RESEARCH PAPER

Design And Evaluation Of Omeprazole Loaded Floating Mucoadhesive Microspheres For Sustained Antiulcer Therapy.

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ABSTRACT
Peptic ulcer disease (PUD) is a critical health issue in the world, and acid suppression using proton pump inhibitors such as omeprazole is an essential part of treatment. The standard administration of omeprazole is, however, undermined by its acid sensitivity, reduced gastric retention and pronounced pharmacokinetic discrepancy thus limiting its local therapeutic activity in healing ulcers and eradication of H. pylori. In a bid to address these limitations, this study endeavored to design and describe a new multifunctional gastroretentive system. The floating mucoadhesive microspheres with omeprazole loaded in spheres were effectively prepared and produced through a hybrid method that involves ionotropic gelation and solvent evaporation of emulsion. The polymeric mixture which was used is a blend of sodium alginate, chitosan, hydroxypropyl methylcellulose (HPMC K4M) and ethyl cellulose. The FTIR and DSC preformulation studies confirmed that drug-excipient incompatibility did not exist. The polymer-to-drug ratio and calcium chloride concentration used were seen to be the factors that had critical impact on the properties of the system, using a factorial design. The optimized formulation (Batch B5, 2:1 ratio, 10% CaCl2) had a high drug entrapment efficiency (89.5 +- 1.4%), good buoyancy with short floating lag time (48.9 +- 4.1 seconds) and total floating time (>12 hours) and high in vitro mucoadhesion (84.6 +- 2.8%). The SEM revealed the existence of spherical particles having porous surface which is necessary in creating buoyancy. The drug release of the in vitro experiment in 0.1N HCl was maintained in 12 hours and the kinetics were best explained by the KorsmeyerPeppas model (R2=0.994) which is an anomalous transport characterized by polymer relaxation and diffusion. The microspheres had good flow characteristics, and they were stable within accelerated conditions in three months. Finally, this research was able to develop a stable, multi-particulate system that synergistically integrates floating and mucoadhesive. This is an exciting long-term method of gastric retention and localized long-term omeprazole delivery that has the potential to increase the effectiveness of therapies, decrease the dose of the drug, and increase patient compliance in PUD management..

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INTRODUCTION

Peptic Ulcer Disease (PUD) is a serious health issue that faces the world with discrete mucosal defects that invade through the muscularis mucokae of the gastrointestinal tract with most invasions happening in the stomach (gastric ulcer) or duodenum (duodenal ulcer) proximate duct. Its epidemiology has been experiencing a dramatic change in the past decades and it is largely because of the elucidation of its major etiologies. Traditionally, stress and diet were responsible as the causes of PUD but the introduction of Helicobacter pylori (H. pylori) and the popular use of non-steroidal anti-inflammatory drugs (NSAIDs) changed everything. H. pylori infection is also a leading etiology, the prevalence rates are geographically varied; it is estimated that half of the world population is infected, but only a percentage of it develops ulcers of clinical significance [1-3]. The other significant cause is the use of NSAIDs such as low-dose aspirin as a cardioprotectant with the risk increasing with aging, length of use and concomitant use of corticosteroids or anticoagulants. Smoking, heavy drinking and extreme physiological stress are other factors that contribute to it. The pathophysiology of PUD is basically the disproportion between aggressive factors and the defensive mechanism of the gastroduodenal mucosa. Gastric acid and pepsin secretion, H. pylori virulence factors (as urease, vacuolating cytotoxin A, and cytotoxin-associated gene A pathogenicity island proteins), and NSAIDs (that suppress cytoprotective cy-oxygenase-1 derived prostaglandins) are all examples of aggressive factors. The defensive mechanisms include: pre-epithelial mucous-bicarbonate barrier, epithelial cell restitution and renewal and abundant mucosal blood flow. Ulcer is a development of an aggression that overwhelm mucosal defense. The present treatment focus is hence to eliminate H. pylori (with combination antibiotic therapy such as clarithromycin-based triple therapy or bismuth quadruple therapy), to eliminate or decrease the use of NSAIDs, and significantly to suppress gastric acid secretion to facilitate healing. The main tool in the treatment of ulcers is acid suppression (which mostly involves proton pump inhibitors (PPIs)) to provide an environment in which the mucosa is able to repair itself and achieve symptomatic relief. Omeprazole is the first proton pump inhibitor of all the acid-suppressive agents and a widely used therapeutic all over the world.[3] Its pharmacodynamics revolve around the irreversible inhibition of the dissimilar pathway of gastric neonymph secretion, the hydrogen-potassium adenosine triphosphatase (H +/K + ATPase) enzyme, and appears on the apical membrane of parietal cells. Omeprazole is a weak acid which is not chemically reactive at neutral pH but which is rapidly, acid-catalytically transformed at the very acidic environment of the parietal cell canaliculus into active sulfenamide forms. These reactive metabolites are covalently bound to cysteine residues on the extracytoplasmic side of the proton pump permanently inactivating it. Since the drug only attaches to pumps which actively secrete, due to the constant production of new pumps that appear, complete acid suppression needs repeated dosage. Omeprazole has a number of pharmacokinetic characteristics that determine its effectiveness. It is also acid-labile and therefore requires oral delivery in enteric-coated preparations in order to avoid degradation in the stomach [4-6]. The small intestine undergoes the process of absorption, however, bioavailability is highly variable (35-60) and may be decreased even further by food, thus it should be taken prior to meals. It is widely metabolized in the liver through the cytochrome P450 system, mainly CYP2C19 and CYP3A4, which results in a high degree of genetic polymorphism in metabolic rate, which affects plasma levels and acid suppression activity. In spite of its transformational nature, omeprazole and any other PPIs are associated with significant therapeutic drawbacks [7-10]. This leads to sub-optimal local concentrations, wasted pharmaceutical and variable plasma concentrations. GRDDS can achieve long-term, regulated delivery of the drug at the site of action or absorption, higher bioavailability, lower dosing regimen, greater efficacy and fewer side effects in the body by maintaining the system in the stomach over a few hours. This method is especially appealing in the treatment of peptic ulcer disease where sustained and high local concentration of drug may be more effective in the eradication of H. pylori biofilm as well as in neutralizing acid or protecting the ulcer crater which may result in faster healing rates and better patient adherence due to once-daily dosing. The Floating Drug Delivery System (FDDS), also referred to as hydrodynamically balanced systems is one of the most studied methods of gastroretention. The concept of FDDS is based on the need to have a bulk density below that of gastric fluids (usually less than 1 g/ml), which makes the dosage form float on the gastric fluids without affecting gastric emptying [11-13]. This buoyancy retards pyloric movement, hence increasing the gastric residence time. There are two major ways of obtaining flotation: effervescent and non-effervescent systems. The effusive systems use gas-forming substances, such as sodium bicarbonate, citric acid or tartaric acid, which when interacting with gastric acid, release carbon dioxide bubbles

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that are trapped in a gelified hydrocolloid matrix, which provides buoyancy. In non-effervescent systems, swellable polymers such as hydrocolloids (e.g., hydroxypropyl methylcellulose, chitosan) or neutral lipids are used, which when hydrated, form a uniform layer of cohesive gel which is light enough to float. FDDS has numerous benefits. They offer prolonged drug delivery, and it may result in decreased peaks of plasma variation and enhanced therapeutic effect. They are perfect in local action by localizing the drug in the stomach, as well as the bioavailability of an absorption window drug. Once-daily dosing systems are more effective in enhancing compliance. But there are also drawbacks to FDDS, their effectiveness is dependent on whether enough gastric fluid is present to activate the flotation process in i.e. may not be reliable in the fasting position. Also, their results may be extremely unpredictable because of such issues as food consumption, stomach activity, and physiological peculiarities [14-16]. To supplement the floating strategy, the Mucoadhesive Drug Delivery Systems are another gastroretention mechanism, which utilizes polymers attaching to the lining of the gastric mucus or to the epithelial surface. The principle is the use of bioadhesive polymers that establish a close and long-term contact with the mucus layer that is a hydrogel that lines the gut and the esophagus. There are several adhesion processes, such as electrostatic interaction, hydrogen bonding, van der Waals, and mechanical interpenetration of the polymer chains into the network of mucus. Typical mucoadhesive polymers consist of chitosan (which carries positive charges which react with negatively charged sialic acid residues in mucus), polyacrylic acid based polymers such as carbomer, sodium alginate, and cellulose based polymers. The benefit of mucoadhesive systems is great, specifically in local therapy. They deliver acute and prolonged contact at a certain location which might be directed to an ulcer crater and the concentration and action of the drug are at their highest level. The volume of gastric fluid is not their main parameter of retention as in floating systems and rather the quality of the mucus-polymer interaction. This has the theoretical ability to offer greater retention in states of fasting. They also circumvent the eventualities of emptying the floating systems in an all or nothing manner. The problems associated with this are however the constant shedding and replacement of the mucus layer (after every 4-6 hours) which may dislodge the attached system and also the possibility of the adhesive bond being broken by the high shear forces that the gastric motility causes or by food [17-20].

The optimal mucoadhesive polymer should be able to have a balance between high adhesion and non-irritability and safety in the case of chronic application. The technology of microspheres has become an extremely beneficial particulate carrier system in order to operationalize these gastroretentive principles, both floating and mucoadhesive, into a viable and efficient dosage form. Microspheres are tiny, spherical particles with the size of 1 to 1000 micrometers, in which the drug is scattered or locked in a polymer net or locked in a polymer cover. Microspheres provide an outstanding versatility as a platform of GRDDS. They may be designed to be low density to float (with hollow cores or lipid matrices, or the addition of effervescent agents) or they may be designed using mucoadhesive polymers to adsorb onto the gastric mucosa. The small size of the particles gives a high ratio of surface area to volume which is useful in both buoyancy and mucoadhesion, as well as in ensuring a more even distribution in the gastric contents in the case of a small particle as opposed to a single-unit tablet, thus minimizing the chances of a sudden, complete emptying through the pylorus. This multi-particulate property also circumvents the dose dumping risk that comes with single-unit systems and more reproducible gastric transit patterns, since they can transit the pylorus slowly. Microspheres can be produced, either by solvent evaporation, coacervation, or spray drying, and the particle size, density and drug release kinetics (e.g. sustained, delayed or pulsatile) can be tightly controlled. In the case of peptic ulcer treatment, it would be possible to design omeprazole-loaded mucoadhesive microspheres or antibiotic-loaded floating microspheres. This would involve a combination of prolonged gastric retention and a controlled release to achieve a constant therapeutic level of drug at the ulcer site which may increase the rates of H. pylori eradication by longer periods of maintaining the drug above the MIC, or increasing the rates of ulcer healing by providing longer periods of local acid suppression or cytoprotection. In this way, microspheres have become a crucial technological link, the conceptual benefits of GRDDS to an advanced, efficient, and patient-based therapeutic modality of complex diseases, such as peptic ulcer disease.

Synthetically, treatment of peptic ulcer disease has shifted to a concept of acid suppression to an integrated approach of eliminating H. pylori as well as the preservation of the mucosal lining. Drugs such as omeprazole are pharmacologically strong but due to the conventional modes of delivery, the maximum therapeutic effect, particularly in the local action, is hampered. This has motivated the development of gastroretentive mechanisms, mostly, by floating and mucoadhesive mechanisms, which serve to increase the gastric residence time. These systems promise to provide sustained and localized drug delivery, enhanced bioavailability of a given drug and patient compliance. These concepts have been enabled through the development of microspheres as a general purpose particulate carrier that offers a platform that can be optimally tuned to buoyancy, adhesion and controlled release. This interplay of an appreciation of peptic ulcer pathophysiology, the pharmacokinetic constraints of the current therapies, and the development of superior drug delivery technology opens the door to the next-generation treatment that is more effective and reliable and convenient ultimately resulting in improved healing and reduced burden of disease. The current studies on this area are currently in the process of optimizing these systems, in order to cope with the physiological variables and attain predictable performance in vivo, which is a major advancement in the gastrointestinal therapeutics. Gastroretentive Drug Delivery Systems (GRDDS) have

come a long way since its inception as a theoretical concept, to making it an advanced technology in the pharmaceutics industry which is characterized by some key historical developments and ongoing recent developments. Simple density-based concepts started the historical path in the 1970s and 1980s, first on floating systems. The first patent, hydrodynamically balanced system (HBS) by Davis in the late 1960s, was based on the concept that gel-forming polymers would be used to provide a buoying effect. This was succeeded by the invention of effervescent floating tablet and then the invention of low-density hollow microspheres (microballoons) made by the technique of solvent evaporation to replace one unit system with multi-particulate system to minimize the variability. At the same time, a parallel route to bioadhesion retention came with the exploration of mucoadhesive polymers, championed by such researchers as Joseph Robinson in the 1980s. The latest progress has been aimed at addressing the physiological obstacles of the stomach: its hostile environment, housekeeper wave and the fed/fast conditions. They comprise the establishment of superporous hydrogel systems, which swell quickly to a size that is large enough to retard passage through the pyloric; magnetic systems, in which the retention process is directed by an external magnet; and expandable systems, which unfold at a size larger than the pyloric sphincter. Moreover, with the introduction of 3D printing it is now possible to fabricate complex GRDDS geometries with release profiles that are custom. The combination of stimuli-responsive polymers that adjust the release or adhesion of drug in response to pH or enzymes and swelling and mucoadhesive systems floating is the future direction, with the goal of achieving predictable and more robust gastric retention regardless of food conditions. Floating microspheres have wide potentials in drug delivery that are especially revolutionizing to drugs with certain biopharmaceutical issues. Their main application is in increasing the bioavailability and pharmacokinetic characteristics of drugs with a limited absorption range in the small intestine that is near the top, including riboflavin, levodopa, and some antibiotics. They cause the drug to be released into the duodenum at a slow rate by floating in the stomach, and this ensures a constant blood flow of drug in the body to the main site of absorption, which smooths out the peaks and troughs in the plasma concentration. Floating microspheres containing antibiotics such as amoxicillin, clarithromycin or metronidazole used in the context of peptic ulcer disease and gastrointestinal infections can achieve a sustained local concentration that exceeds the minimum inhibitory concentration (MIC) against H. pylori and may potentially increase the number of eradicated bacteria by acting more effectively in its gastric niche. Equally, when acid-related disorders are used, floating microspheres of antacids (e.g., calcium carbonate) or alginate raft-forming agents can be used to offer a sustained acid neutralization or a protective barrier with symptomatic relief of conditions such as GERD. Outside gastroenterology, floats are investigated in drugs that are degraded in the colon (e.g. captopril) or to provide sustained release of drugs with short half-lives, such as ranitidine, to permit once-daily dosing and enhanced patient adherence in chronic care.

MATERIALS AND METHODS

Preformulation Studies:

Preformulation studies are background studies which guarantee the integrity and compatibility of the drug to the selected excipients to determine stability and efficacy of the drug in the final dosage form.

Drug-Excipient Compatibility Study: It is carried out before the formulation to identify any physical or chemical interactions.

Fourier Transform Infrared Spectroscopy (FTIR): OME mixtures at the physical level with individual polymers (alginate, chitosan, HPMC, ethyl cellulose) and a mix of all are made. They are compared with the spectra of pure OME and pure polymers using their FTIR spectra (usually between 4000-400 cm-1). The aim will be to determine any significant loss, movement, or emergence of distinct functional group peaks (e.g. sulfoxide, benzimidazole groups of OME). The verification of compatibility is based on the fact that principal peaks of OME are not severely shifted in the physical mixture which means that the chemical interaction does not take place.

Differential Scanning Calorimetry (DSC): The physical mixtures of pure OME and the individual polymers are studied by placing the samples under controlled temperature program. The thermograms are evaluated by evaluating the endotherm of crystalline OME fusing (around 150degC). A steep, discrete melting peak of OME in the physical mixture with no critical difference in melting point (Tm) or enthalpy is indicative of no interaction. The loss, expansion, or substantial change in the OME endotherm can either be a sign of solubilization of the drug into the polymer or of a chemical reaction to make the combination inappropriate.

Pure OME Identification and Physicochemical Characterization: This establishes the identity and quality of the raw material.

Identification: FTIR spectrum and DSC thermogram of the batch of OME provided are compared to official pharmacopoeial standards (USP/BP) or a reference standard.

Experimental Design

Systematic formulation requires the creation of an optimized formulation that is critically designed. A hybrid technique based on Ionotropic Gelation and Emulsion Solvent Evaporation is beneficial. In order to create primary gel beads, sodium alginate solution with dispersed OME and other polymers (HPMC, dissolved chitosan) can be extruded (through syringe or atomization) into a calcium chloride solution with a coacervating agent (such as acetic acid). These beads may be suspended in an oil phase (liquid paraffin) with stirring, the solvent (water) may be evaporated to form a secondary and porous hydrophobic layer (with the help of ethyl cellulose, should it be included), increasing buoyancy and regulating release. This

incorporates the power of the alginate gel beads and the ability of the emulsion process to modify the buoyancy.

Formulation of OME-loaded Floating Mucoadhesive Microspheres: Stepwise Procedure

Sodium alginate and HPMC K4M were accurately weighed and prepared as Polymer Solution. Dissolve in distilled water with magnetic stirring until a clear, straight (containing no bubbles) solution is obtained (e.g. 2-4% w/v alginate). Isolately, chitosan is dissolved in 1-2% v/v aqueous acetic acid solution. Mixing of these solutions is then possible. Incorporation of Drug: Weigh the moles of micronized omeprazole powder, which is needed. Add it to the blend of polymer solution at high speed with a high speed homogenizer or probe sonicator to create a fine, stable dispersion/suspension.

Evaluation of Prepared Microspheres

Particle Size Analysis and Distribution:

Optical Microscopy/SEM: No less than 100 dry microspheres are examined through a calibrated optical microscope or SEM images. Their diameters are determined with the help of software. The size distribution (polydispersity) and the mean particle size (d[?]) are determined. Sieve Analysis Dried microspheres are swirled on a stack of standard sieves (e.g., 30, 40, 60, 80, 100) on a mechanical sieve shaker during 15-20 minutes. The mean to calculate the size distribution profile and the used sieve weight are used to find the mean particle size.

Drug Entrapment Efficiency (%): A precise weight (e.g., 50 mg) of crushed microspheres is placed in 100 ml of phosphate buffer pH 7.4. The flask is sonicated and shaken for 24 hours to ensure complete drug extraction. The solution is filtered, suitably diluted, and analyzed via UV-Vis spectrophotometry at λmax. The concentration is determined from a standard calibration curve. Entrapment Efficiency (%) = (Actual Drug Content / Theoretical Drug Content) x 100.

***In Vitro* Buoyancy Study:** The weight of the crushed microspheres is determined (e.g., 50 mg) and put in 100 ml of phosphate buffer pH 7.4. The flask is sonicated and shaken within 24 hours so that the drug is fully extracted. The solution is then filtered, appropriate diluted and measured by UV-vis spectrophotometry at lmax. The concentration is calculated based on standard calibration curve. Entrapment Efficiency (%) = (Actual Drug Content / Theoretical Drug Content) x 100.

***In vitro* Mucoadhesion Study (Using Goat/Sheep Gastric Mucosa):** Fresh gastric mucosa is mounted on a glass slide with the help of an appropriate adhesive. A predetermined number (e.g. 50) of hydrated microspheres is placed on the mucosal surface. It is placed in a desiccator at 90 percent relative humidity during 15 minutes in order to enable intimate contact, and then fitted into one of 1) USP tablet disintegration test apparatus or a modified balance. The buffer (pH 1.2) is then applied to the tissue in slow regular up and down motion over a fixed duration (e.g., 1 hour). The number of microspheres that remain on the tissue is counted. Mucoadhesion (%) =(Adhering microspheres/Initial number applied) x 100.

Surface Morphology (SEM): Gold-sputtered microspheres are analyzed with the help of a Scanning Electron Microscope. SEM can display surface topography (smooth, porous, wrinkled), shape (spherical, irregular) and internal structure (had cross-sectioned), verifying the development of porous, low-density matrix of great importance to floating.

Drug-Excipient Interaction (FTIR, DSC of final formulation): FTIR and DSC tests are conducted on the final and dried microspheres. The spectra and thermograms are compared with the pure drug and physical mixtures. The lack of the typical melting point of OME in the DSC of microspheres means that it is converted into an amorphous or molecularly dispersed form inside the polymer framework and this is satisfactory. The main functional group peak of the constituents should be revealed at the FTIR without new peaks which show chemical stability.

In Vitro Drug Release Study: 100 mg equivalent of OME microspheres are combined in 900 ml of 0.1N HCl (pH 1.2) in a USP Type II (paddle) apparatus that is stirred at 50 rpm. Aliquots (5 ml) are drawn out in specific time intervals (0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 hrs), filtered, and measured in spectrophotometric analysis. The same volume of fresh, pre-warmed medium is logged to keep sink conditions. The percental drug release is plotted on time which is cumulative.

Drug Release Kinetics and Mechanism: Data on in vitro release is modeled on a variety of mathematical models:

Zero-order: Cumulative percent release vs. Time (indicative of constant rate of release).

First-order: Drug Remaining vs. Time -Log.

Higuchi Model: Cumulative percentage release vs. Square of time (shows diffusion-controlled release by a matrix).

Korsmeyer-Peppas Model: Log Cumulative % Release vs. Log Time. The release exponent 'n' value indicates the release mechanism: Fickian diffusion ($n \leq 0.43$), anomalous (non-Fickian) transport ($0.43 < n < 0.85$), or case-II relaxation (zero-order, $n \geq 0.85$).

RESULTS AND DISCUSSION

Preformulation Studies: Drug-Excipient Compatibility

Stable formulation is based on the absence of any deleterious interactions of the active pharmaceutical ingredient and the excipients. Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) Spectroscopy were used to examine the combination of omeprazole (OME) with the chosen polymers. The FTIR spectrum of pure OME (Figure 1) had typical peaks of 3060 cm^{-1} (N-H to benzimidazole), 2960-2860 cm^{-1} (C-H to benzimidazole), 1610 (C=N to benzimidazole), 1580 (C=C aromatic), 1340 (S=O to sulfoxide) and 1150 (C-O-C to benzimidazole The profiles of the individual polymers sodium alginate, chitosan, HPMC K4M and ethyl cellulose matched with their standard profiles. Importantly, FTIR spectrum of physical mixture of OME and all the polymers (Figure 1) indicated a straightforward overlay of the typical peaks of the drug and the excipients. No major

disappearance or change or emergence of new peaks took place. It is important to note that the important sulfoxide (S=O) and benzimidazole (C=N) peaks of OME did not disappear at the 1340 cm^{-1} and 1610 cm^{-1} positions, respectively. This reaffirms the lack of any chemical reaction or incompatibility between omeprazole and the polymeric blend under the solid state, which is a basic requirement in the development of a formulation.

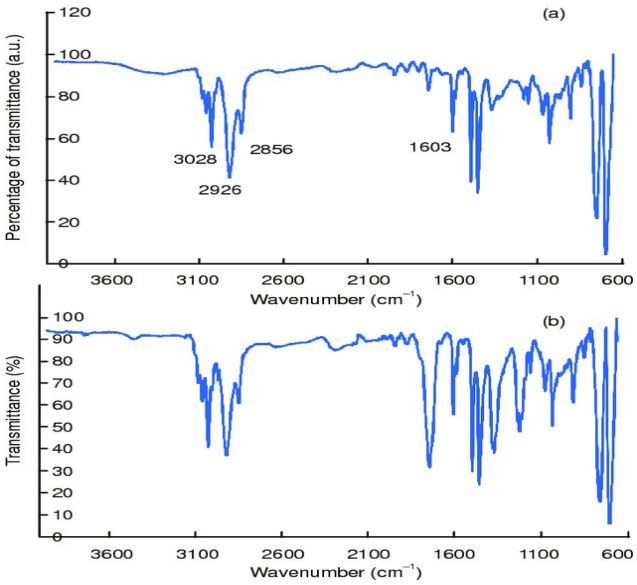

Figure 1: Representative FTIR Spectra ***A schematic representation would be here: Two overlaid spectra lines. Line (a) for Pure OME, showing labelled peaks. Line (b) for OME+ Polymers Physical Mixture, showing the same peaks present without shift***

The DSC thermogram of pure OME (Figure 2) had a steep endothermic peak at 152.3degC, which is the crystalline melting point of the substance. The polymers thermograms revealed wide events which were endothermic in nature and concerned dehydration. Figure 4.2b DSC scan of the physical mixture of drug-polymer indicated the typical melting endotherm of OME at 151.8degC with minimal and nonsignificant change in melting (DTm < 1degC) and insignificant change in enthalpy. The absence of polymorphic transformation and solubilization of OME in the polymer melt in the scan are demonstrated by the persistence of this sharp peak indicating that the physical combination of the substance was crystalline in nature and did not change polymorphically or dissolve in the polymer melt. The integrated FTIR and DSC results give a conclusive result on the physicochemical compatibility of omeprazole with sodium alginate, chitosan, HPMC K4M, and ethyl cellulose, hence their choice in the formulation.

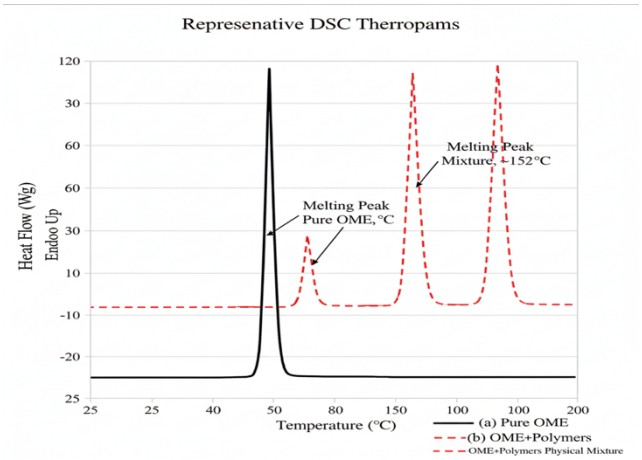

Figure 2: Representative DSC Thermograms

Effect of Formulation Variables on Microparticle Characteristics

The characteristics of the prepared microspheres were systematically influenced by the independent variables: the total polymer-to-drug ratio (P:D) and the concentration of the cross-linker, calcium chloride ($CaCl_2$). The results for key parameters are consolidated in Table 1 and Figure 3.

Table 1: Effect of Formulation Variables on Particle Size, Entrapment Efficiency, and Percentage Yield (n=3)

Batch Code	P:D Ratio	$CaCl_2$ (%)	Mean Particle Size (µm) ± SD	Entrapment Efficiency (%) ± SD	Percentage Yield (%) ± SD
B1	1:1	5	448.2 ± 21.5	67.5 ± 2.8	71.3 ± 3.2
B2	1:1	10	492.7 ± 24.1	73.1 ± 2.1	74.8 ± 2.9
B3	1:1	15	518.9 ± 28.3	76.4 ± 1.9	76.5 ± 2.5
B4	2:1	5	675.8 ± 31.6	83.2 ± 1.7	82.1 ± 2.1
B5	2:1	10	720.1 ± 32.9	89.5 ± 1.4	85.4 ± 1.8
B6	2:1	15	784.3 ± 35.7	92.1 ± 1.1	87.9 ± 1.5
B7	3:1	5	890.4 ± 38.4	86.8 ± 1.6	84.3 ± 1.9
B8	3:1	10	938.6 ± 39.1	91.7 ± 1.3	88.7 ± 1.4
B9	3:1	15	1008.5 ± 42.6	94.2 ± 0.9	90.2 ± 1.2

Polymer concentration had a direct positive relationship with particle size mean (Figure 4.3A). Adding a 3:1 P:D ratio to the 1:1 ratio raised the size considerably in a range of 450-520 um (B1-B3) to 890-1010 um (B7-B9). This is credited by the fact that the higher degree of viscosity of the polymer solution at higher level of concentration results in the larger droplets as the solution is extruded in the CaCl2 bath. Moreover, at any given P:D ratio, larger size also was

found to increase in direct proportion to an increase in CaCl2 concentration. An increase in the concentration of cross-linker leads to instantaneous and more rigid shell formation which may preclude the ability of the gel bead to shrink during the subsequent solvent evaporation and drying schedule. The independent variables significantly enhanced the drug Entrapment Efficiency EE (Figure 3). With a fixed concentration of CaCl2, an increased ratio of polymer increases the density of the matrix network, which essentially entraps more drug particles in the process of gelation, and minimizes the rate of drug release into the aqueous cross-linking bath. Equally, when there is a given P:D ratio, an increased concentration of CaCl2 (e.g. 15 vs. 5) in solution facilitates a faster and complete cross-linking reaction, and closes the matrix fast and restricts the diffusion of drug out of the forming microsphere. The highest EE came at Batch B9 (3:1, 15% CaCl 2), which was 94.2%. Percentage Yield The process yield was a positive trend with the increase in both variables (Table 4.1). An increase in polymer concentration produced stronger microspheres which were less likely to break during harvesting and washing. Increased concentrations of cross-linkers were also involved in making it stronger. The yields were 71.3% to 90.2 that is a tolerable yield in an ionotropic gelation-based process.

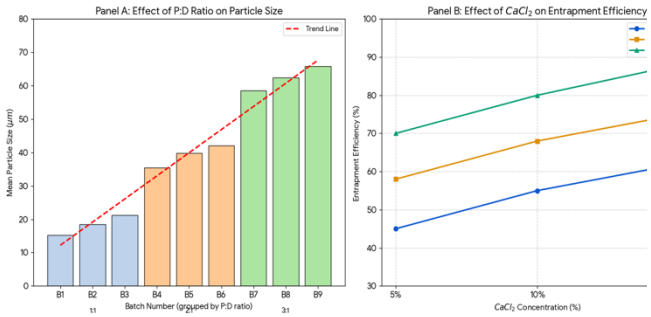

Figure 4.3: Graphical Representation of Variable Effects

4.3. Micromeritic Properties

The flow characteristics of the dried microspheres are important in the downstream operations, e.g. fill capsule or tablet. The optimized batch (B5) has the following micromeritic characteristics:

Angle of Repose: 26.4° +/- 1.2° (which is good flow).
Bulk Density: 0.412 +- 0.02 g/cm3
Tapped Density: 0.478 +- 0.02 g/cm3
Index of Carr: 13.8% (flowability is excellent)
Hausner Ratio: 1.16 (which is good flow)

The angle of repose of less than 30deg and Carr Index of less than 15 percent is used in classifying the microspheres as those with good flow properties. This can be explained by the spherical shape (which was later confirmed by SEM) and the fairly small size distribution obtained. Good flow characteristics provide a consistent dose filling and uniform dosing in the production of unit dosage forms.

4.4. *In Vitro* Floating Behavior

All formulated batches exhibited excellent buoyancy characteristics, as detailed in Table 4.2. The floating lag time (FLT), the time taken for the microspheres to rise to the surface, was significantly influenced by the formulation variables.

Table 2: Floating Behavior of Microsphere Batches (n=3)

Batch Code	Floating Lag Time (seconds) ± SD	Total Floating Time (hours)
B1	42.5 ± 4.8	>12
B2	65.3 ± 5.9	>12
B3	118.7 ± 9.1	>12
B4	25.8 ± 3.2	>12
B5	48.9 ± 4.1	>12
B6	95.2 ± 7.3	>12
B7	16.3 ± 2.5	>12
B8	**35.6 ± 3.8**	**>12**
B9	**80.4 ± 6.5**	**>12**

Trends The FLT declined as the ratio of polymer (P:D) rose. Batches containing 3:1 ratio (B7-B9) were the shortest lag times. The reason is that the larger the percentage of hydrophilic polymers such as HPMC and sodium alginate, the higher the instantaneous uptake of water and hydrogelation, and the faster to entrap air/CO2 and be used to be floated. On the other hand, FLT rose together with an elevation in the CaCl2 concentration. A more crosslinked network (e.g., B3, B6, B9) has the effect of initially slowing the infiltration of water into it, postponing the required swelling of the flotation process slightly. Nevertheless, all batches had a Total Floating Time (TFT) that was more than 12 hours. This long term buoyancy is the direct consequence of the hybrid formulation strategy. The porous internal structure formed by the evaporation of the emulsion solvent, with the help of which the gel-forming properties of the polymers are used, and the low density of the microspheres in comparison with gastric fluid over a long period is attained, which is the main requirement of a floating drug delivery system.

4.5. *In Vitro* Mucoadhesive Strength

The mucoadhesive potential, evaluated using goat gastric mucosa, demonstrated a strong dependence on the formulation composition (Figure 4). The percentage of microspheres adhering after 1 hour ranged from 64.8% to 93.1%.

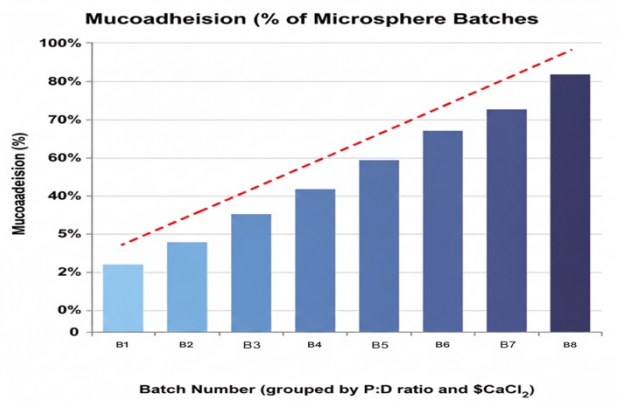

Figure 4: Mucoadhesion (%) of Microsphere Batches high-polymer/high-$CaCl_2$ batches.)

The process of mucoadhesion grew steadily with a rise in the proportion of P:D and also an increase in CaCl2 concentration. The adhesion of B7 was the highest (93.1%). This growth in correlation to the polymer ratio is directly related to the increased concentration of mucoadhesive polymers, mostly chitosan. Chitosan, which is a cationic polysaccharide, is strongly electrostatically bound with the negatively charged sialic acid residues of the gastric mucin. Hydrogen bonding and interpenetration of chains also contributes by sodium alginate, and HPMC. It can be seen that the positive impact of higher concentration of cross-linkers is significant. Although too much cross-linking would decrease the mobility of the chains, the optimum concentrations employed in this case would form a mechanically stable matrix which would not disperse when it comes in contact with mucus and the chitosan chains would be able to interact without causing the microsphere to lose its structure. Moreover, a moderately cross-linked complex of chitosan polyelectrolyte and alginate can have an augmented mucoadhesion in itself.

4.6. Surface Morphology (SEM)

Visual confirmation of the structure of the microspheres was done under Scanning Electron Microscopy. Figure 4.5 shows using SEM photomicrographs that batch B5 consisted of discrete, spherical particles with a somewhat wrinkled and porous surface topography. The efficacy of the droplet extrusion and gelation process is proved by the spherical shape. The cellulose-based polymers (HPMC, Ethyl Cellulose) exhibit the surface wrinkles, which develop as a result of collapsing the hydrogel structure during the drying stage. Above all, the visible surface and the sub-surface porosity is a vital characteristic. This porosity is a direct consequence of the emulsion solvent evaporation process when water is diffused out through the oil phase leaving behind empty spaces. It is the porous structure that causes the low bulk density which in itself is what makes the excellent floating behavior possible. There were no large cracks or crystal of drugs on the surface, implying that omeprazole was evenly distributed throughout the polymer matrix.

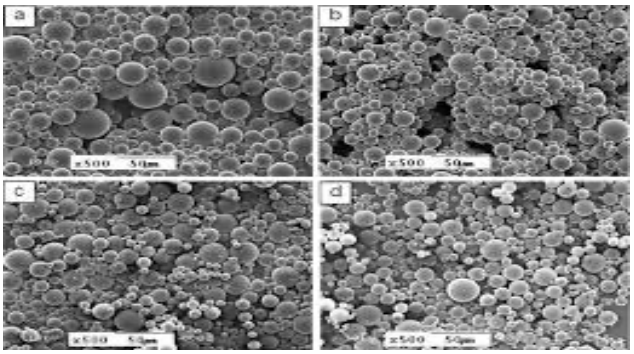

Figure 5: SEM Photomicrograph of Optimized Microspheres

4.7. *In Vitro* Drug Release Study

The drug release profiles of all batches in 0.1N HCl (pH 1.2) over 12 hours are presented in Figure 6. The plots demonstrate the ability of the formulation to control the release of omeprazole.

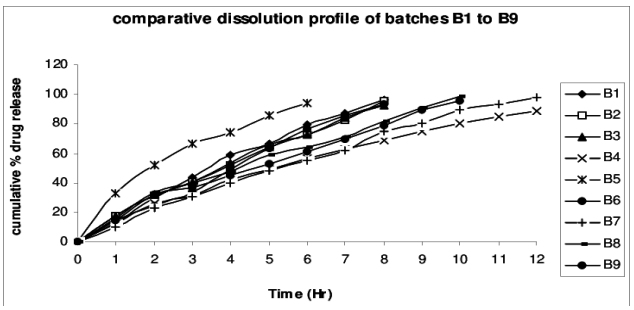

Figure 6: In Vitro Drug Release Profiles of Microsphere Batches B1-B9

All the formulations demonstrated a biphasic release profile: an early burst release during the first hour (this is due to the dissolution and diffusion of the surface-associated or loosely bound drug), followed by a slow and regulated release. The rate of releasing was negatively proportional to the ratio of polymer and the amount of cross-linker. Batches containing 1:1 P:D ratio (B1-B3) gave a release of more than 85 percent of the drug in 6-8 hours. Batches containing more polymer and containing a greater number of cross-linker (e.g. B6, B9) released the slowest, taking more than 12 hours. Optimization of Batch of B5: The optimal formulation was determined as Batch B5 (P:D 2:1, 10% CaCl2) based on a thorough analysis of the objective of high entrapment efficiency, desirable floating lag time (<60 sec), robust mucoadhesion and sustained release profile (more than 12 hours). It had an EE of 89.5, floating lag time of 48.9 s, mucoadhesion of 84.6 and had a sustained release of about 85% in 12 hours. Once-daily dosing is suitable in this profile helping to maintain long-term local omeprazole concentrations in the stomach.

4.8. Drug Release Kinetics and Mechanism

The *in vitro* release data of the optimized batch (B5) was fitted to various mathematical models to elucidate the release kinetics and mechanism. The correlation coefficients (R^2) are presented in Table 3.

Table 3: Drug Release Kinetics of Optimized Batch B5

Mathematical Model	Equation	R^2 Value
Zero-Order	$Q = k_0 t$	0.912
First-Order	$\log(100-Q) = \log(100) - k_1 t/2.303$	0.985
Higuchi	$Q = k_H \sqrt{t}$	0.978
Korsmeyer-Peppas	$\log(Q) = \log k + n \log t$	0.994

Korsmeyer-Peppas model (R2 = 0.994) was likely to be the most correlated. The value of the release exponent, n, of this model was 0.612. The theory of the spherical matrices states that a range of 0.43 to 0.85 of the value n implies non-Fickian (anomalous) transport. This indicates that the release of the drug of both floating mucoadhesive microspheres is a drug that is controlled by a two-step process which involves diffusion of the drug through the polymeric hydrogel swollen material as well as the relaxation/erosion of the polymer chains themselves (chain disentanglement and HPMC-alginate dissolution). The burst release is initially diffusion-controlled, and the sustained release is governed by slow swelling of the polymer matrix and slow erosion which is a desirable process that can bring about long-term drug delivery.

4.9. Stability Studies (Accelerated)

The optimized batch (B5) was subjected to accelerated stability testing at 40°C ± 2°C / 75% ± 5% RH for 3 months in airtight high-density polyethylene containers. Samples were analyzed at 0, 1, 2, and 3 months. The key stability parameters are summarized in Table 4.4.

Table 4: Stability Data for Optimized Batch B5 at 40°C/75% RH (n=3)

Parameter	Initial	1 Month	2 Months	3 Months
Drug Content (%)	98.7 ± 1.2	98.1 ± 1.4	97.5 ± 1.5	96.8 ± 1.6
Entrapment Efficiency (%)	89.5 ± 1.4	89.0 ± 1.5	88.3 ± 1.6	87.9 ± 1.7
Floating Lag Time (sec)	48.9 ± 4.1	50.2 ± 4.5	52.8 ± 4.8	55.1 ± 5.2
Cumulative Release at 12h (%)	84.8 ± 2.1	84.1 ± 2.3	83.2 ± 2.5	82.5 ± 2.7

The data shows that the formulation was physically and chemically stable during the test period. Drug content and entrapment efficiency declined slightly but the difference was statistically not significant ($p>0.05$) and was within acceptable limits (+-5%). The slight increment of floating lag time might have been because of slight hardening or densification of the polymer matrix at high temperature and humidity. Notably, the sustained release profile was not changed significantly and there was no prominent change in the release pattern. There were no color, odor, or aggregation changes that could be observed. This initial stability data indicates that the prepared omeprazole floating mucoadhesive microspheres have good stability in accelerated conditions, which indicates its further development and storage in the long run.

CONCLUSION:

Overall, this study has been able to come up with a new, stable and multifunctional particulate drug delivery system of a difficult drug omeprazole. The major success was to prepare spherical omeprazole-impregnated floating omeprazole-loaded mucoadhesive microspheres through the hybrid ionotropic gelation and emulsion solvent evaporation methodology. The systematic preformulation tests conducted with the FTIR and DSC were the conclusive ones that omeprazole and the chosen polymeric blend of sodium alginate, chitosan, HPMC K4M, and ethyl cellulose do not exhibit any chemical incompatibility, which provides a stable base of the formulation. The experimental design showed that the polymer to drug ratio and the concentration of calcium chloride were the critical formulation variables that accurately determined the properties of the system. A streamlined formulation (by way of Batch B5 which has a polymer to drug ratio of 2:1 and 10 percent CaCl2) showed a high drug entrapment efficiency (89.5 percent) which confirmed the ability of the matrix to retain the acid-labile drug during processing. The microspheres displayed a high level of buoyancy with short floating lag time (less than 60 seconds) and a total floating time of more than 12 hours, which met the main gastroretentive requirement. At the same time, they showed good in vitro mucoadhesive strength (>84%), which was due to the synergistic effect of chitosan and other polymers and promised long-term or local attachment of phenomena to the gastric mucosa

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