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Research Article

Beta Histamine Floating Tablets

Innovative Formulation and Evaluation of Betahistine Floating Tablets for Vertigo Management

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Abstract: Floating tablets are designed to improve the effectiveness and consistency of medication delivery. These specialized oral drug delivery systems are engineered to float on the gastric fluid in the stomach for an extended period, ensuring prolonged gastric retention that leads to a slow and controlled drug release, ultimately enhancing its bioavailability and therapeutic efficacy. Meniere's disease comprises recurrent spontaneous rotatory vertigo spells that patients describe as a spinning or whirling feeling and sensorineural hearing loss (SNHL) accompanied by recruitment and tinnitus. This study aimed to create buoyant tablets containing Betahistine (BTH) for treating Meniere's disease, designed to float in fluids and discharge the drug gradually. The approach involved the utilization of HPMC K4M 100 and Chitosan in combination as agents for swelling. Gas generation was facilitated by sodium bicarbonate and citric acid, while lactose was incorporated as a bulking agent. Tablets were fabricated using the direct compression technique and subjected to various assessments, including thickness, hardness, weight consistency, friability, BTH content, swelling capacity, buoyancy, and BTH release patterns. Notably, FTIR analyses indicated the absence of significant interactions between the BTH and its constituents. This comprehensive strategy underscores the potential of these tablets as a reliable and enduring treatment choice for Meniere's disease. Among nine formulations, F5 displayed the least BTH discharge (73.47±1.27% over 12 h), while F2 demonstrated the highest discharge (85.92±2.36% over 12 h). These findings highlight formulation F5's potential for controlled BTH discharge, which could be beneficial in managing Meniere's disease symptoms. This thorough investigation contributes to optimizing the formulation to treat Meniere's disease with buoyant tablets incorporating Betahistine efficiently.

Keywords: Betahistine, Chitosan, Citric acid, Floating, Meniere's disease, Tablets.

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1. INTRODUCTION

During the last two decades, there has been a remarkable increase in interest in controlled-release drug delivery systems. This is due to various factors, viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, the discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Nowadays, controlled release technology is also being applied to veterinary products[1]. The Oral route of drug administration is the most important method of administering drugs for systemic effect. Oral delivery is the most popular route of drug administration due to its versatility, ease of administration, and patient compliance[2]. To achieve and maintain the concentration of the administered drug within the therapeutically effective range, it is often necessary to take the dosage several times, resulting in fluctuating levels in plasma. Controlled drug delivery systems have been introduced to overwhelm the drawbacks of fluctuating drug levels associated with conventional dosage forms[3]. The oral route is the preferred route of administration of drugs because of the low cost of therapy, ease of administration, and increased patient compliance. However, the poor bioavailability (BA) of orally administered drugs is still challenging, though extensive advancements in the drug discovery process are made[4]. Patient compliance has been observed when taking oral dosage forms due to the ease of administration and handling. Many advancements have been seen in oral controlled drug delivery systems in the last few decades. But still, the oral sustained drug delivery system is complicated by limited gastric residence time. Rapid GI transit can prevent complete drug release in the absorption zone and reduce the efficacy of the administered dose since most drugs are absorbed in the stomach or in the upper part of the small intestine. To overcome these limitations, various approaches have been proposed to increase gastric residence of drug delivery systems in the upper part of the gastrointestinal tract, such as floating drug dosage systems (FDDS) [5]. GRDDS can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help continuously release the drug before it reaches the absorption window, thus ensuring optimal bioavailability[6]. Floating tablets are designed with the primary objective of improving the effectiveness and consistency of medication delivery. These specialized oral drug delivery systems are engineered to float on the gastric fluid in the stomach for an extended period, ensuring prolonged gastric retention that leads to a slow and controlled drug release, ultimately enhancing its bioavailability and therapeutic efficacy. They are particularly beneficial for drugs with poor solubility, low bioavailability, or those requiring constant blood levels for optimal therapeutic outcomes. By offering controlled release, reduced dosing frequency, targeted delivery, improved patient compliance, minimized side effects, and tailored formulations, floating tablets are a valuable tool in pharmaceutical design, optimizing drug delivery to achieve the best possible treatment results while enhancing the overall patient experience [7]. Floating drug delivery systems or hydrodynamically balanced systems have a bulk density lower than gastric contents and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in plasma drug concentrations. However, besides the minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. A novel apparatus was used to measure the floating force kinetics to determine the resultant weight (RW). The RW apparatus continuously measures the force equivalent to F (as a function of time) required to maintain the submerged object. The object floats better if RW is on the higher positive side. The generation of gas bubbles can achieve floatability. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g., chitosan) and effervescent Components (e.g., sodium bicarbonate, citric acid, or tartaric acid). The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. In this system carbon dioxide is released and causes the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose, and polyvinyl pyrrolidone (PVP) coated with hydroxyl propyl methylcellulose (HPMC), and floating system based on ion exchange resin technology. A bilayer or multilayer system has also been designed. Drugs and excipients can be formulated independently, and the gas-generating material can be incorporated into any layer. Further modifications involve coating the matrix with a polymer permeable to water but not carbon dioxide[8]. Floating tablets are crucial, especially for medications with specific absorption challenges. Drugs absorbed in the stomach, have poor solubility or are sensitive to variations in gastric emptying time can significantly benefit from extended gastric retention. Floating drug delivery systems achieve this by prolonging the residence time of the medication in the stomach. This extended stay is accomplished by generating gas within the tablet matrix or using buoyant materials, causing the system to float on the gastric fluid and swell, forming a gel layer on its surface. This gel layer not only prevents the tablet from exiting the stomach prematurely but also controls the release of the drug, ensuring a gradual and sustained delivery into the gastrointestinal tract. These mechanisms contribute to improved drug absorption, bioavailability, and therapeutic effectiveness, addressing the unique challenges posed by certain medications and medical conditions[9]. This gel layer acts as a barrier, preventing rapid drug discharge in the stomach and thus delaying its absorption. This approach is especially advantageous for drugs with a narrow absorption window and those requiring localized effects. By extending the stomach's residence time, these floating systems significantly enhance the drug's availability for absorption[10]. Furthermore, these systems often improve patient adherence due to reduced pill burden. The main purpose of a floating drug delivery system is to increase the gastric residence time of the dosage form by generating gas and followed by swelling of the system, which retards the drug release by forming a gel layer around the surface of the system[11]. Histamine (HA) functions as a neuromodulatory transmitter within the central nervous system, overseeing diverse cognitive functions. The central

nervous system contains three primary types of histamine receptors: postsynaptic histamine H1 and H2 receptors and presynaptic histamine H3 receptors. Betahistine hydrochloride is an orally administered antihistaminic drug. The chemical name of betahistine is N-methyl2-(pyridine-2-yl)-ethanamine. Betahistine has a very strong affinity for histamine H3 receptors and a weak affinity for histamine H1 receptors. It has been used to control vertigo in patients with Meniere's disease; it possibly acts by causing vasodilation in the internal ear. However, the short biological half-life of betahistine 2-3 h necessitates frequent 4 times a day administration of the drug[12]. Betahistine dihydrochloride (BTH), recommended for alleviating vertigo in individuals with Meniere's disease, acts as a potent antagonist for histamine H3 receptors while demonstrating moderate effects as an agonist for histamine H1 receptors. Beyond its affinity for histamine receptors, the therapeutic impact of BTH is not solely attributed to this interaction, as its actions within the central nervous system significantly contribute to its efficacy[13]. Meniere's disease comprises recurrent spontaneous rotatory vertigo spells that patients describe as a spinning or whirling feeling and sensorineural hearing loss (SNHL) accompanied by recruitment and tinnitus. An unpleasant sensation of aural fullness on the affected side may also occur. Meniere's disease is also called idiopathic endolymphatic hydrops (ELH), a term that describes a disorder of the inner ear with a build-up of endolymph[14]. Several distressing symptoms characterize Meniere's disease. Sensorineural hearing loss, tinnitus, and recurrent episodes of vertigo are the hallmark manifestations. Patients undergoing vertigo spells often experience a sensation of rotational movement, likened to spinning or whirling. This vertigo is frequently accompanied by a sensation of fullness in the ears. Vertigo attacks, known for their sudden onset, are profoundly incapacitating, lasting anywhere from minutes to days[15]. These episodes significantly disrupt daily activities, challenging work, or social interactions. Nausea and vomiting are common during these attacks, exacerbating the discomfort. Furthermore, the aftermath of an attack, characterized by lingering feelings of imbalance and drowsiness, can persist for several days. As the disease progresses, the quality of life further deteriorates due to the additional burden of sensorineural hearing loss, distorted sound perception, recruitment (abnormal loudness growth), and tinnitus. The present work was planned to make floating tablets of BTH for extended release of medicament for Meniere's disease.

2. MATERIALS AND METHODS

2.1. Materials

BTH Hydrochloride was obtained from Dhemtec Pharma and Consultants, a supplier located in Mumbai, India. The necessary pharmaceutical ingredients, including HPMC K4M 100, Chitosan, Sodium bicarbonate, Citric acid, and Lactose, were sourced from Yarrow Chemicals, another Mumbai-based company in India. It's important to note that all other chemicals utilized in this research, including those mentioned earlier, were of analytical reagent (A.R) grade.

2.2. Solubility analysis

The solubility of BTH was assessed using a traditional technique in various solvents, including water, ethanol, methanol, isopropanol, and 2-propanol. This method is commonly employed to determine the quantity of a substance dissolves in different solvents. It provides valuable information about its physical and chemical properties and potential applications in various fields such as pharmaceuticals, chemistry, and industry. The solubility data obtained from these experiments can be instrumental in formulation development, process optimization, and the design of drug delivery systems, among other applications.

2.3. Melting Point

The melting point of BTH was determined using Thiel's tube method. Finely powdered BTH was placed into one end of a sealed capillary tube. The other end of the capillary tube was connected to a thermometer. The capillary tube was then introduced into a Thiel's tube filled with liquid paraffin. The Thiel's tube containing the capillary tube was gradually heated. As the temperature increased, the BTH powder inside the capillary tube began to melt and transition into a liquid state. The temperature at which this transition occurred was carefully observed and recorded. This method is a precise and widely used technique for determining the melting point of a substance. The recorded melting point provides valuable information about the substance's purity and identity and its suitability for various applications in chemistry and pharmaceuticals[16].

2.4. Standard calibration curve

A specific weight of 100mg of the substance was accurately measured and subsequently placed into a 100 ml volumetric flask. The substance was dissolved in adequate distilled water, and the volume was adjusted to reach the calibration mark on the flask using distilled water. This process yielded a solution with a concentration of 1000 µg/ml. This particular solution was utilized as the standard stock solution, encompassing 1 mg/ml of the representative compound (Stock 1) [17]. Following this, 1 ml of the solution above was diluted using water until the total volume reached 100 ml, producing a stock solution with a concentration of 10 µg/ml. After this, UV scanning was conducted for the drug solution with a 10 µ g/ml concentration, spanning the wavelength range from 200 to 400 nm. In the Shimadzu UV 1700 spectrophotometer, a blank sample of distilled water was employed as a reference. The examination revealed a peak wavelength of 244 nm[18]. Beginning with the initial stock solution, portions of 2, 4, 6, 8, 10, and 12 ml were separately dispensed into individual 10 ml volumetric flasks. Following this, each flask was topped with water until the meniscus aligned with the flask's calibration mark. This procedure yielded corresponding solutions with concentrations of 2, 4, 6, 8, 10, and 12 µg/ml. The absorbance of every solution was then gauged at a wavelength of 244 nm through the employment of the UV spectrophotometer[19]. To construct the standard curve with precision, this procedure was replicated three times to ensure accuracy. The resultant absorbance values were graphed against their corresponding concentrations. The linear correlation equation was derived using this graph, and the coefficient of determination (r^2 value) was computed to evaluate the quality of the data fitting.

2.5. BTH-excipient compatibility by FTIR Studies

FT-IR (Fourier-Transform Infrared) analyses were conducted on both pure BTH and the excipients used in the formulation

to assess the compatibility of BTH with these components. During the analysis, the spectral peaks of the combination of BTH and the polymer were compared to the spectral peaks of pure BTH. This comparative analysis allows for evaluating any changes or shifts in the infrared spectra that could indicate interactions or compatibility issues between BTH and the excipients. The absence of significant shifts or alterations in the peaks suggests that BTH and the selected excipients are chemically compatible, meaning they can coexist harmoniously within the formulation. This compatibility is essential for maintaining the stability and effectiveness of the active pharmaceutical ingredient (BTH) within the formulation, ensuring the quality and safety of the pharmaceutical product.

2.6. Formulations

Floating drug delivery systems (FDDS), also called hydrodynamically balanced systems (HBS), stand out because of their intrinsic low-density characteristics, allowing them to remain afloat on the surface of stomach contents for extended durations. This inherent buoyancy is crucial for achieving controlled drug discharge at a predetermined and controlled rate. Through this mechanism, FDDS extends the retention time within the stomach, effectively reducing variations in drug discharge. The fundamental principle underlying FDDS involves modulating the pharmacokinetic discharge profile of a BTH within a gastro-retentive drug delivery system, ensuring targeted and sustained therapeutic effect[s15].

2.7. Effervescent Floating Tablet

A buoyant tablet contains air, water, a vacuum, or an inert gas in this system. Effervescence can be induced through the reaction of carbonate or bicarbonate salts with an organic acid such as citric acid, resulting in the generation of CO_2. This discharged gas contributes to the floating effect. The system encompasses matrices composed of swellable polymers, including chitosan-like polysaccharides and effervescent agents like citric acid, sodium bicarbonate, and tartaric acid. Alternatively, the system may involve chambers filled with a liquid capable of gasification at body temperature[16].

2.8. Development of BTH Floating Tablet

Floating tablets of BTH were developed using the direct compression technique, which involved incorporating swelling polymers like HPMC K4M 100 and Chitosan, both individually and in combination. Gas-generating agents such as sodium bicarbonate and citric acid, along with lactose, were included in the formulation to act as a bulk-forming agent. The quantities of the BTH, polymers, and excipients were accurately measured as per the batch formula. To ensure homogeneity, all components were meticulously mixed for 15 min using a mortar and pestle. Following this, the powder equivalent to a single tablet's dose was precisely weighed and subjected to punching through a multi-station rotary punching machine[17,18].

Table 1: Composition of BTH floating tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
BTH	16	16	16	16	16	16	16	16	16
HPMC K4M 100	100	140	98	123	101	102	98	95	77
Chitosan	169	129	171	146	-	-	-	-	-
HPMC K4M 100 + Chitosan	-	-	-	-	168	167	171	174	192
$NaHCO_3$	75	75	75	75	75	75	75	75	75
Citric acid	25	25	25	25	25	25	25	26	26
Lactose	15	15	15	15	15	15	15	14	14
Total Weight	400	400	400	400	400	400	400	400	400

2.9. Flow properties

2.9.1. Angle of Repose

The angle of repose was assessed using both the fixed funnel and free-standing cone techniques. A funnel was securely positioned with its tip set at a defined height (H) above a sheet of graph paper placed on a level surface. Gradually, powder or granules were introduced into the funnel, allowing them to flow gently through until the highest point (apex) of the formed conical heap came into contact with the tip of the funnel. In this setup, the parameter "R" denoted the radius of the base of the conical heap[19].

The angle of repose (α) is calculated using the formula:

$$\tan \alpha = H/R$$

2.9.2. Bulk Density

The pre-sieved (40-mesh) bulk drug was poured into a graduated cylinder with a large funnel to calculate the bulk density. Both the volume and weight of the material were carefully measured. The bulk density (denoted as δb) is then computed by dividing the mass (M) of the material by its volume (Vb), following the formula[20]:

$$\delta b = M/Vb$$

2.9.3. Carr's Index

Carr's index offers valuable information about the potential cohesive strength that a powder might exhibit, particularly in forming an arch within a hopper. Also, it indicates the ease with which such an arch could disintegrate. This index is computed using the following formula[21]:

$$\text{Carr's index} = (\text{Tapped density} - \text{Bulk density}) / \text{Tapped density} \times 100$$

2.9.4. Hausner Ratio

The Hausner ratio serves as an indicator of the flowability of a powder or granular material. It is derived using the following formula[22]:

$$H = \delta t / \delta b$$

Where: δb represents the freely settled bulk density of the powder; δt represents the tapped density of the powder.

2.10. *Post-compression evaluation*

2.10.1. Floating Lag Time and Floating Time

The tablets' in-vitro buoyancy was assessed by measuring two critical factors: the lag time for floating initiation and the duration of floating. The evaluation was done by placing the tablets into a 250 ml glass beaker containing a citric acid buffer with a pH of 3. The floating lag time, indicating the time taken for the tablet to begin floating and rise to the solution's surface, was established by noting the elapsed time. Following this, the complete duration for which the tablet sustained buoyancy on the solution's surface was recorded as the floating duration[23, 24].

2.10.2 Weight Variation Test

The weight variation examination involved the weighing of 20 separate tablets. The mean weight of these tablets was calculated, and subsequently, the % weight variation was computed utilizing the following formula:

$$\%\ \text{Deviation (PD)} = (W_{\text{Individual}} - W_{\text{Average}}) / W_{\text{Average}} \times 100$$

Where:
$W_{\text{Individual}}$ = Weight of an individual tablet; W_{Average} = Average weight of the tablets

2.10.3 Tablet Hardness

Tablet hardness, a critical parameter in pharmaceutical tablet manufacturing, is assessed by measuring the force required to break a tablet in diametric compression. This measurement is typically performed using a Pfizer tester. The Pfizer tester is an instrument designed specifically for this purpose and provides a standardized method for evaluating tablet mechanical strength and integrity. A tablet is placed in the Pfizer tester during the test, and a controlled force is applied diametrically until the tablet fractures or breaks. The force applied is recorded as tablet hardness, usually expressed in kilograms per square centimeter (kg/cm^2) or Newtons (N). Tablet hardness is a crucial quality control parameter, as it ensures that tablets are robust enough to withstand handling, packaging, and transportation without breaking or crumbling. Tablet hardness testing helps maintain the uniformity and reliability of pharmaceutical products, ensuring that each tablet meets the required mechanical strength specifications and delivers the intended dosage accurately. It also plays a vital role in preventing issues like capping, sticking, or chipping during tablet compression and subsequent processing steps [25].

2.10.4 Tablet Thickness

The thickness of a tablet is typically measured using a vernier caliper, a precision instrument designed for such measurements. During the measurement process, the vernier caliper is carefully placed over the tablet, and the caliper's jaws are gently closed to make contact with the tablet's surface. The reading on the caliper's scale indicates the tablet's thickness. In pharmaceutical manufacturing and quality control, it is crucial that the tablet's thickness falls within a specified range and stays within the standard value. The acceptable tolerance for tablet thickness is often set at ±5%, meaning that the measured thickness of the tablet should not vary more than 5% above or below the specified standard thickness. This tolerance range ensures that tablets produced in large batches maintain uniformity in size, which is essential for consistent dosing and the effectiveness of the pharmaceutical product. Tablets with thicknesses outside this acceptable range may be subject to quality control issues and could impact patient safety and therapeutic efficacy. Therefore, meticulous measurement and adherence to the specified thickness standards are essential in tablet manufacturing.

2.10.5. Friability Test

Tablet friability is assessed through the utilization of a Roche Friabilator. Tablets with a known weight (Wi), or a sample of 10 tablets, are subjected to dedusting inside a drum for a set period (100 revolutions). Following this, the tablets are reweighed (Wf). The % of friability is subsequently determined by considering the weight reduction and applying the following equation[26]:

$$\text{Percentage friability} = (Wi - Wf) / Wi \times 100$$

The weight loss should not exceed 1%. The test is conducted in triplicate.

2.10.6 BTH Content

For BTH content determination, ten tablets are selected, and the quantity of BTH present in each tablet is measured. The tablet is crushed using a mortar and pestle, and an amount equivalent to 100mg of the BTH is transferred into a standard 100 ml volumetric flask. This powder is diluted with citric acid buffer at pH 3, filling the flask up to the mark. The resulting solution may be further diluted as required, and its BTH content is analyzed using a UV spectrophotometer at a wavelength of 276nm. A citric acid buffer at pH 3 is used as a blank during the analysis to account for any background signals. This process allows for accurately determining the BTH content in the tablets[27].

2.10.7 In-Vitro BTH Discharge Studies

The release rate from the buoyant tablets is evaluated using the paddle method with the USP XXIV dissolution testing apparatus II. This examination is carried out under specific conditions: utilizing 900 ml of 0.1 N HCl at a controlled temperature of 37 ± 0.5°C and with the paddle rotating at 100 rpm. The assessment occurs hourly over 24 h, during which a 5 ml sample is extracted from the dissolution apparatus. Simultaneously, an equivalent fresh dissolution medium is introduced to uphold the volume. These extracted samples are suitably diluted using 0.1 N HCl. Subsequently, the absorbance of these solutions is gauged at a wavelength of 284 nm using a Shimadzu UV-Vis double-beam spectrophotometer. The cumulative % of BTH release is determined employing an equation derived from a standard curve. This calculation quantifies the BTC's discharge from the floating tablets[28].

2.10.8 Swelling Index of BTH Floating Tablet

The swelling index of the tablets is evaluated using 0.1 N HCl with a pH of 1.2 at room temperature. The tablets' swollen weight is measured at designated time intervals. The swelling index is then calculated utilizing the following formula[29]:

$$\text{Swelling index (SI)} = (Wt - Wo) / Wo \times 100$$

Where Wt = Weight of tablet at time t; Wo = Initial weight of the tablet.

2.11 Statistical analysis

The statistical data, initially presented in the mean ± standard deviation (SD) format, underwent a comprehensive analysis using Microsoft Excel 2016. Leveraging Excel's built-in functions and tools, the dataset was subjected to further scrutiny, encompassing the calculation of additional statistics such as confidence intervals. Moreover, visual representations, including bar charts and histograms, were crafted to convey data distribution and variability effectively. Additionally, statistical tests like t-tests and ANOVA were employed to evaluate the significance of differences between means when applicable. This systematic approach greatly streamlined the analysis process, making data interpretation more accessible and enhancing the clarity of the findings. Excel's capabilities were pivotal in efficiently handling and analyzing the statistical data, ultimately contributing to a more robust understanding of the dataset.

3. RESULTS

3.1. Solubility Studies

BTH exhibited high solubility in water, indicating that it readily dissolved in this solvent. It was also found to be freely soluble in methanol, which implies a strong solubility in this solvent. Additionally, the compound showed good solubility in ethanol (95%). However, its solubility in isopropanol was only slight, indicating a lower level of dissolution in this solvent. On the other hand, BTH was practically insoluble in 2-propanol, implying that it did not dissolve significantly in this particular solvent.

3.2. Melting Point

The melting point of BTH was determined using the capillary method, resulting in a recorded melting point of 148°C.

3.3. Calibration curve of BTH

A standard calibration curve of BTH was constructed using distilled water as the solvent, encompassing concentrations ranging from 2 to 12µg/ml. The dataset demonstrated a linear correlation, as indicated by an r^2 value of 0.998. This high coefficient of determination affirmed the adherence of the data to the Beers-Lambert law (Figure 1).

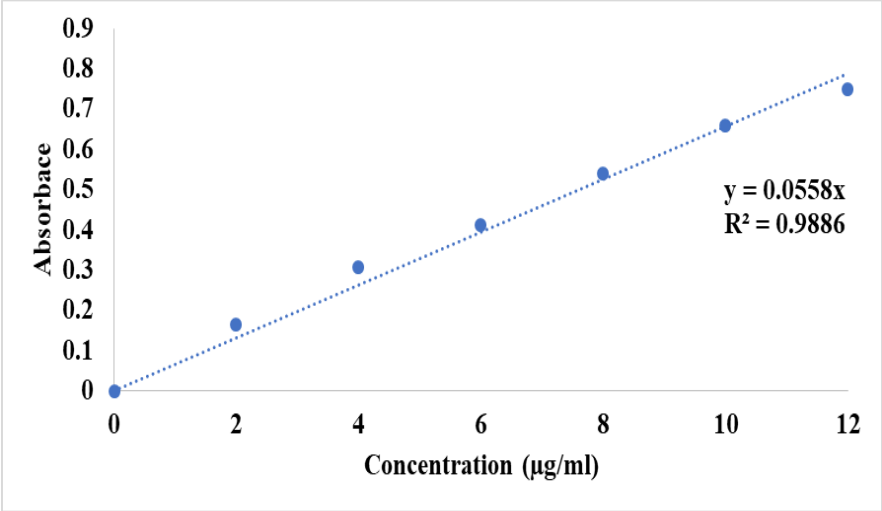

Fig.1. Standard calibration curve of BTH

3.4. FTIR spectral results

The FTIR analysis of the BTH and the formulation's excipients revealed well-defined peaks corresponding to the BTH's specific wavelengths. Notably, no notable shifts were observed, suggesting compatibility between the BTH and the chosen excipients. This observation is illustrated in Figure 2.

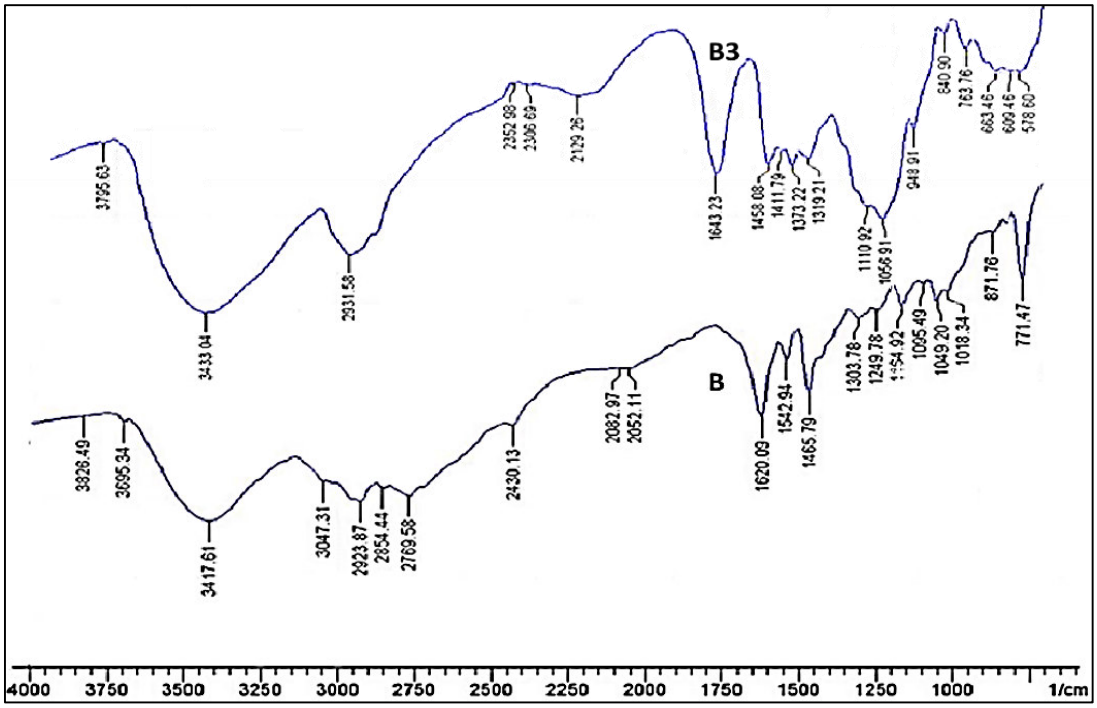

Fig.2. FIIR spectra of BTH (B); BTH+ excipients (B3)

3.5. *Pre-compression Studies*

The results of pre-compression tests conducted on the powder blend for formulations F1 to F9 are summarized in Table 2. The angle of repose measurements fell within the range of 26.01°±0.07 to 30.96°±0.35, signifying favorable flow characteristics of the powder. The compressibility index ranged from 9.71±0.10 to 16±0.32, while the Hausner's ratio spanned from 1.10±0.01 to 1.19±0.01. These values collectively indicate that the powder blend is suitable for tablet compression.

Table 2: Pre-compression studies of BTH floating tablet formulations

Formulations	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Hausner's ratio	Compressibility index (%)	Angle of repose(°)
F1	0.42±0.02	0.50±0.03	1.19±0.06	16.00±0.32	26.56±0.11
F2	0.47±0.02	0.54±0.01	1.13±0.08	12.10±0.45	30.96±0.35
F3	0.41±0.01	0.46±0.02	1.11±0.07	11.00±0.30	30.96±0.24

F4	0.42±0.03	0.47±0.04	1.12±0.01	11.29±0.14	25.64±0.11
F5	0.47±0.04	0.52±0.03	1.11±0.05	10.03±0.25	29.59±0.26
F6	0.39±0.01	0.44±0.02	1.12±0.02	10.83±0.14	30.15±0.03
F7	0.41±0.05	0.46±0.01	1.13±0.03	11.70±0.20	26.01±0.07
F8	0.45±0.06	0.52±0.02	1.10±0.01	09.71±0.10	26.56±0.19
F9	0.45±0.01	0.50±0.01	1.11±0.04	11.76±0.44	27.11±0.20
Values in mean±SD; n=3					

3.6 Post-compression Evaluation

In Table 3, the post-formulation evaluation parameters across all variations are presented. Tablet thickness displayed a uniformity range of 3.00±0.01 to 3.06±0.02. Every tablet successfully passed the weight variation test, confirming that the average percentage deviation fell within the acceptable ±5% range defined by the pharmacopoeia. Formulations exhibited friability values ranging from 0.50±0.02 to 0.98±0.03, within the 1% range. This serves to affirm the tablets' resilience against mechanical shock and abrasion. The hardness of the formulations ranged from 4.1±0.01 to 4.6±0.02, adhering to the official standard of 4 kg/cm². This indicates the tablets' robust mechanical strength. The BTH content across all formulations spanned from 97.13±2.65 to 100.08±2.15, aligning with the established pharmacopoeia standards. The floating lag time spanned from 107 to 115 seconds, while the floating time extended beyond 12 hours for all formulations.

Table 3: Post-compression studies of BTH floating tablet formulations

Formulations	Thickness (mm)	Hardness (kg/cm^2)	Weight of the Tablets (mg)	Friability (%)	BTH content (%)
F1	3.00±0.01	4.1±0.01	394±2.02	0.51±0.02	100.08±2.15
F2	3.05±0.04	4.6±0.02	409±5.03	0.98±0.03	98.92±2.34
F3	3.00±0.01	4.3±0.02	394±3.01	0.76±0.01	97.84±3.26
F4	3.00±0.01	4.4±0.01	395±6.02	0.50±0.02	95.97±4.15
F5	3.03±0.02	4.3±0.01	395±2.03	0.75±0.01	97.50±6.38
F6	3.02±0.03	4.4±0.02	372±6.12	0.53±0.03	98.02±4.18
F7	3.05±0.01	4.5±0.01	392±5.21	0.51±0.01	97.95±3.95
F8	3.06±0.02	4.3±0.02	392±4.17	0.51±0.02	97.13±2.65
F9	3.04±0.02	4.4±0.01	390±3.29	0.76±0.01	97.69±1.97

Values in mean±SD; n=3

3.7 *In vitro Buoyancy*

3.7.1 Floating Lag Time

F6 has the longest floating delay, lasting 115 seconds, while F9 experiences the shortest floating delay, which lasts only 107 seconds. These observations indicate variations in floating delay times among different entities or conditions (presumably labeled as F6 and F9), with F6 having a delay in floating compared to F9.

3.7.2 Floating time

The floating times for two groups of entities, labeled as F1, F3, F6, and F9 on one hand and F2, F4, F5, F7, and F8 on the other, have been measured and summed: The combined floating time for F1, F3, F6, and F9 is 16 h; and the combined floating time for F2, F4, F5, F7, and F8 is 15 h. This information highlights the differences in floating times between these two groups, with the first group (F1, F3, F6, and F9) having a total floating time of 16 h, while the second group (F2, F4, F5, F7, and F8) collectively has a slightly shorter total floating time of 15 h. These differences in floating times could be relevant for various purposes, such as product performance evaluation or experimental analysis.

Table 4: Floating lag time and Total Floating Time BTH floating tablet formulations

Formulations	Floating lag time (sec)	Total Floating Time (h)
F1	109	16
F2	112	15
F3	108	16
F4	110	15
F5	113	15
F6	115	16
F7	112	15
F8	110	15
F9	107	16

3.8 Swelling index

The swelling characteristics of each formulation were evaluated by measuring the swelling index at various time intervals. These findings are graphically depicted, illustrating a gradual increase in swelling over time. Of particular note among all formulations, F1, which employed HPMC K4M 100 (100mg) and chitosan (169mg) as the polymer, exhibited the most substantial swelling index at 52.50±1.26%. In contrast, F8 combining HPMC K4M 100 (95mg) with HPMC K4M and chitosan (174mg) displayed the lowest swelling index at 20.51±0.25% (Figure 3A).

3.9 In-vitro BTH discharge studies

The investigation into BTH discharge spanned a duration of 12 h, employing the USP paddle method and 0.1N HCl (900ml) as the dissolution medium. *In-vitro* discharge data for all formulations is comprehensively detailed in Table 8, with the discharge profiles visually depicted in Figure 3. Remarkably, within the array of formulations, F2, incorporating HPMC K4M 100 (140mg) and Chitosan (129mg) as the polymer, showcased the highest BTH discharge, reaching 85.92±2.36%. Notably, F5, which combined HPMC K4M 100 and chitosan (168mg), along with the individual utilization of HPMC K4M 100 (101mg) as a swelling-inducing polymer, exhibited sustained BTH discharge of 73.47±1.27% after the 12 interval. This demonstrated an extended and prolonged BTH discharge profile compared to other formulations (Figure 3B).

3.9.1 Kinetic modeling of the BTH discharge

To characterize the BTH's discharge behavior, the *in-vitro* discharge data was subjected to various kinetic models, including zero-order, first-order, Higuchi, and Korsemeyer-Peppas equations. Among the formulations, F1 through F5 demonstrated conformity to zero-order kinetics, yielding r^2 values of 0.9941, 0.9938, 0.9891, 0.9874, and 0.9906, respectively. These findings imply that the discharge rate of these formulations remains consistent across different concentrations. On the other hand, formulations F6 to F9 exhibited r^2-squared values of 0.9955, 0.9890, 0.9901, and 0.9959, respectively, suggesting that a combination of diffusion and erosion mechanisms influences the BTH discharge mechanism in these cases. The value of the solute's diffusion exponent (n) exceeded 0.89, which categorizes the BTH discharge mechanism as super case II transport (Table 4 and Figure 3C to 3F). This indicates that the BTH discharge process deviates from Fickian diffusion and involves complex transport phenomena.

Table 5: Kinetic modeling and regression values for the Nateglinide tablets

Formulation	Zero-order	First order	Higuchi model	Korsmeyer-Peppas	
				r^2	N
F1	0.9941	0.9357	0.9757	0.9902	0.77
F2	0.9938	0.9391	0.9727	0.9811	0.76
F3	0.9891	0.9394	0.9631	0.9715	0.83
F4	0.9874	0.9576	0.9669	0.9826	0.66
F5	0.9906	0.9583	0.9625	0.9817	0.69
F6	0.9900	0.9263	0.9858	0.9955	0.99
F7	0.9823	0.9115	0.9889	0.9890	0.98
F8	0.9894	0.9218	0.9839	0.9901	0.99
F9	0.9929	0.9171	0.9853	0.9959	0.99

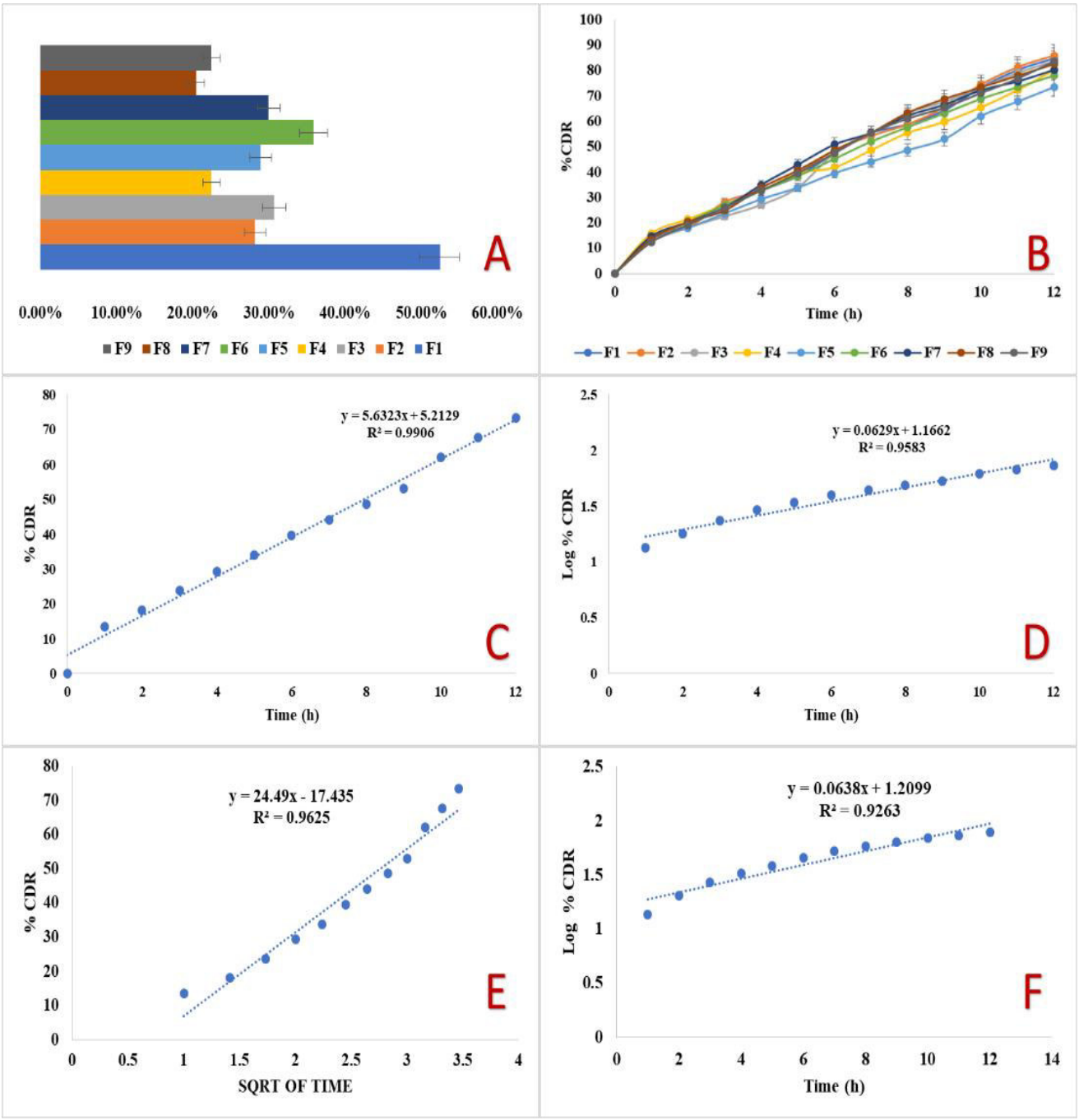

Fig.3. A) Swelling index; B) *in-vitro* BTH discharge; C) Zero-order discharge (F5); D) First order (F5); E) Higuchi (F5); F) Korsmeyer Peppas (F5)

4. DISCUSSION

Using floating drug delivery systems to prolong gastric retention and control drug release is particularly advantageous for medications with a narrow absorption window and a limited time frame for optimal absorption[30]. In such cases, the extended gastric retention achieved by floating tablets becomes crucial as it allows the drug to remain in the stomach longer, increasing the chances of its absorption within the narrow absorption window. By regulating the drug's release rate and maintaining consistent drug levels in the stomach, these systems enhance the drug's bioavailability and therapeutic efficacy, ensuring the medication can exert its intended effects even when specific physiological factors or constraints limit the absorption process. This tailored approach to drug delivery addresses the unique requirements of these medications, ultimately improving patient outcomes and treatment effectiveness. The melting point determination of a substance using the capillary method is a fundamental technique in chemistry, providing valuable insights into its purity and identity. A sharp, well-defined melting point like this suggests high purity, as impurities typically lower or broaden the melting point range[31]. The melting point is also a characteristic property used for compound identification. By comparing the measured melting point to known values in reference sources, scientists can confidently confirm BTH's identity. This information not only aids in quality control and research, but also plays a pivotal role in assessing the suitability of BTH for various chemical applications. Constructing a standard calibration curve for BTH and employing distilled water as the solvent represent fundamental steps in quantitative analysis. The absorbance of BTH solutions at a specific wavelength was systematically measured during this process. The resulting dataset revealed a clear and consistent linear correlation, affirming the

adherence of the data to the Beer-Lambert law[33]. The Beer-Lambert law is a fundamental principle in spectrophotometry. It is based on the premise that the absorbance of a substance is directly proportional to its concentration in a solution. In the context of this calibration curve, it means that as the concentration of BTH increases, the absorbance of light by BTH at the specified wavelength also increases linearly. This linear relationship is pivotal for accurately quantifying the concentration of BTH in unknown solutions[34]. The standard calibration curve, representing this linear relationship, is a powerful tool for analytical chemistry. Analysts can use this curve to determine the concentration of BTH in samples of unknown concentration by simply measuring their absorbance at the same specified wavelength. By referring to the calibration curve, the exact concentration of BTH in the unknown solution can be ascertained with high precision. In summary, constructing a standard calibration curve for BTH in distilled water, demonstrating adherence to the Beer-Lambert law, is a critical step in quantitative analysis. It empowers analysts to accurately determine the concentration of BTH in various solutions, offering valuable applications in pharmaceuticals, chemistry, and research. The Fourier-Transform Infrared (FTIR) analysis of BTH in conjunction with the formulation's excipients has provided valuable insights into the chemical compatibility of the components. During the analysis, distinct peaks corresponding to specific wavelengths associated with BTH were observed in the spectra. What's particularly noteworthy is the absence of significant shifts in these peaks. This absence of notable shifts suggests high chemical compatibility between BTH and the selected excipients[35]. The lack of significant peak shifts in the FTIR spectra is an encouraging sign in pharmaceutical formulation. It indicates minimal interaction between BTH and the excipients, which is desirable for maintaining the stability and effectiveness of the active pharmaceutical ingredient (BTH) within the formulation. Any major shifts or interactions could potentially lead to chemical instability or altered drug behavior, which is generally undesirable in drug development. The FTIR analysis results affirm that the chosen excipients are compatible with BTH, indicating a harmonious coexistence within the formulation. This compatibility is critical in ensuring the quality, efficacy, and safety of the pharmaceutical product, making it a positive outcome in the formulation process. The results obtained from the pre-compression tests conducted on the powder blend for the formulations are highly encouraging. The angle of repose, which measures the powder's flow properties, indicated excellent flow characteristics. A low angle of repose suggests that the powder particles flow freely and uniformly, which is essential for consistent tablet manufacturing[36]. The compressibility index and Hausner's ratio, which assess flow properties and compressibility attributes, also yielded favorable results. Both values indicated good flow properties and compressibility qualities. A low compressibility index and Hausner's ratio suggest the powder blend can compress well into tablets with minimal capping, sticking, or non-uniformity issues. These results provide evidence that the powder blend is well-suited for the compression process of creating tablets. The excellent flow properties ensure the powder can be evenly distributed within the tablet molds. At the same time, the good compressibility attributes indicate that the powder will effectively bind together during compression, resulting in tablets of consistent quality and dosage. This positive assessment of the powder blend's properties is a significant milestone in tablet formulation, contributing to the overall success and reliability of the pharmaceutical product. Evaluating tablet parameters across various formulations reveals the exceptional quality and reliability of the manufactured tablets. The uniformity in tablet thickness observed across all variations indicates a highly precise and consistent manufacturing process[37]. This level of consistency is essential as it ensures that each tablet meets the exact specifications required for pharmaceutical products, minimizing potential dosing variations that could affect patient outcomes. The successful passage of the weight variation test is a significant achievement. With the average percentage deviation well within the acceptable ±5% range defined by pharmacopeia standards, this result underscores the tablet formulation process's accuracy and precision [38]. It provides strong assurance that each tablet contains the specified amount of the active ingredient, which is paramount for therapeutic efficacy and patient safety. Thirdly, the friability values falling within the acceptable range of 1% are of utmost importance. These results demonstrate that the tablets resist mechanical shock and abrasion, ensuring their structural integrity during transportation and handling[39]. Such durability is crucial in maintaining the tablets' quality and preventing breakage or damage that could compromise their effectiveness. Additionally, the tablets' adherence to the official standard of 4 kg/cm² for hardness signifies their robust mechanical strength[40]. These characteristics enhance the tablets' user-friendliness and reduce the risk of breakage or crumbling during transportation and administration, further solidifying their reliability and usability. Furthermore, the consistently high BTH content in all formulations, exceeding 95%, aligns perfectly with established pharmacopoeia standards. This compliance guarantees that the tablets consistently contain the specified amount of the active ingredient, instilling confidence in their therapeutic reliability and efficacy[41]. The measured floating lag time is crucial for floating drug delivery systems. It reflects the tablets' ability to maintain buoyancy for an extended period, allowing for controlled drug release. This feature enhances the tablets' suitability for specific therapeutic applications, where sustained drug release is desired. In conclusion, the comprehensive evaluation of these tablet parameters collectively reinforces the high-quality standards met by the formulated tablets. These findings are pivotal in assuring the pharmaceutical product's safety and effectiveness, affirming its potential in various therapeutic applications. The evaluation of the swelling characteristics of each formulation has provided valuable insights into their behavior over time. Among the polymers used, HPMC K4M 100 and chitosan exhibited the most significant swelling index, indicating a strong propensity to absorb and retain water or other fluids. This substantial swelling index suggests that these formulations can absorb moisture rapidly and efficiently. Conversely, formulation F8, which combines HPMC K4M 100 with HPMC K4M and chitosan, displayed the lowest swelling index among the tested formulations. This suggests that F8 has a comparatively lower capacity to absorb and retain moisture or fluids[42]. This lower swelling index could be attributed to the specific combination of polymers or the overall formulation composition. The variation in swelling characteristics among different formulations is crucial in pharmaceutical and drug delivery systems. It can impact drug release rates, dissolution profiles, and overall product performance. These characteristics are essential for tailoring formulations to achieve desired drug delivery and therapeutic

efficacy outcomes. All formulations' *in-vitro* drug release data have been comprehensively analyzed, revealing distinct discharge profiles. The performance of formulation F2 is particularly remarkable, as it incorporates HPMC K4M 100 (140mg) and Chitosan (129mg) as the polymer. F2 exhibited the highest BTH discharge among all the formulations, reaching an impressive 85.92±2.36%. This remarkable drug release suggests that the combination of HPMC K4M 100 and Chitosan in F2 effectively facilitated the rapid and efficient release of BTH from the formulation[43]. In addition, formulation F5 also stands out. F5 combines HPMC K4M 100 and chitosan (168mg), utilizing HPMC K4M 100 (101mg) as a swelling-inducing polymer. F5 demonstrated sustained BTH discharge throughout the testing period, with a final release of 73.47±1.27% at the 12-hour interval. This sustained drug release profile suggests that F5 has potential applications in achieving controlled and prolonged drug release for therapeutic purposes[44]. These *in-vitro* discharge data profiles provide valuable insights into the performance of the formulations and their potential applications in drug delivery systems. Formulation F2's rapid release may be suitable for immediate drug delivery needs, while F5's sustained release characteristics could be advantageous for achieving prolonged therapeutic effects. These findings are significant for optimizing drug formulations and tailoring them to meet specific pharmaceutical requirements[45]. Characterizing BTH's discharge behavior involved subjecting the in-vitro discharge data to various kinetic models, including zero-order, first-order, Higuchi, and Korsemeyer-Peppas equations. The results provide valuable insights into drug release mechanisms from the different formulations[46]. Among the formulations, F1 through F5 exhibited conformity to zero-order kinetics. This suggests that the discharge rate of BTH from these formulations remains consistent, regardless of its concentration within the formulation. Zero-order kinetics typically implies a steady and controlled release rate over time, which can be advantageous for achieving precise drug delivery[47]. In contrast, formulations F6 to F9 displayed a different discharge mechanism[48]. In these cases, the release mechanism for BTH is influenced by a combination of diffusion and erosion mechanisms. This suggests that factors beyond simple diffusion play a role in drug release. The solute's diffusion exponent (n) value exceeded one which indicates that the BTH discharge process deviates from typical Fickian diffusion, which involves straightforward movement through a concentration gradient and instead involves complex transport phenomena[49]. These findings highlight the complexity of drug release from different formulations and the importance of understanding the underlying mechanisms[50]. The choice of kinetic model can provide valuable insights into how a particular drug formulation behaves and can guide the development of optimized drug delivery systems tailored to specific therapeutic needs[51].

5. CONCLUSION

The study developed floating tablets for Betahistine using a formulation of HPMC K4M 100, Chitosan, Sodium Bicarbonate, Citric Acid, and Lactose. Various parameters were evaluated, including tablet thickness, hardness, weight variation, friability, BTH content, swelling index, in-vitro buoyancy, and release patterns. Among the formulations, F5 exhibited the lowest BTH discharge (73.47±1.27%) over 12 hours, while F2 had the highest (85.92±2.36%). Kinetic modeling revealed zero-order kinetics for F1 to F5, indicating consistent BTH discharge. In contrast, F6 to F9 exhibited discharge influenced by diffusion and erosion, with a diffusion exponent (n) exceeding 0.89, indicating super case II transport. The study successfully formulated buoyant tablets with diverse discharge profiles, holding significance for improved drug delivery systems targeting Meniere's disease to enhance patient compliance and therapeutic outcomes.

6. ABBREVIATIONS

BTH: Betahistine; HPMC: Hydroxy propyl Methylcellulose; FTIR: Fourier transform Infra-red; HA: Histamine; AR: analytical reagent; ml: milliliter; µg: microgram; nm: Nanometer; FDDS: Floating drug delivery systems; HBS: hydro dynamically balanced systems; (HBS), CO_2: Carbon dioxide; USP: United States Pharmacopoeia; HCl: Hydrochloric acid; SI: Swelling index.

7. AUTHOR CONTRIBUTION STATEMENT

Conception/Design of Study- Pawan Dhamala., Subhash PG; Drafting Manuscript- Hindustan Abdul Ahad., Pavan Kumar, Suprith D.; Final Approval and Accountability- Pawan Dhamala, Subhash PG, Hindustan Abdul Ahad, Pavan Kumar, and Suprith D.

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9. CONFLICT OF INTEREST

Conflict of interest to declared none.

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