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Formulation and *in vitro* Evaluation of Verapamil Hydrochloride Floating Tablets

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Abstract: The present research work aims to formulate and evaluate novel sustained-discharge floating tablets of verapamil hydrochloride (VPH) which is used for the treatment of hypertension. We aim to use a direct compression technique to formulate the floating tablets. The characterization of the formulation of VPH was carried out by employing FT-*IR* and DSC studies, which showed that there was no chemical interaction between the drug and polymers, such as HPMC K100M, chitosan, and sodium alginate. The tablets are designed to have good *in-vitro* buoyancy, and they remain afloat in the dissolution medium. The best formulation (F7) is chosen based on its maximum drug discharge (91.91±2.25%) and drug content (97.20±2.71%) over 12h. The discharge kinetics of the drug from the tablets are analyzed using various mathematical models, such as zero order, first order, Higuchi, and Korsmeyer's equations. These models help explain and predict drug discharge behavior over time. The study concludes that a proper balance between the sustained-release polymer and the gas-forming agent is essential for efficient *in-vitro* buoyancy and sustained drug discharge. Formulation F7, which utilized sodium alginate, appears to be the most promising in terms of drug discharge and content.

Keywords: Chitosan, Floating, Release, Tablets, Verapamil.

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1. INTRODUCTION

Oral drug delivery is widely regarded as the most advisable and preferred method of administering drugs for their systemic effects. More than 90% of the formulations manufactured today are ingested orally. This class of formulation is the most accepted worldwide, and the major attention of the researcher is towards this direction. In the upper intestine, the major part of drugs is preferentially absorbed. So, Gastro retentive drug delivery systems are preferred. Within Floating Drug Delivery Systems (FDDS), the innovation lies in creating tablets that float in gastric juice[1]. It ensures that drugs remain within the stomach for an extended period, substantially prolonging their gastric residence time[2]. This extended retention offers several advantages, including improved bioavailability, increased therapeutic efficacy, reduced time intervals for drug administration, and potentially reduced dosing frequency, improving patient compliance. Such dosage forms are particularly favorable for drugs with an absorption window in the stomach, high solubility in the acidic gastric environment, and those that are sensitive to the alkaline pH of the intestinal In the context of the study; the focus is on Verapamil Hydrochloride (VPH), 5–[(3, 4–Dimethoxyphenethyl) methyl – amino] –2 (3, 4–dimenthoxyphenyl) – 2– isopropyl valeronitrile hydrochloride, a coronary vasodilator introduced in 1962[3]. It belongs to the first class of the Biopharmaceutics Classification System (BCS). Its oral absorption is around 90%, reaching peak concentration within 1-2 h. However, its bioavailability is hindered by hepatic metabolism, resulting in a low bioavailability of 10-20% and a relatively short half-life of 3.7h [4]. It has more than six fold greater solubility in 0.1 mol/l hydrochloride acid than in water, constituting the key argument for better verapamil hydrochloride absorption in the stomach. VPH applies to treating conditions such as Hypertension, Angina Pectoris, Cardiac Arrhythmias, and cluster headaches. Its mechanism includes dilating coronary blood vessels to augment blood and oxygen supply to the heart. Additionally, it reduces the heart's workload, leading to decreased myocardial oxygen consumption. Gastro retentive drug delivery systems (GRDDS) have gained significant attention in pharmaceuticals due to their potential to enhance drug bioavailability, control release rates, and improve patient compliance. The stomach's rapid emptying poses a challenge for the effective delivery of drugs with a short absorption window, low solubility, or those targeting specific sites in the gastrointestinal tract. In response to these challenges, researchers have been exploring innovative approaches to extend the residence time of drugs in the stomach, giving rise to gastroretentive drug delivery. Early research in gastroretentive drug delivery predominantly focused on developing floating dosage forms, mucoadhesive systems, and expandable systems. These early efforts paved the way for understanding the basic principles of GRDDS. Researchers also experimented with various polymers, buoyancy aids, and other excipients for prolonged gastric retention. Early research in gastroretentive drug delivery had limitations such as variable retention times, inconsistent drug release profiles, and potential issues with patient comfort. Our study addresses these gaps by presenting a comprehensive review of recent advancements in GRDDS, emphasizing their design, formulation, and evaluation methods. We also critically analyze the limitations of previous research and propose novel strategies to overcome these limitations, leading to more efficient and patient-friendly GRDDS. The need for gastroretentive drug delivery systems is driven by several factors, including the treatment of localized gastrointestinal diseases, the need for controlled release of drugs with narrow absorption windows, and the enhancement of drug bioavailability. Additionally, GRDDS can improve the therapeutic outcomes of drugs that are prone to degradation or metabolism in the upper gastrointestinal tract. The novelty of gastroretentive drug delivery lies in its ability to prolong drug exposure to the stomach and the upper part of the small intestine. It improves drug absorption and offers the potential for site-specific drug delivery. Novel approaches in GRDDS include magnetic systems, bioadhesive microspheres, and stimuli-responsive systems, which aim to provide better control over drug release kinetics and retention. There are numerous techniques applied to achieve floatation. The design having a bulk density of less than 1 g/ml, with hydrocolloids to decrease water uptake and increase the duration of buoyancy, was investigated. Different types of hydrocolloids of natural and semisynthetic origin have been used for the formulations of HydroBalanced System forms. Many authors suggested polymers used in floating formulation are cellulose ether polymers as the first choice in the group of the different hydrocolloids, especially hydroxypropyl methylcellulose (HPMC). The novelty of gastroretentive drug delivery lies in its ability to prolong drug exposure to the stomach and the upper part of the small intestine. It improves drug absorption and offers the potential for site-specific drug delivery. Novel approaches in GRDDS include magnetic systems, bioadhesive microspheres, and stimuli-responsive systems, which aim to provide better control over drug release kinetics and retention. The crux of the research is the formulation and *in-vitro* evaluation of floating tablets containing VPH as an anti-hypertensive agent. It is achieved through a judicious combination of VPH and various excipients, including HPMC K100M, chitosan, and sodium alginate. Employing the direct compression method, the study aims to create tablets that retain their buoyancy in the stomach environment. This retention ensures prolonged gastric residence and holds the potential to enhance the bioavailability of the drug. By optimizing gastric retention time, the work could contribute to more effective treatment strategies for hypertension and associated conditions.

2. MATERIALS AND METHODS

2.1 Materials

VPH was obtained from Mylan Pharmaceuticals Private Limited, Bangalore. HPMC K100M, Chitosan, Sodium Alginate, Sodium Bicarbonate, Citric Acid, Lactose, Talc, and Magnesium Stearate were sourced from SD Fine Chemicals in Bangalore. Additionally, all remaining reagents used were of analytical (AR) grade.

2.2 Methodology

2.2.1 Pre-formulation Studies Solubility

The solubility of the drug was assessed in various solvents, including distilled water, methanol, chloroform, ether, and 0.1N HCl[5].

2.2.2 Melting point

The melting of VPH was determined using Thiel's Tube Method[6]. Thiel's Tube Method is a reliable technique for precisely determining the melting point of solid substances. The procedure begins with carefully preparing the powdered

sample, loaded into a capillary tube. This tube is placed vertically within a Thiel's tube setup, securely clamped to a heat-resistant surface. The sample is gradually heated, typically using a Bunsen burner or a dedicated melting point apparatus, while closely observing the substance within the capillary tube. The temperature at which the solid starts to melt is recorded as the melting point. The process can be repeated for accuracy or to detect impurities if needed. By calculating the average of multiple trials, researchers ensure the reliability of their results. Proper safety precautions, such as wearing safety goggles and gloves, are essential when working with heat sources and chemicals, making Thiel's Tube Method a valuable tool for accurate melting point determination in chemical and pharmaceutical laboratories.

2.2.3 DSC studies

Differential Scanning Calorimetry (DSC) studies evaluate the thermal properties of materials, particularly in the context of pharmaceuticals. The primary goal is to identify interactions, transformations, and stability of drug-excipient mixtures and determine the melting points, glass transition temperatures, and enthalpic changes associated with these substances. This analysis is vital for assessing pharmaceutical products' compatibility, formulation development, and stability. In a typical DSC procedure, a sample containing the drug and excipient is subjected to controlled heating or cooling, while a reference sample undergoes the same thermal treatment. The heat flow difference between the sample and the reference is recorded, generating a thermogram. By comparing the thermogram of the mixture to those of the pure components, physical and chemical interactions, as well as changes in thermal behavior, are identified, helping guide the formulation and ensure product stability.

2.2.4 Fourier Transform Infrared Spectroscopy

FTIR spectroscopy investigated the compatibility of VPH (pure drug) and excipients intended for transdermal patch formulation. Using a Tensor 27 instrument and KBr pellets, spectra were obtained for the pure drug and the drug-excipient mixture. Notably, both spectra exhibited distinct sharp peaks indicative of specific functional groups. It suggests minimal chemical interactions between the drug and excipients, implying potential compatibility for transdermal patch formulation. Further studies may be warranted for comprehensive formulation optimization[7].

2.2.5 Method of Preparation of Floating Tablets

Floating tablets of VPH were prepared using the direct compression method, wherein various polymers, such as HPMC K100M, chitosan, and sodium alginate, were utilized. Additional components like sodium bicarbonate and citric acid were incorporated to facilitate floating, while lactose served as a component[8]. Talc and magnesium stearate were included in the formulation to act as glidant and lubricating agents, respectively (Table 1). This formulation strategy aimed to create tablets that remain buoyant in the stomach for prolonged drug discharge.

Table 1: Formulations of Floating Tablets of VPH

Batch	VPL (mg)	HPMC K100M(mg)	Chitosan (mg)	Sodium alginate (mg)	Sodium bicarbonate (mg)	Citric acid (mg)	Lactose (mg)	Talc (mg)	Magnesium stearate (mg)	Total weight (mg)
F1	120	50	-	-	30	10	32	5	3	250
F2	120	60	-	-	30	10	22	5	3	250
F3	120	70	-	-	30	10	12	5	3	250
F4	120	-	50	-	30	10	32	5	3	250
F5	120	-	60	-	30	10	22	5	3	250
F6	120	-	70	-	30	10	12	5	3	250
F7	120	-	-	50	30	10	32	5	3	250
F8	120	-	-	60	30	10	22	5	3	250
F9	120	-	-	70	30	10	12	5	3	250
F10	120	25	25	-	30	10	32	5	3	250
F11	120	-	30	30	30	10	22	5	3	250
F12	120	35	-	35	30	10	12	5	3	250

2.3 Evaluation of Floating tablets of VPH

2.3.1 Thickness

The thickness of the floating tablets was determined using a Digital Vernier caliper. Three tablets were measured, and the average thickness of these three tablets was considered as the representative thickness of the tablets. This method helps ensure a reliable measurement of tablet thickness by accounting for potential variations between individual tablets[9].

2.3.2 Hardness

Tablet hardness, representing the force needed to fracture a tablet under diametrical compression, was evaluated using the Monsanto tester. Three tablets were individually subjected to this testing method. The force required to break each tablet was measured, and subsequently, the average of these forces was calculated. This approach provides a reliable assessment of the tablets' mechanical strength and aids in ensuring consistent tablet quality and manufacturing processes [10].

2.3.3 Friability

Ten tablets were precisely weighed and introduced into Roche's Friabilator, which underwent 100 revolutions. Following this, the tablets were de-dusted and reweighed. Tablets that experienced a weight loss of < 1% were deemed compliant[11]. This friability test assesses the tablets' durability and resistance to abrasion during handling and transportation, helping ensure their structural integrity and quality (e.q. 1).

$$\%\ friability\ =\ Weight\ initial - Weight\ (final)/Weight\ (initial)X100 \text{---}\ (1)$$

2.3.4 *Weight Variation*

Twenty tablets were randomly selected and individually weighed. The average weight of these tablets was determined, and the standard deviation was calculated to assess weight variation. Following pharmacopoeial standards, the tablets are acceptable if no more than two tablets fall outside the specified percentage limit and if none deviate by more than twice that percentage. This procedure ensures the uniformity of tablet weights and compliance with quality standards[12].

2.3.5 In Vitro Buoyancy Studies

The tablets were introduced into a 250 ml beaker that contained 200 ml of 0.1 N HCl. The duration taken for the tablet to ascend to the surface and achieve flotation was recorded as the floating lag time (FLT). Additionally, the tablet's duration remained afloat and was measured as the total floating time (TFT)[13]. These parameters provide insights into the tablet's buoyancy and disintegration characteristics in the acidic environment, which are crucial for certain drug delivery applications, like gastroretentive formulations[14].

2.3.6 *Drug Content Uniformity*

Ten tablets were chosen randomly, and their weights were recorded. These tablets were then crushed to form a triturate. A portion of the triturate equivalent to 100 mg of VPH was transferred to a 100 ml volumetric flask and dissolved in 0.1 N HCl. The solution was subjected to sonication for 30 min and then filtered through a 0.45 µm membrane filter. After appropriate dilutions, the resulting solution's absorbance was measured using a UV-visible spectrophotometer at a wavelength of 278 nm, with 0.1 N HCl as the blank reference. This procedure is used to quantitatively determine the concentration of VPH in the sample, utilizing its absorbance properties in the UV-visible range[15].

2.3.7 *In-vitro Dissolution Studies*

The discharge rate of all formulated tablets was investigated throughout 12 h, utilizing a USP Type II dissolution apparatus employing the Rotating Paddle method at 75 rotations per minute (rpm). The distance between the paddle and the bottom of the dissolution vessel was kept at 2.5±0.2 cm. The dissolution medium consisted of 900 ml of 0.1N HCl with a pH of 1.2, and it was maintained at a temperature of 37±0.5°C. At specific time intervals during the 12 h dissolution study, 5 ml samples were withdrawn, and a fresh dissolution medium was introduced to the vessel. The withdrawn samples were appropriately diluted and subjected to analysis for VPH content using a UV-visible spectrophotometer at a wavelength of 278 nm. This procedure enables the assessment of the discharge profile of VPH from the tablets in a controlled and standardized dissolution environment, mimicking conditions in the gastrointestinal tract[14].

2.3.8 *Swelling Index studies*

The swelling behavior of the polymers was evaluated based on their water absorption and expansion capacity. The water uptake study for the tablet was conducted using a USP dissolution apparatus type-II, employing 900 ml of pH 1.2 HCl buffer at a rotation speed of 100 rpm. The temperature of the medium was kept consistent at 37±0.5°C throughout the experiment[16]. At specified intervals, tablets were withdrawn from the medium, excess water was gently blotted off, and their weights were measured. This study enables the assessment of how effectively the polymers in the tablet absorb water and swell over time, which is important for understanding the tablet's behavior in a simulated physiological environment (e.q.2).

$$\text{Swelling Index (\%)} = \frac{(\text{weight of the swollen Tablet-Initial weight of the tablet})}{\text{Initial weight of the tablet}} \text{ X } 100$$

2.3.9 *Kinetics of drug discharge*

The drug discharge kinetics and mechanism were investigated using in-vitro drug discharge data from the discharge study. The data was plotted using various mathematical models, including Zero-order, First order, Higuchi, and Korsmeyer-Peppas. The plots were then analyzed, and the determination coefficient values (r^2) were compared. Based on the r^2 values, the most suitable discharge model was chosen as the best-fit representation of the drug discharge behavior[17, 18]. This approach helps to identify and understand the underlying mechanisms of drug discharge from the formulated tablets, aiding in the optimization of the drug delivery system.

2.3.10 *Stability studies*

The formulation of optimized VPH tablets was packed in an amber-colored bottle and aluminum foil laminated on the upper part of the bottle, and these packed formulations were stored in a stability chamber. A stability study of formulations was performed at accelerated stability conditions, i.e., 40 ± 2°C temperature and 75 ± 5% relative humidity for 3 months. The samples were withdrawn at 1, 2, and 3 monthly intervals and evaluated for physical parameters such as drug content, *in vitro* drug release, and floating behavior.

3. STATISTICAL ANALYSIS

The statistical data, initially provided as mean ± standard deviation (SD), were analyzed using Microsoft Excel 2016. The dataset was further examined using Excel's built-in functions and tools. Additional statistics like confidence intervals were calculated, and visual representations, such as bar charts and histograms, were generated. Statistical tests, including t-tests and ANOVA, were conducted to assess the significance of differences between means when applicable. This approach streamlined the analysis process, facilitating data interpretation and enhancing the accessibility of findings.

4. RESULTS

4.1 *Solubility studies*

Solubility studies were conducted to assess the solubility of VPH in various solvents. The results indicated that VPH exhibited slight solubility in water, higher solubility in methanol, and solubility in chloroform. However, it was found

to be insoluble in diethyl ether. These findings provide valuable information about the compound's solubility characteristics in different solvent systems, which is essential for formulation and drug delivery considerations.

4.2 Melting point

The melting point of VPH was determined using Thiel's tube method, yielding a value of 142.33±1.85°C. This result aligns with the specified monograph, affirming the drug's purity. Matching the expected melting point signifies the high quality and consistency of the VPH sample analyzed.

4.3 Determination of λ_{max}

When a standard solution of VPH with a concentration of 10 µg/ml was subjected to UV-Visible spectrophotometry within the wavelength range of 200 to 400 nm, the highest absorbance was observed at a wavelength of 278 nm. This characteristic absorption peak at 278 nm is used as a reference point for further analysis and quantification of VPH in samples, as it corresponds to the wavelength where the compound exhibits its maximum absorbance.

4.4 Standard calibration curve

A series of drug solutions with concentrations ranging from 5 to 25 µg/ml were prepared, and their corresponding absorbance values were measured. A calibration curve was then constructed using these data points. Notably, the calibration curve displayed excellent linearity with a coefficient of determination (r^2) value of 0.9981. This high r^2 value indicates that the data adheres closely to the Beers-Lambert law, demonstrating the relationship between concentration and absorbance for VPH. This linearity underscores the validity of using the UV-visible spectrophotometric method for quantitative analysis of VPH within the given concentration range (Figure 2A).

4.5 DSC thermos grams

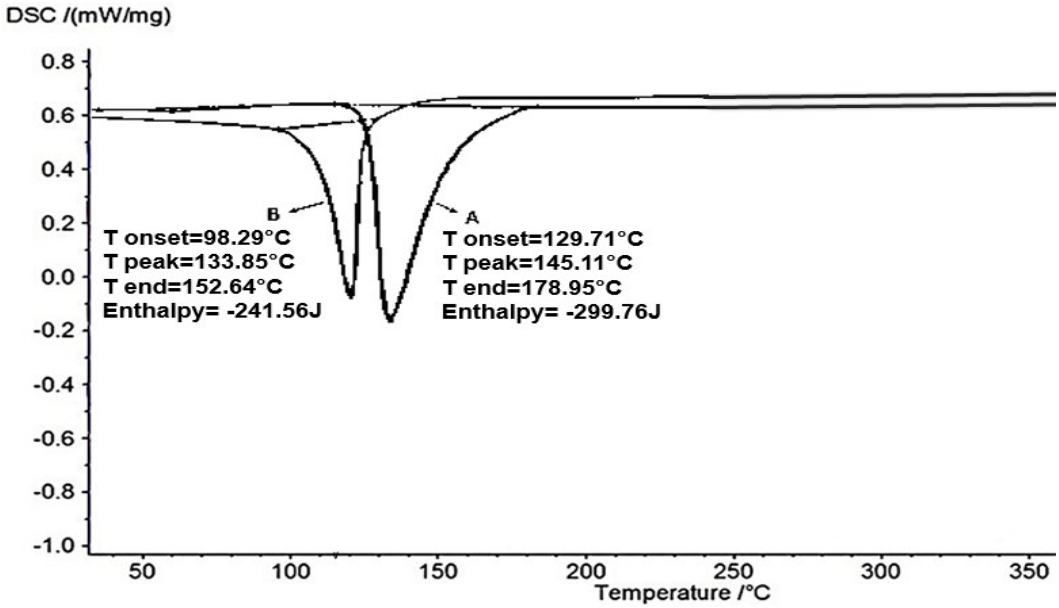

Fig 1: DSC thermos grams A) pure Verapamil B) Verapamil with excipients

4.6 FTIR Spectroscopy

The compatibility of VPH with the excipients used was investigated through FTIR spectra analysis. By comparing the FTIR spectra of VPH with those of the excipients, potential interactions or changes in functional groups can be identified, helping to assess the compatibility between the drug and the excipients in the formulation (Figure 1). This analysis is crucial to ensure the stability and effectiveness of the final product.

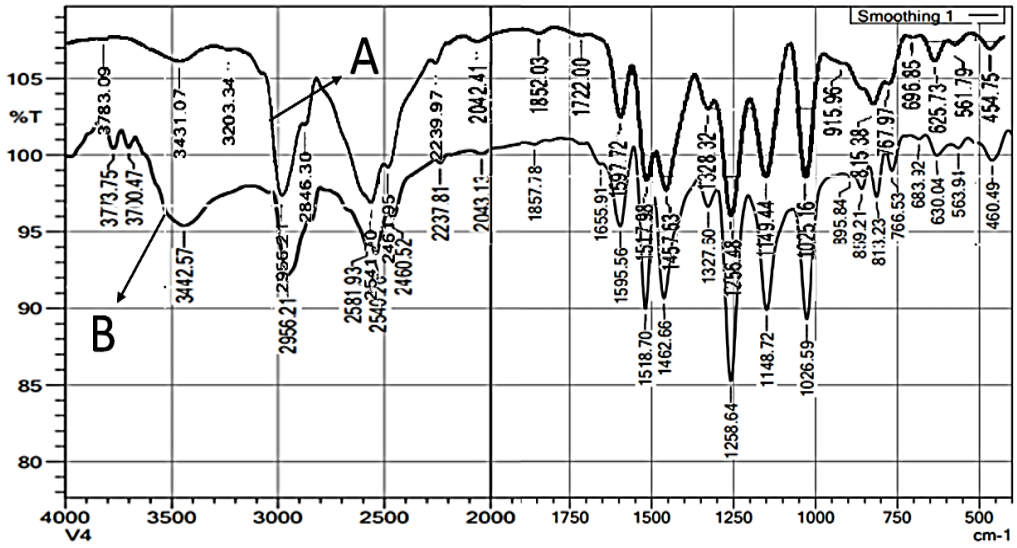

Fig 2: FIIR spectrum of pure drug VPH (A) and VPH with excipients used (B)

4.7 Pre-Compression Evaluation Parameters

Assessing pre-compression parameters across different powder blends (F1 to F12) offers valuable insights into crucial aspects like flow characteristics, compressibility, and interactions between particles. These factors hold significant importance in tablet formulation and manufacturing processes. The angle of repose values, spanning from 27.77°±0.89 to 30.86°±0.45, indicate favorable flow properties of the powder blends. It suggests that the particles possess a tendency to flow smoothly. Carr's index values, ranging from 7.21±0.16 to 14.8±0.70, reflect variable degrees of compressibility among the powders. This parameter indicates how easily the powders can be compressed into tablet form. Similarly, Hausner's ratio values, ranging from 1.07±0.07 to 1.19±0.05, also emphasize diverse compressibility levels (Table 2). Hausner's ratio is indicative of the ease of powder flow and compressibility. In conclusion, these pre-compression parameters collectively offer crucial insights into the feasibility and potential challenges in tablet formulation and production based on the powders' behavior and characteristics.

Table 2: Pre Compression Evaluation Parameters of Powder blend

Batch	Parameter				
	Angle of repose(°)	Bulk density (g/cm^3)	Tapped density(g/cm^3)	Carr's index (%)	Hausner's ratio
F1	29.70±0.42	0.337±0.07	0.388±0.07	12.8±0.22	1.14±0.07
F2	29.97±0.80	0.317±0.07	0.355±0.01	12.9±0.66	1.13±0.06
F3	29.98±0.79	0.310±0.01	0.354±0.08	12.2±0.22	1.13±0.05
F4	30.64±0.74	0.369±0.01	0.433±0.09	14.8±0.77	1.17±0.04
F5	29.96±0.79	0.372±0.04	0.447±0.01	12.8±0.05	1.19±0.05
F6	29.98±0.79	0.318±0.09	0.360±0.05	11.4±0.37	1.13±0.04
F7	27.77±0.89	0.358±0.00	0.386±0.06	7.21±0.19	1.07±0.07
F8	28.84±0.78	0.322±0.01	0.364±0.04	11.3±0.77	1.12±0.02
F9	29.14±0.36	0.338±0.03	0.366±0.05	7.67±0.20	1.08±0.04
F10	30.86±0.45	0.321±0.04	0.369±0.08	12.6±0.99	1.14±0.02
F11	30.9±0.516	0.326±0.07	0.374±0.01	12.7±0.88	1.14±0.01
F12	30.53±0.01	0.310±0.01	0.352±0.03	12.4±0.32	1.13±0.07

Values in mean±SD

4.8 Post-Compression Evaluation parameters

4.8.1 Thickness

The thickness of the prepared tablets ranged from 3.90±0.14 mm (F-5) to 4.01±0.01 mm (F-7). In evaluating the formulated tablets, their thickness was a key parameter assessed, consistently measuring around 4 mm across all tested formulations. Notably, this uniform thickness was maintained across different formulations, highlighting the quality control measures during manufacturing. This consistency in tablet thickness is significant for ensuring uniform drug content and dissolution rates, thus contributing to the overall effectiveness and reliability of the tablets.

4.8.2 Hardness results

The prepared tablets underwent a hardness evaluation, revealing consistent results across all formulations. Hardness values ranged from 5.33±0.57 (F-1) to 6.60±0.17 (F-8) kg/cm². These findings indicate that the tablets exhibited satisfactory mechanical strength, a vital attribute ensuring their robustness and integrity when being handled and used. This mechanical resilience contributes to the tablets' overall quality and usability.

4.8.3 Uniformity in weight

The prepared tablets were subjected to a weight variation assessment, revealing consistent outcomes across the

formulations. Tablet weights ranged from 0.243±0.01 (F-2) to 0.249±0.01 (F-9) mg. These results indicated compliance with acceptable standards, as the % weight variation fell within the specified limits of±7.5% of the designated weight, aligning with the guidelines outlined in the Indian Pharmacopoeia. It demonstrates the tablets' adherence to rigorous quality control measures, ensuring consistent dosing and efficacy.

4.8.4 The loss of friability

Friability testing was performed on the prepared tablets, yielding values ranging from 0.393±0.05 to 0.803±0.11%. These outcomes suggest that the tablets experienced minimal abrasion or damage during testing, highlighting their capacity to endure mechanical strain and preserve structural integrity. This resilience is crucial in ensuring the tablets' durability and suitability for practical handling and use.

4.8.5 Results of floating constraints

A floating lag time assessment was performed on all formulations (F1 to F12) using 0.1N HCl. The observed floating lag time ranged from 29.66±0.57 to 6911±1.52 sec. This measurement indicates the time the tablets begin floating on the dissolution medium's surface, reflecting their buoyancy and ability to stay suspended. Notably, the prepared tablets exhibited buoyancy for over 12 hours, underlining their sustained capability to remain afloat in the medium.

4.8.6 Drug content

The formulated tablets were subjected to VPH content evaluation. The VPH content within the tablets varied from 90.12±4.30% (F3) to 97.20±2.71% (F-7). Among the formulations tested, formulation F-7 displayed the highest VPH content.

Table 3: Post-formulation evaluation parameters of VPH Tablets

Batch	Parameters						
	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Floating lag time (sec)	Floating time (h)	Drug content (%)
F1	4.00±0.01	5.33±0.57	0.246±0.05	0.425±0.05	32.33±0.57	>12	92.56±2.63
F2	4.00±0.02	5.66±0.28	0.243±0.01	0.393±0.05	33.31±1.54	>12	90.39±6.62
F3	3.90±0.22	5.35±0.57	0.246±0.05	0.530±0.25	29.66±0.57	>12	90.12±4.30
F4	4.00±0.04	4.83±0.28	0.245±0.05	0.667±0.05	69.11±1.52	>12	92.40±2.54
F5	3.90±0.14	5.43±0.40	0.246±0.05	0.526±0.28	62.58±0.57	>12	94.35±3.25
F6	4.00±0.01	5.20±0.20	0.247±0.02	0.800±0.01	66.66±0.57	>12	93.03±0.23
F7	4.01±0.01	6.33±0.28	0.248±0.02	0.321±0.05	33.33±1.54	>12	97.20±2.71
F8	3.90±0.19	6.60±0.17	0.244±0.05	0.457±0.05	41.34±0.57	>12	93.13±5.31
F9	4.00±0.01	6.16±0.28	0.249±0.01	0.796±0.01	40.27±1.52	>12	95.27±0.30
F10	4.00±0.05	5.50±0.50	0.245±0.05	0.396±0.05	64.19±2.08	>12	93.70±0.58
F11	4.00±0.07	5.39±0.28	0.246±0.05	0.803±0.11	50.37±2.51	>12	95.91±2.19
F12	4.00±0.05	5.45±0.57	0.247±0.03	0.530±0.25	45.67±2.08	>12	94.86±1.38

Values in mean±SD

4.8.7 Swelling Index

This study aimed to understand how different formulations of tablets behave in terms of swelling and how polymers influence the hydration and expansion of the tablets. A swelling index study measures the extent to which a material (in this case, the tablets) swells or expands in a specific solution. This study exposed the tablets to 0.1N HCl, likely to mimic the stomach's acidic environment. Notably, formulation F7, which incorporates sodium alginate as a polymer, exhibited the highest swelling index of 138.11±2.35%. On the other hand, formulation F3, containing HPMC-K100, displayed the lowest swelling index of 114.22±5.23% (Figure 2B). These findings reveal the distinct swelling characteristics of different formulations, shedding light on the influence of polymers on the tablets' hydration and expansion behaviors.

4.8.8 In-vitro Dissolution Studies

In-vitro dissolution studies were meticulously carried out on a range of VPH tablet formulations labeled F1 to F12. Such studies involve measuring the drug's discharge rate from its dosage form, in this case, tablets within a simulated physiological environment. The widely-used USP type II dissolution apparatus was employed for this purpose. The dissolution assessments were performed using 0.1N HCl, mirroring the acidic conditions of the stomach where the tablets are designed to dissolve and discharge the drug. These formulations integrated diverse concentrations of polymers, including HPMC K100M, chitosan, and sodium alginate polymers often harnessed in pharmaceutical formulations to adjust drug discharge patterns and enhance tablet properties. The dissolution profiles provide valuable insights into how the drug is gradually discharged from the tablets over time, offering a glimpse into the kinetics of drug discharge for each formulation. Notably, amid the array of formulations examined, formulation F7 emerged as distinct, featuring sodium alginate as a polymer component. Impressively, F7 achieved the highest drug discharge, liberating 91.91±2.25% of the drug throughout the 12h duration of the study (Figure 2C).

4.8.9 Accelerated stability studies results

The stability studies for the optimized formulation (F7) were carried out. There were no significant changes in the drug after storage for 3 months. The results of the stability are given in the following table.

Table 4 : Stability Studies results of the prepared floating tablets			
Parameters	**Drug content**	***In-vitro* release**	**Floating behavior**
Initial month	97.20±2.71	91.91±2.25%	> 12h
1st month	97.20±2.71	91.90±2.2%	> 12h
2nd month	97.19±2.70	91.90±2.24%	> 12h
3rd month	97.19±2.69	91.89±2.23%	> 12h

4.8.10 Kinetics of Drug Discharge

Kinetic discharge studies were systematically conducted on various formulations (F1-F9), yielding valuable insights into their specific discharge behaviors. The collected data underscores that all formulations adhere to Zero-order kinetics, as evidenced by the high r^2 values within the range of 0.9388 to 0.9915. Additionally, the Higuchi model aligns with their discharge patterns, indicating a diffusion-controlled mechanism. This assertion is supported by R2 values spanning 0.9602 to 0.9874. Notably, the Korsmeyer-Peppas plot signifies a super case II transport for all formulations, with n values spanning from 0.5060 to 0.9952 (Table 4) (Figures 2C, 2D, 2E, and 2F). These significant findings collectively contribute to a comprehensive understanding of the diverse formulations' discharge mechanisms and transport dynamics. Such insights serve as a foundation for refining and optimizing their performance in achieving controlled drug delivery, thus holding implications for the formulation's efficacy and therapeutic applications.

Table 5: Kinetic values for the VPH discharge from the dosage forms					
Batch	**Zero-order**	**First order**	**Higuchi model**	**Korsmeyer Peppas**	
				r^2	**N**
F1	0.9837	0.6317	0.9650	0.7440	0.5060
F2	0.9915	0.9323	0.9399	0.9898	0.7974
F3	0.9631	0.8403	0.9658	0.9893	0.8103
F4	0.9851	0.8860	0.9602	0.9952	0.9952
F5	0.9435	0.8462	0.9705	0.9870	0.7261
F6	0.9598	0.8192	0.9723	0.9871	0.8103
F7	0.9659	0.5969	0.9791	0.9960	0.8057
F8	0.9527	0.8465	0.9783	0.9909	0.7202
F9	0.9468	0.8509	0.9814	0.9917	0.6867
F10	0.9687	0.9005	0.9674	0.9909	0.7092
F11	0.9388	0.8335	0.9863	0.9891	0.6652
F12	0.9439	0.8377	0.9874	0.9901	0.6710

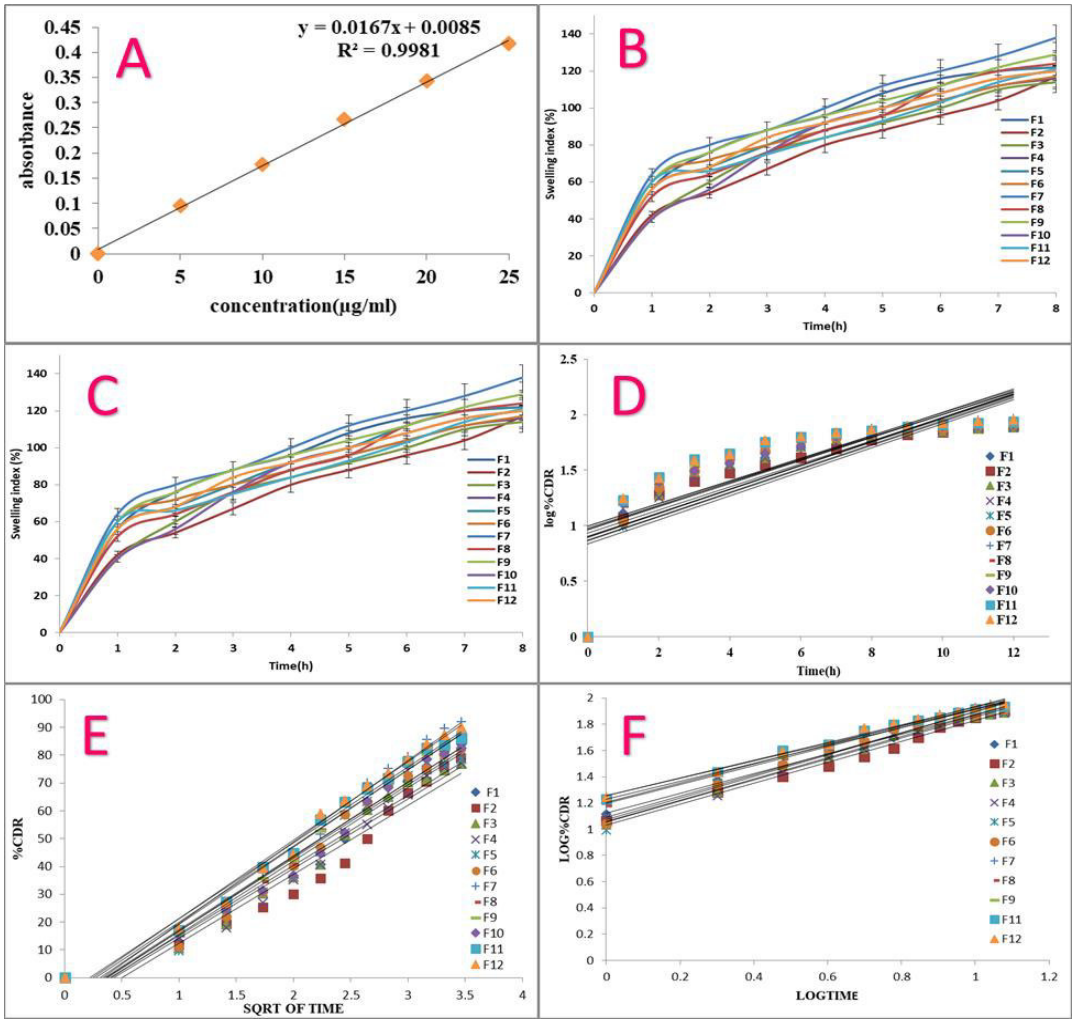

Fig.3. A) Calibration curve of VPH B) Swelling index; C) Zero-order discharge plots; D) First Order Plots; E) Higuchi's Plots; F) Korsemeyer- Peppas Plots of F1-F12 formulations

5. DISCUSSION

The solubility study of VPH in different solvents is critical in understanding the compound's dissolution behavior, which is slightly soluble in water, soluble in methanol and chloroform, and freely soluble in 0.1N HCl. It provides insights into potential solvents for drug preparation and selection of dissolution media[19]. This information is essential for formulation development and optimizing drug discharge profiles. The average melting point of 142.33±1.85°C for VPH signifies its purity and conformity with established standards[20]. A consistent melting point indicates the compound's chemical identity and quality, ensuring it's devoid of impurities and conforms to pharmacopoeial requirements. The calibration curve is fundamental for quantifying VPH content in various formulations. The constructed curve's adherence to Beer-Lambert's law within the range of 2-10 µg/ml, with a high r^2 value and low standard deviation, affirms the robustness and reproducibility of the method[21]. It means accurate and reliable quantification of the drug within specified concentrations. The FTIR analysis of VPH alone and in combination with polymers serves to identify potential interactions. The fact that the characteristic peaks of VPH and the drug-polymer combinations were unaffected indicates that the drug remained pure during formulation development[22]. It is vital to maintain the intended drug delivery and therapeutic effects. The angle of repose measures how freely particles flow and settle. A lower angle of repose indicates better flow characteristics, meaning the particles can flow easily and consistently[23]. The compressibility index, or Carr's, measures a powder's compressibility. It indicates how easily a powder can be compressed into tablets. A lower compressibility index signifies better compressibility[24]. Hausner's ratio is another measure related to powder compressibility. It's the ratio of tapped density to bulk density and provides insight into the powder's ability to be compressed and the inter-particle interactions within the blend. A higher Hausner's ratio indicates poorer flow and compressibility. These pre-compression parameters collectively provide information about the flow behavior, compressibility, and interparticle interactions of the powder blends[25]. This information is crucial for determining the feasibility of using these blends for tablet formulation and production processes. The powder blends with favorable flow characteristics, reasonable compressibility, and well-controlled interparticle interactions are more likely to produce consistent and high-quality tablet production. The evaluations of tablet properties encompass dimensions (thickness and diameter), hardness, friability, and weight variation. These tests ensure that the tablets are of the correct size, hardness, durability, and weight, maintaining uniformity and quality across batches. The buoyancy study provides insights into the tablets' floating behavior. All formulations floated for over 12 h and displayed varied floating lag times, indicating successful formulation for gastro-retentive applications[26]. Uniform drug content among different batches of tablets, along with the percentage values falling within the

specified range, assures consistent dosing and therapeutic effectiveness. The study involved observing and measuring the swelling behavior of each formulation at various time intervals. This investigation helps to understand how the tablets interact with the solution and absorb moisture over time[27]. The results, likely presented in a Figure, show the swelling behavior of all formulations over time. The key finding is a general increase in swelling for all formulations as time progresses. Among all the formulations tested, formulation F7, which includes sodium alginate as a polymer, displayed the highest swelling index of 138.11±2.35%. It means the tablets incorporating sodium alginate swelled the most in the given time frame when exposed to the acidic solution[28]. On the other hand, formulation F3, containing HPMC-K100, exhibited the lowest swelling index of 114.22±5.23% %. It suggests that HPMC-K100 imparts lower swelling characteristics to the tablets than sodium alginate. The distinct swelling characteristics of different formulations highlight how the choice of polymer influences the hydration and expansion behaviors of the tablets[29]. Based on the results, sodium alginate enhances swelling more significantly than HPMC-K100. The swelling index study conducted in an acidic solution provides insights into how different formulations of tablets react in terms of swelling behavior[30]. The higher swelling index of formulation F7 with sodium alginate and the lower index of formulation F3 with HPMC-K100 illustrate the impact of polymers on the tablets' hydration and expansion behaviors. This information is valuable for understanding how the tablets will behave in a biological environment and can contribute to optimizing tablet formulation design[31].The fact that formulation F7 with sodium alginate showed the highest drug discharge suggests that the composition of the tablet formulation has a significant impact on drug discharge kinetics[32]. Different polymers can influence the dissolution rate and discharge characteristics of the drug. The observation that sodium alginate enhanced drug discharge from the tablets underscores its potential as a polymer to improve the performance of the VPH tablets. It suggests that sodium alginate can modify drug discharge and potentially achieve the desired therapeutic effect[33]. The *in-vitro* dissolution studies reveal how different formulations of VPH tablets containing various polymer concentrations affect drug discharge. Formulation F7, containing sodium alginate, demonstrated the highest drug discharge, showcasing the potential of sodium alginate as a polymer to enhance drug discharge kinetics in tablet formulations[34].

6. CONCLUSION

The formulation and evaluation of a gastro retentive floating drug delivery system for VPH tablets were conducted to achieve sustained drug action over 12h. Employing a direct compression technique, the tablets were formulated using a combination of polymers, including HPMC K100M, chitosan, and sodium alginate. Rigorous evaluations were carried out to ensure the tablets' quality and performance. Compatibility studies utilizing FTIR spectroscopy revealed no interactions between the drug and excipients. The tablets' physicochemical properties fell within acceptable limits, demonstrating their consistent characteristics. In-vitro drug discharge studies were conducted in a simulated stomach environment (0.1N HCl) to assess the discharge profiles over 12h. Among the various formulations tested, formulation F7 emerged as the optimized choice based on comprehensive physico-chemical evaluation criteria. In summation, the developed gastro retentive floating drug delivery system presents a promising approach for treating hypertension, with successful drug discharge, absence of drug-excipient interactions, and the selection of an optimized formulation suggesting its potential efficacy in achieving prolonged drug discharge for therapeutic benefit.

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8. AUTHORS CONTRIBUTION STATEMENT

All authors equally contributed to the research, manuscript preparation and publication.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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