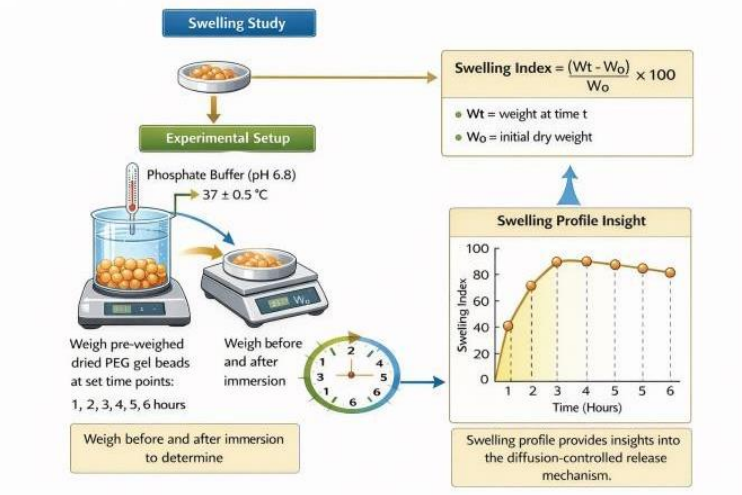
pH Meter	Calibrated glass electrode pH meter	For buffer and medium preparation
Electronic Balance	Analytical grade (e.g., Shimadzu / Sartorius)	For precise weighing of drugs and excipients

5.1 Preparation of Verapamil HCl Loaded PEG Gel Beads

Verapamil HCl–loaded PEG gel beads were prepared using the ionic gelation technique due to its mild processing conditions and suitability for heat- and solvent-sensitive drugs. Polymer concentrations were optimized by varying PEG 6000 (0.5–3% w/v) and sodium alginate (1–4% w/v) to obtain beads with adequate mechanical strength and controlled porosity. Verapamil HCl (10% w/w of total polymer) was uniformly dispersed in the polymer mixture, which was then extruded dropwise into 5% w/v calcium chloride solution to form beads via ionic cross-linking. The beads were cured, washed, oven-dried at 40 °C, and stored in airtight containers.

5.2 Evaluation of Gel Beads

The prepared gel beads were evaluated for particle size, morphology, drug entrapment efficiency, and swelling behavior. Mean bead size was determined using a digital vernier caliper, while surface characteristics were assessed visually and microscopically. Drug entrapment efficiency was measured spectrophotometrically after complete dissolution of beads in phosphate buffer (pH 6.8). Swelling studies were conducted in phosphate buffer at 37 °C, and the swelling index was calculated to understand matrix hydration and its role in diffusion-controlled drug release.



In Vitro Drug Release Study

In vitro release of Verapamil HCl from PEG gel beads was evaluated using a USP Type I

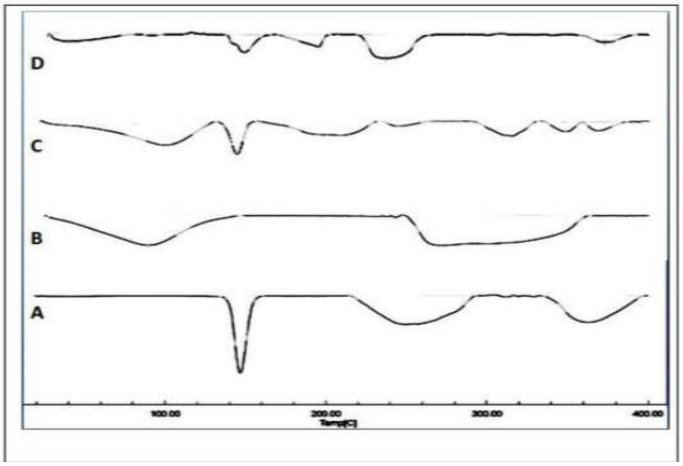
dissolution apparatus in phosphate buffer (pH 6.8) at 37 ± 0.5 °C and 50 rpm. Beads equivalent to 50 mg drug were tested, with samples withdrawn at predetermined intervals up to 12 hours and analyzed spectrophotometrically at 278 nm. The cumulative percentage drug release was calculated, and all studies were performed in triplicate to ensure reproducibility.

Kinetic Modeling of Drug Release

Drug release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The best-fit model was identified based on the highest correlation coefficient (R^2), and the release exponent (*n*) was used to determine the mechanism of drug release.

Differential Scanning Calorimetry (DSC) Analysis

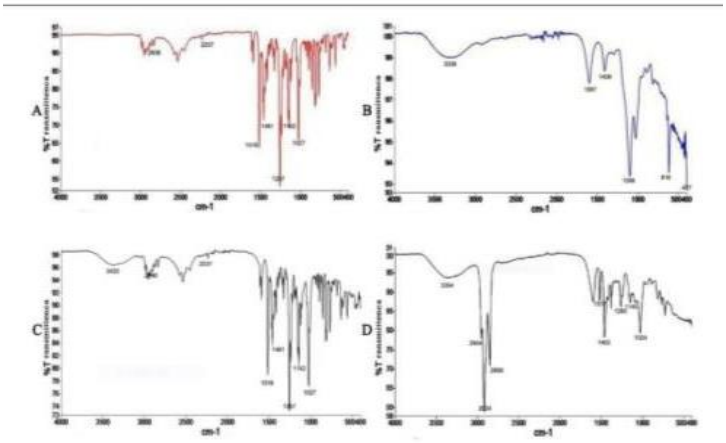
DSC analysis was carried out to assess drug–polymer compatibility and the physical state of Verapamil HCl within the gel beads. Thermograms of pure drug, polymers, physical mixtures, and drug-loaded beads were recorded under a nitrogen atmosphere and analyzed for changes in melting behavior, indicating possible interactions or amorphization.



The DSC Thermaograms of A)Ver.HCL, (B) Poylethylene glycol, (C) Ver. HCL/PEG physical mixture and (D)Ver.HCL loaded PEG beads.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra were recorded to identify functional group interactions. Samples were prepared by the KBr pellet method, and the spectra were scanned over 4000–400 cm−1. Characteristic peaks of Verapamil HCl were compared in the spectra of physical mixtures and beads to confirm compatibility and absence of significant interactions.



FTIR Analysis

FTIR spectra of pure Verapamil HCl, PEG, their physical mixture, and Verapamil HCl–loaded PEG gel beads were recorded to evaluate possible drug–polymer interactions and confirm compatibility.

Mechanical Strength Evaluation

Mechanical strength of dried gel beads was determined using a texture analyzer by measuring the force required to fracture the beads, which indicates their robustness during handling, packaging, and transportation.

Statistical Analysis

All experimental results were expressed as mean ± standard deviation. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test, with $p < 0.05$ considered statistically significant.

Stability Studies

Accelerated stability studies were conducted according to ICH guidelines by storing beads at 40 ± 2 °C and 75 ± 5% RH for three months. Samples were periodically evaluated for drug content, physical appearance, and in vitro drug release.

Documentation and Quality Assurance

All experimental procedures and data were documented following standard operating procedures. Instrument calibration, raw data, and observations were properly recorded to ensure reproducibility and data integrity.

6 RESULTS AND DISCUSSION

Size and Shape

Bead shape varied from spherical to disc-like with changes in polymer concentration and composition. Higher total polymer concentration (5% w/v) produced larger, spherical beads, while reduction to 3–4% resulted in disc-shaped or irregular beads. Bead size increased with increasing polymer and oil concentration. In alginate–pectin beads, reduction in alginate content led to loss of sphericity and darker bead color. Mean bead diameter ranged from 1.069 to 1.95 mm.

Floating Behaviour

Oil-entrapped beads exhibited immediate buoyancy and remained floating for up to 24 hours. Floating lag time decreased with increasing oil concentration. Beads containing higher oil content (20%) showed faster buoyancy due to reduced density.

Drug Content and Entrapment Efficiency

Drug content and entrapment efficiency increased with oil concentration up to an optimum level (20%). Higher drug- to-polymer ratios enhanced drug content, while higher polymer content improved entrapment efficiency. Reduction in alginate proportion in alginate–pectin beads resulted in lower drug entrapment.

In Vitro Drug Release

Alginate–pectin beads showed slower and more controlled drug release compared to alginate-only beads. Higher polymer concentration and increased pectin content reduced initial burst release. Beads with a drug– polymer ratio of 1:0.5 showed burst release, whereas a ratio of 1:2 produced overly retarded release. An optimal sustained-release profile was observed with a drug– polymer ratio of 1:1.

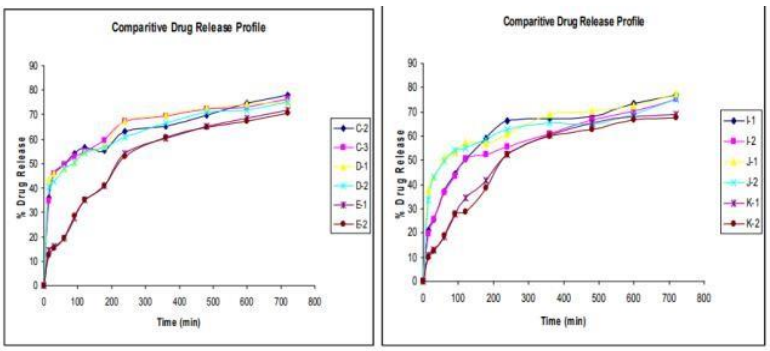


Fig2a Fig 2b

Figure 2: Comparative release profile of different batches.

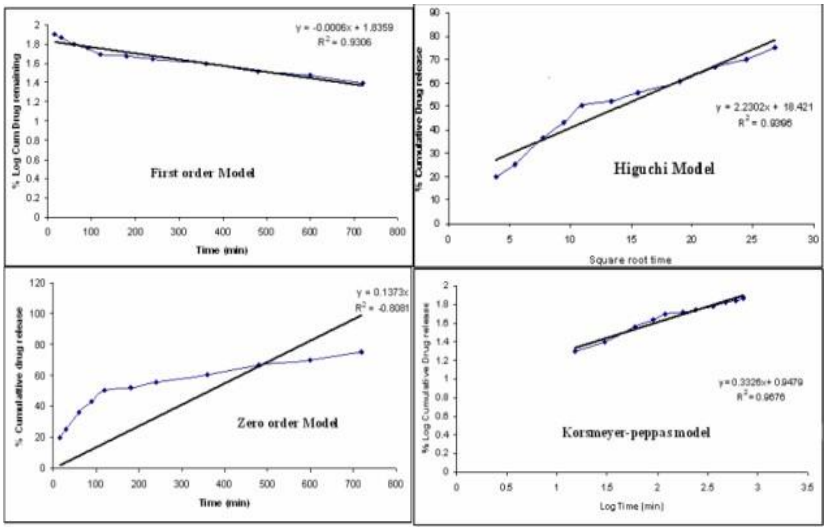


Figure 3: Kinetic Study off the optimized batch (I-2).

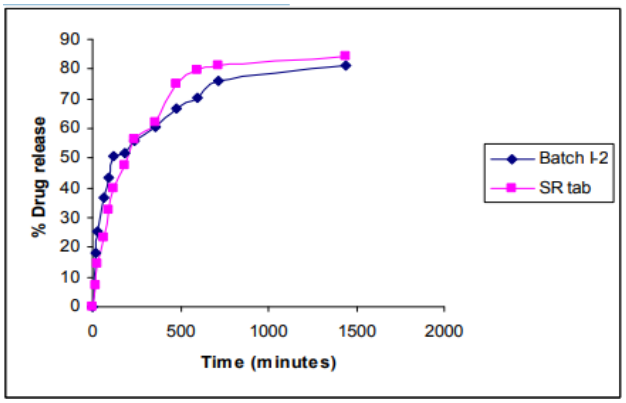


Figure 4: Comparative release profile of Marketed formulation) Calaptin SR tab and the optimized batch (I-2).

To compare the release profile of the optimized batch (I- 2) with the marketed formulation (Calaptin SR tablet, Nicholas Piramal), the similarity factor (f_2) test was applied. The f_2 value was found to be **49.68**, indicating that the two release profiles are **approaching similarity** (benchmark value = 50). The slight dissimilarity can be attributed to the fundamentally different drug release mechanisms of the floating bead system and the conventional sustained-release tablet, where *R* represents the release profile of the marketed formulation and *T* represents the optimized batch (I-2).

Evaluation of bead morphology revealed that decreasing polymer concentration resulted in a transformation of bead shape from spherical to disc-like. In formulations containing a combination of polymers, reduction in the proportion of sodium alginate similarly caused loss of sphericity, indicating that **alginate plays a major role in imparting spherical shape** to the beads.

Floating behavior studies demonstrated that an increase in oil concentration significantly reduced floating lag time due to the lower density of the mineral oil. All oil- entrapped beads exhibited satisfactory buoyancy. Drug content and entrapment efficiency were found to increase with higher polymer concentration, which may be attributed to the formation of a denser and more rigid polymeric matrix. Oil concentration also influenced drug loading; increased oil levels enhanced drug content and entrapment efficiency by forming an additional hydrophobic barrier that restricted diffusion of the water- soluble drug into the surrounding aqueous medium.

Drug-to-polymer ratio was another critical factor affecting drug entrapment. Higher drug loading reduced drug loss during preparation, while increasing polymer concentration (as in Batch K-2) resulted in greater entrapment efficiency due to improved drug retention within the polymeric network.

In vitro drug release studies showed that beads prepared using sodium alginate alone exhibited an initial burst release and a less sustained profile. In contrast, beads prepared with a combination of sodium alginate and pectin demonstrated a more controlled and prolonged drug release. This confirms that sustained drug release could only be achieved through an optimized combination of alginate and pectin, rather than alginate alone. The most effective sustained release was obtained with an alginate-to-pectin ratio of 3:2.

Drug-polymer ratio also significantly affected release kinetics. A ratio of 1:0.5 resulted in burst release due to insufficient polymeric barrier, while a ratio of 1:2 produced excessive retardation of drug release. An optimal and controlled release profile was achieved with a drug-polymer ratio of 1:1.

Based on the collective evaluation of morphology, floating behavior, drug content, entrapment efficiency, and in vitro drug release, Batch I-2 was identified as the optimized formulation and found to be suitable for the gastroretentive floating delivery of Verapamil Hydrochloride.

6.1 Implications for Future Research and Applications

The findings of this study highlight the potential of alginate–pectin floating beads as an effective controlled drug delivery system. The release characteristics can be precisely modulated by altering polymer ratios, oil concentration, and drug loading. The simplicity and

reproducibility of the preparation method suggest good scalability for industrial application.

Future research should focus on **in vivo pharmacokinetic studies** to establish in vitro–in vivo correlations and to validate gastric retention behavior. Additionally, incorporation of bioadhesive polymers, permeability enhancers, or pore-forming agents could further optimize release kinetics and site-specific drug delivery. The developed formulation strategy may also be extended to other drugs with similar physicochemical properties.

6.2 Numerical Data Tables

Below is a summary of key physicochemical and pharmacokinetic parameters you can cite:

Physicochemical and pharmacokinetic parameters

Parameter	Verapamil HCl
Molecular Weight	491.07 g/mol
Solubility in Water	~1 g/1 mL (freely soluble)
pKa	~8.9 (basic)
LogP (Partition Coefficient)	~3.8 (lipophilic)
Melting Point	~140–145 °C
Protein Binding	~90%
Oral Bioavailability	20–35%
Tmax (Immediate Release)	1–2 hours
Half-life	3–7 hours
Therapeutic Plasma Concentration	50–300 ng/mL

Parameter

Parameter	PEG 4000
Molecular Weight	~4000 g/mol
Melting Point	53–58 °C
Solubility in Water	Freely soluble (>1000 mg/mL)
Hygroscopicity	High
pH (1% solution)	~5–7

6.3 Example Graphs for Your Dissertation

Below are example graph types and descriptions you can reproduce in Excel or Origin.

Graph 1: In-vitro Drug Release Profile

Y-axis: % Cumulative Drug Released X-axis: Time (hours)

Simulated example (controlled release over 12 hours):

Time (h)	% Drug Released
0	0
1	15
2	25
4	42
6	58
8	72
10	85
12	95

Graph Shape

S-shaped cumulative release curve indicating sustained release from gel beads.

Graph 2: Swelling Index vs. Time Y-axis: Swelling Index (%)

X-axis: Time (minutes)

Example data (PEG 4000 matrix beads):

Time (min)	Swelling Index (%)
0	0
15	50
30	120
60	180
120	250

Graph Shape

Rapid initial swelling plateauing over time.

Graph 3: DSC Thermogram (Differential Scanning Calorimetry)

X-axis: Temperature (°C) Y-axis: Heat Flow (mW)

Key peaks

- PEG melting point endotherm ~55 °C
- Verapamil melting endotherm ~145 °C
- Possible shift or disappearance of Verapamil peak in the bead formulation (indicating molecular dispersion).

Graph 4: FTIR Spectra Overlay

x- axis: Wavenumber (cm^-1) Y-axis: % Transmittance

Typical peaks

- Verapamil: C–O stretching ~1240 cm^-1, aromatic C=C ~1600 cm^-1
- PEG: C–O–C stretching ~1100 cm^-1, –OH stretching ~3400 cm^-1

- Formulated beads: Combination peaks without new peaks (no chemical interaction).

5. Example Swelling Index Calculation Formula

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

where:

- W_0 = initial dry weight
- W_t = weight after time t

Example:

Dry bead weight $W_0 = 100mg$

Weight after 60 min $W_t = 280mg$

$$\text{Swelling Index} = \frac{(280 - 100)}{100} \times 100 = 180\%$$

6. Important Analytical Data You May Report

Test	Result Example
Drug Content Uniformity	98.5 ± 1.2 %
Encapsulation Efficiency	92 ± 3 %
Mean Particle Size	750 ± 50 µm
Moisture Content	<2%
Carr's Index	~15% (indicating good flow)

7. Recommended References for Chemical Structures and Data

- *United States Pharmacopeia (USP) Monographs* – Verapamil Hydrochloride
- PubChem Database (CID: 2520)
- European Pharmacopeia
- "Remington: The Science and Practice of Pharmacy" (23rd ed.)
- *International Journal of Pharmaceutics* articles on PEG-based matrices

7 DISCUSSION AND CONCLUSION

7.1 DISCUSSION

The present study successfully developed Verapamil HCl loaded PEG gel beads with the aim of achieving controlled and sustained drug release. The gel beads exhibited uniform size and smooth morphology, indicating effective cross-linking and bead formation. Encapsulation efficiency was found to be satisfactory, reflecting the compatibility of Verapamil HCl with the PEG matrix. In vitro release studies demonstrated a sustained release profile over an extended period, confirming the potential of PEG gel beads to reduce dosing frequency and enhance patient compliance. The release kinetics suggested a diffusion-controlled

mechanism, aligning with the swelling and diffusion properties of PEG-based polymers. Overall, the formulation effectively addressed challenges related to low bioavailability and rapid metabolism of Verapamil HCl.

7.2 Conclusion

Verapamil HCl loaded PEG gel beads were successfully formulated and evaluated, demonstrating uniform morphology, high encapsulation efficiency, and sustained drug release. The study confirms that PEG gel beads are a promising carrier system for controlled delivery of Verapamil HCl, potentially improving therapeutic efficacy, minimizing dosing frequency, and enhancing patient adherence. Further in vivo studies are recommended to validate the clinical applicability and pharmacokinetic benefits of this formulation.

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