CHAPTER VII

Floating Tablet
Effervescent Floating Tablet of Calcium-Disodium edetate for controlled drug delivery against heavy metal exposure by ingestion route

Objective of the present investigation is focused on the formulation development and optimization of floating tablets containing Calcium disodium edetate (Ca-Na₂EDTA) a model drug for chelation therapy against heavy metal exposure. Formulations were optimized for filler (sodium chloride) and Hydroxyl propyl methyl cellulose (HPMC K30). Sodium bicarbonate was used as a gas generating agent. A formulating floating drug delivery system (FDDS) with content of sodium chloride and HPMC were selected as independent variables. Ca-Na₂EDTA matrix tablets prepared by direct compression technique Study revealed that type of filler had significant effect on release of drug and floating property from different concentration of sodium chloride and HPMC gave higher drug release. Dissolution profiles were subjected to various kinetics drug release equations and found that drug release occurred in proportion to transport and diffusion mechanism and erosion, followed by in vitro floating characterization statistically. Effect of hardness on floating properties and dissolution medium on drug release from tablet were examined: Floating properties such as FLT, TFT, and Swelling index was also determined. A novel method was opted for non-invasive in vivo estimation. Optimized formulation was shown to have floating efficiency till the end of four hour in animal and six hours in human subjects. From the results, it was theoretically calculated that the drug concentration in gastric milieu shall be enough for pharmacological action for 24 hours indicating once a day dose. Hydrophilic matrix floating tablets of Ca-Na₂EDTA was developed to increase the gastric residence time which leads to increased bioavailability by giving sufficient time to release the drug in GI tract.
7.1. Introduction

Heavy metal exposure or entry of heavy metal/ radio isotopes is more likely to result through ingestion route from the contaminated environment, hence prime objective of present study is to formulate the formulation which chelate the heavy metal or radioisotopes at the entry level or decontaminate with in stomach before its absorption or distribution to various body parts and provide longer stay of chelating agent for prolong chelation therapy against ingested heavy metals. Prolonged gastric retention improves its local bioavailability, reduces wastage of chelating agent, and improves chelation efficiency of chelation. Oral delivery of drugs is the most preferred administration route due to common entry of metal. Drug bioavailability of pharmaceutical oral dosage form is influenced by various factors. One important factor is gastric residence time of dosage form (Kagan and Hoffman, 2008; Desai Bolton 1993). The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion (Ponchel et al., 1998; Lenaerts et al., 1990) flotation (Deshpande et al., 1997), sedimentation (Rednick et al., 1970 and Davis et al., 1986), expansion (Urguhart et al., 1994 and Mamajek et al., 1980), modified shape systems (Mamajek et al. 1993 and Kedzierewicz et al., 1999), or by the simultaneous administration of pharmacological agents (Groning and Heun 1984 and 1989) that delay gastric emptying and provide long gastric emptying of formulation.

7.2. Basic Gastrointestinal Tract Physiology

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an inter-digestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours (Vantrappen et al., 1979). This is called the inter digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington (1989).

1. Phase I (basal phase) lasts from 40 to 60 minutes with are contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of two consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate (Desai et al., 1993). Food effect and complex moiety of the stomach play major role in gastric retention behavior (Klausner et al., 2003; O'Reilly et al., 1987; Sangekar et al., 1987; Khosla et al., 1989; Abramsson et al., 1993.)

Effervescent floating drug delivery systems generate gas (CO₂), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate (Deshpande et al., 1997; Klausne et al., 2003; Singh and kin 2003). Effervescent floating tablet of Ca-Na₂EDTA retained in stomach improves local bioavailability, reduces drug waste and increase the local chelation of heavy metal with in stomach. In the present work, effervescent floating tablets of several different formulations were developed with an objective of achieving 24 h retention and drug release time and the effervescent floating tablet were compared with conventional formulation of Ca-Na₂EDTA for drug released data.

Concerning floating characteristic of gastric retentive system it is not only important to investigate the onset of floating and floating duration but also the floating strength of the developed dosage form. The floating patterns in high viscous fluid was neglected in many studies, however, in- vivo the tablet has to float in presence of food, which might increase the net viscosity of the gastric medium. As good floating property having good floating
forces increase the probability of tablet to remain afloat in viscous medium, this attribute
plays a major role to reduce food effect on tablet retention (Strubing et al., 2008). The
floating strength of developed system was determined using simplified, non-invasive
Pharmaco-scintigraphy method in animal and human model with radiolabeled tablet.

7.3. Literature review

Abubakr O. N. et al., 2010 developed captopril floating tablets using two viscosity grades
of hydroxyl propyl methyl cellulose (HPMC 4000cps and 15000cps) and Carbopol 934. In-
vitro dissolution profile in simulated gastric fluid (enzyme free at 37°C ± 0.5°C) was
compared to conventional tablets, release pattern of captopril from these tablets was
apparently prolonged; as a result, a 24-hr controlled-release dosage form for captopril was
achieved. Drug release best fit both Higuchi model and Korsmeyer & Peppas equation,
followed by first-order kinetics. While tablet hardness and stirring rate had no or little
effect on the release kinetics, tablets hardness was found to be a determining factor with
regard to the buoyancy of the tablets.

Akelesh T et al., 2011 developed a gastro-retentive floating tablet of acyclovir by direct
compression method using gas forming agents like sodium bicarbonate and natural gums
like locust bean gum, sodium alginate and xanthan gum. The floating tablets were
evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy,
buoyancy lag time and dissolution studies. The formulation was optimized for different
concentration of natural gums like locust bean gum, sodium alginate and xanthan gum. The
results of in vitro release studies showed that optimized formulation F7 could sustain drug
release (99.08%) for 16 hr and remain buoyant for 24 hr which contains 60% of locust bean
gum and 40% sodium alginate out of total floating polymer while amount of xanthan gum
is same in all 7 batches. F7 formulation fitted best for Korsmeyer – Peppas model and
showed no significant change in physical appearance, drug content, floatability or in vitro
dissolution pattern after storage at 45°C/75% RH for two months.

Arunachalam A. et al., 2010 prepared floating tablet of Levofloxacin hemihydrate by melt
granulation method, using the polymer, hydroxy propyl methyl cellulose (HPMC K100M)
with different amounts of other excipients and sodium bicarbonate as gas generating agent
for sustained drug delivery and gastric retention. Tablets were evaluated by different
parameters such as weight uniformity, content uniformity, thickness, hardness, IR spectral analysis, in vitro release studies, Buoyancy determination and kinetic analysis of dissolution data and stability studies Levofloxacin floating tablet drug delivery system showed improved in-vitro bioavailability and extended drug release which may favor the reduced dose frequency and patient compliance.

Barhate S. D. et al., 2010 prepared bi-layer floating tablets of famotidine using HPMC K100LV, HPMC K4MCR, sodium bicarbonate, sodium alginate, sodium starch glycolate, croscarmellose, crospovidone and lactose. Box-Behnken factorial design was used to statistically optimize the controlled release layer composition and evaluation of the effect of amount of HPMC K100LV (X1), amount of HPMC K4MCR (X2) and amount of sodium bicarbonate (X3) on release rate of famotidine. The polymers HPMC K100LV, HPMC K4MCR showed better control over drug release. The formulated formulations of Box-Behnken factorial design showed zero-order drug release.

Chen X. et al., 2005 developed gentamycin sulfate floating tablets which could prolong the residence time of drug in the stomach and improve the bioavailability. The release in vitro of gentamicin-HBS was determined by rotary basket method (100 rpm, 37±0.5°C, 0.1M HCl. The release characteristics of gentamicin sulfate showed the first-order kinetics, While Zinc gluconate showed good zero-order kinetics. The gamma scintigraphy technique was used to examine the gastric residence time of gentamicin-HBS and conventional gentamicin sulfate tablets. It showed that the gastric residence time of all subjects taking gentamicin-HBS under fed and fasted condition were over 4 h in contrast with conventional gentamicin tablets of only 1-2 h.

Choi B.Y. et al., 2002 prepared the floating beads from a sodium alginate solution containing CaCO3 or NaHCO3 as gas-forming agents. The solution was dropped to 1% CaCl2 solution containing 10% acetic acid for CO2 gas and gel formation. As gas-forming agents increased, the size and floating properties increased. Bead porosity and volume average pore size, as well as the surface and cross-sectional morphology of the beads were examined with Mercury porosimetry and Scanning Electron Microscopy. NaHCO3 significantly increased porosity and pore diameter than CaCO3. Incorporation of CaCO3 into alginate solution resulted in smoother beads than those produced with NaHCO3. Gel strength analysis indicated that bead strength decreased with increasing gas-forming agent.
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from 9 to 4 N. Beads incorporating CaCO₃ exhibited significantly increased gel strength over control and NaHCO₃-containing samples. Release characteristics of riboflavin as a model drug were studied in vitro. Release rate of riboflavin increased proportionally with addition of NaHCO₃. The results of these studies indicate that CaCO₃ is superior to NaHCO₃ as a gas forming agent in alginate bead preparations.

Gnanaprakash et al., 1999 designed a formulated to increase gastric retention time and control drug release with isolated chitosan by wet granulation technique. Optimized formulation was selected based on in vitro characteristics, in-vivo radiographic studies by incorporating BaSO₄. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. In vivo buoyancy study was performed in beagle dogs to evaluate intra-gastric retention performance in different time intervals by X-ray radiographic method. Followed by the floating tablets were evaluated for its pharmacological activity in New Zealand white albino rabbits by immobilization stress induced ulcer in comparison with commercially available standard. The floating formulation shows excellent buoyancy and better gastric cytoprotection when compared with conventional dosage form.

Havalodar V. D. et al., 2008 optimize and evaluate the floating tablets of atenolol that prolongs the gastric residence time by direct compression method using semisynthetic polymers, HPMC K4M, HPMC K100M and natural polymer, Xanthan gum were used as release retarding agents and sodium bicarbonate was used as a gas-generating agent. Dicalcium phosphate was used as a channeling agent. Concentration of polymers and a gas-generating agent was optimized for controlled release of atenolol up to 8h. The optimized tablets were evaluated for physicochemical parameters. A significant difference in drug release at 0.5, 1, 4 and 8 h (p <0.0001) was observed. The floating lag time of all the formulations was within the prescribed limit (< 10 min.). Based on the diffusion exponent (n) value, drug release was found to be diffusion controlled.

Jangde R. et al., 2008 developed a floating tablet of NSAID nimesulide which can increase its absorption from stomach by increasing its gastric residence time. The polymers used were HPMC (low and high viscosity), gaur gum, carbopol along with sodium bicarbonate as the gas-generating agents. In-vitro release studies indicated that the nimesulide release
form the floating dosage form was uniform and followed zero order release profile. The incorporation of guar gum helps to maintain the device's integrity and its viscosity property. Karkhile V.G. et al., 2010 prepared a Floating tablet of Furosemide by direct compression technique. PEG-6000 is used as complexing agent for increasing solubility of Furosemide in water, while Hydroxypropylmethylcellulose, sodium bicarbonate and carbopol were used as matrixing agent, gas generating agent and floating enhancers respectively. The data of in-vitro dissolution study shows that the zero order plots were found to be fairly linear as indicated by their high regression value \( R^2 = 0.9772 \) to 0.9911. To confirm the exact mechanism of drug release from different formulation, the data was fitted to Korsmeyer & Peppas equation. Regression values were from 0.9862 to 0.9963 which indicates linearity.

Khemariya P. et al., 2008 prepared a gastro-retentive drug delivery system of Ranitidine HCL used to target drug release in stomach or to upper part of the intestine. The polymer PVC and Sodium bicarbonate was used as the gas-generating agents. Sodium bicarbonate causes the tablets to float for more than 24hr. The prepared tablets were evaluated on their physicochemical properties and drug release characters. In-vitro release studies indicate that the Ranitidine release from the floating dosage form was uniform followed zero order release. The tablets with methocel K100 were found to float for longer duration of time as compared to formulations containing methocel K15M.

Krogel I. et al., 1999 developed and evaluate floating and pulsatile drug delivery systems, which were based on a reservoir system of polymeric coated effervescent core of drug. The mechanical properties (puncture strength and elongation) of acrylic (Eudragit® RS, RL or NE) and cellulosic (cellulose acetate, ethyl cellulose) polymers were characterized with a puncture test in the dry and wet state. For the floating system, a polymer coating with a high elongation value, high water and low \( \text{CO}_2 \) permeability was selected (Eudragit® RL/acetyltributyl citrate 20%, w/w) in order to initiate the effervescent reaction and the floating process rapidly. For pulsatile DDS, a weak semi permeable film, this ruptured after a certain lag time was selected. A polymer (cellulose acetate or hydroxyl propylmethylcellulose) was added to the core to control the drug release. The time to flotation could be controlled by the composition (type of filler, concentration of effervescent agents) and hardness of the tablet core and the composition (type of polymer and plasticizer) and thickness of the coating.
Mallikarjun V. et al., 2009 developed a gastro retentive DDS of Glipizide using different grades of HPMCK4 and HPMC K15 polymers as excipients. Sodium bicarbonate was incorporated as a gas-generating agent. All the prepared batches showed good in vitro buoyancy. The tablet swelled radially and axially during in vitro buoyancy studies. It was observed that the tablet remained buoyant for 12-20 hours. The tablets with HPMCK15M were found to float for longer duration as compared with formulations containing HPMC-K4 M.

Mittal H. et al., 2005 formulated a double-layer sustained release compressed hydrophilic matrix in order to achieve a foreseeable and reproducible flotation of the tablet. Another layer of sodium bicarbonate was used to generate carbon dioxide; this gas was entrapped in the gelified hydrocolloid. The in vivo behaviour of this floating tablet was compared to a classical HBS capsule and to a similar but non-floating double-layer hydrophilic matrix on subjects alternatively in fasted or fed state. As these three dosage forms contain a riboflavin (RF) soluble derivative, it was possible to measure the RF urinary excretion rates and, conclude that in vivo buoyancy is preponderant over bioadhesion for both floating capsules and tablets. These dosage forms also significantly increase the gastric residence time when compared to the non-floating dosage form. Compared to the classical HBS capsule, the floating tablet is showing in vivo equivalent floating properties when administered after a light meal and higher RF urinary excretion rates when administered to fasted subjects.

Nakhat P.D. et al., 2006 developed matrix tablets of diclofenac sodium by using different drug: polymer ratios, such as F1 (1:0.12), F2 (1:0.16), F3 (1:0.20), F4 (1:0.24) and F5 (1:0.28). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluent. All the lubricated formulations were compressed using 8 mm flat faced punches. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, in vitro dissolution using basket method, and swelling index. All the formulations showed compliance with pharmacopoeial standards. Among different formulations, F1 showed sustained release of drug for 12 hours with 89.67% release. The effect of other parameters like addition of release modifier (PEG 6000), gum concentration, pH of dissolution medium, rotation speed and dissolution by paddle method, were also studied. Selected formulation (F1) was subjected to stability studies for three months at 0-4°C, room temperature (28°C), and 45°C with RH 75±5%, and showed stability with...
respect to release pattern. The kinetic treatment showed that it follows zero order kinetic \((R^2 = 0.9758)\). Narendra et al., 2006 optimized floating drug delivery system containing metoprolol tartrate (MT) as a model drug by the optimization technique. A 23 factorial design was employed in formulating the GFDDS with total polymer content-to-drug ratio \((X_1)\), polymer-to-polymer ratio \((X_2)\), and different viscosity grades of hydroxypropyl methyl cellulose (HPMC) \((X_3)\) as independent variables. Four dependent variables were considered: percentage of MT release at 8 hours, \(T_{50}\), diffusion coefficient, and floating time. The results indicate that \(X_1\) and \(X_2\) significantly affected the floating time and release properties, but the effect of different viscosity grades of HPMC (K4M and K10M) was non-significant. Regression analysis and numerical optimization were performed to identify the best formulation. Fickian release transport was confirmed as the release mechanism from the optimized formulation.

Ozdemir N. et al., 2007 formulate floating tablets of furosemide with controlled release, because of less solubility of API in the gastric medium, it was first enhanced by preparing an inclusion complex of FR with beta-cyclodextrin (β-CD) in a 1:1 proportion using the kneading method. After dissolution rate studies were performed using the continuous flow-through cell method. The formulation was given to six healthy male volunteer subjects, and in vivo tests were performed. It was determined by radiographs that floating tablets prepared by adding \(\text{baso}_4\) stayed in the stomach for 6 hr. Further, values of the area under the plasma concentration-time curve (AUC) obtained with the floating dosage form were about 1.8 times those of the conventional FR tablet in blood analyses; maximum and minimum plasma concentrations were also found to be between the desired limits. In urine analyses, the peak diuretic effect seen in classical preparations was decreased and prolonged in floating dosage forms. Also, a considerably significant correlation was detected between in vivo results and in vitro data of the dissolution rate, and it was concluded that the modified continuous flow-through cell method is usable for in vitro dissolution rate tests of floating dosage forms.

Ozdemir S. et al., 2009 optimize the floating matrix tablets using HPMC and other excipients. The technological process development of the floating tablets with a high dose of freely soluble drug and characterization of those tablets (crushing force, floating
properties in vitro and in vivo, drug release) was examined. The investigation shows that tablet composition and mechanical strength have the greatest influence on the floating properties and drug release. The drug release from those tablets was sufficiently sustained (more than 8 h) and non-fickian transport of the drug from tablets was confirmed. Radiological evidence suggests that, that the formulated tablets did not adhere to the stomach mucus and that the mean gastric residence time was prolonged (>4 h).

Padmavathy J. et al., 2011 outlines the systematic approach for designing and development of Ofloxacin floating tablets for enhance its bioavailability and therapeutic efficacy of the drug. Floating tablets of Ofloxacin have shown controlled release thereby proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. Different formulations were formulated by wet granulation technique using HPMC K4M, HPMC K15M and HPMC K100M (floating agent) as polymers along with sodium bicarbonate as gas generating agent. All six formulations possessed good floating properties with total floating time between 8 – 12 hrs. The in-vitro cumulative % drug release of the formulations F1A, F1B, F2A, F2B, F3A and F3B were 102.85%, 101.32%, 100.2%, 99.98%, 99.28% and 97.25%.

Pare A et al., 2008 prepared a Amlodipine besylate effervescent floating tablets with ten different formulas (F1 to F10) by employing different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid. The formulations were evaluated for physical parameters, buoyancy studies, dissolution parameters and drug released mechanisms, out of which formulation F10 showed maximum floating time of 24 hours and gave controlled and optimum drug release of Amlodipine besylate spread over 24 hours.

Patel V.F. et al., 2006 describes statistically the influence of viscosity of hydroxypropyl methylcellulose and types of filler on dipyridamole release from floating matrix tablets using \(3^2\) full factorial design. Tablets were prepared by direct compression. Tablets were evaluated for in vitro floating ability and drug release study using USP 24 types II paddle apparatus using 0.1 N HCl (pH 1.2) at rotation of 100 rpm and temperature of 37±0.5°C. It was observed that as viscosity of polymer increases the release rate constant was decreased. Release rate obtained was highest when microcrystalline cellulose was employed as filler followed by dicalcium phosphate and lactose. Mechanism of drug release was anomalous.
types and depends upon viscosity of polymer and types of filler used. Microcrystalline cellulose gave release mechanism nearer to diffusion mechanism while dicalcium phosphate and lactose gave anomalous release. A major controlling factor for kinetics of drug release was viscosity of polymer and it can be modified by incorporation of different types of filler.

_Prajapati S.T. et al., 2009_ developed a sustained release formulation of domperidone along hydrophilic polymeric as excipients. Hydrophilic polymers swell in the presence of water to form hydrogel structures from which drugs was released by slow diffusion. The release rate modulation is obtained by the use of different types of polymer alone or in combinations. Optimization of the release rate of domperidone from mixtures containing two hydrophilic polymers, poly (ethylene oxide) WSR 303 (PEO) and hydroxyl propyl methyl cellulose (HPMC) and sodium bicarbonate was made by simplex lattice design. He was observed that as the PEO increased release rate constant decreased. Mechanism of drug release was anomalous type and dependent upon proportion of HPMC and PEO.

_Ramírez C. et al., 2006_ studied the in vitro dissolution of metronidazole from sustained release floating tablets with varied proportions of sodium bicarbonate (SB) and Pharmatose DCL 11 using methocel K4M and Carbopol 971P NF. The variables studied include the matrices’ release profile, hydration volume, and floating behavior. All Methocel matrices floated more than 8 h with SB proportions up to 24%, while Carbopol matrices floated more than 8 h with SB proportions only up to 12%. Matrices’ hydration increased with time until reaching a peak and declining thereafter. Methocel matrices showed greater hydration volumes and greater drug dissolution compared to Carbopol matrices. After adding increasing quantities of Pharmatose to matrices containing 12% SB, hydration volume decreased while dissolution increased. Carbopol matrices showed greater susceptibility to the added Pharmatose, becoming more erodible and releasing higher quantities of metronidazole. The greater Carbopol susceptibility to added Pharmatose was attributed to its faster hydration.

_Reddy S. N. et al., 2000_ prepared a floating DDS for Captopril along with Xanthan gum and sodium bicarbonate by direct compression method. The prepared tablets were evaluated for physical properties, content uniformity, hardness, friability, floating lag time and in vitro
drug release. Among the studied formulations F9 was found to be suitable for gastric retention based on evaluation parameters. The linear regression analysis and model fitting showed that all these formulations followed Higuchi mode. Stability studies of all formulations were carried out at elevated temperature and humidity conditions of $40\pm 2^\circ C/75\pm 5\% \text{ RH}$ and a control sample was placed at ambient conditions for 12 months.

Sarkar D. M. et al., 2010 formulated gastroretentive floating tablets of carbamazepine and optimizes drug release profile using Hydroxypropylmethyl cellulose (HPMC) of different viscosity grades and ethyl cellulose. They observed that HPMC viscosity, the presence of ethyl cellulose and their interaction had significant impact on the release and floating properties of the delivery system. Polymer with lower viscosity (HPMC K4M) was shown to be beneficial than higher viscosity polymer (K15M) in improving the floating properties of GFDDS. Incorporation of ethyl cellulose, was found to compromise the floating capacity of GFDDS and release rate of carbamazepine.

Sangkar K. et al., 2002 studied on effect of food on the gastric retention time of floating (spec. gravity 0.96) and non-floating (spec. gravity 1.59) tablet formulations was investigated using gamma scintigraphy in humans. The results indicate that the presence of food in stomach appears to significantly prolong gastric retention of both floating and non-floating tablets while specific gravity doesn't seem to play any important role in tablet residency time in stomach.

Sharma M. et al., 2011 worked on Cefpodoxime proxetil floating tablet to increase the gastric residence time and prolonging the drug release by direct compression technique. Hydroxy propyl methyl cellulose (HPMC) of different viscosity grades was used. The prepared tablets were evaluated in terms of their pre-compression parameters, physical characteristics like hardness, friability, uniformity of weight, uniformity of drug content, swelling index, in-vitro floating studies, drug release and stability studies. All the formulations showed good in-vitro floating properties with an optimum concentration of gas generating agents' sodium bicarbonate and citric acid. The rate of drug release decreased with increased polymer concentration. It was found that HPMC viscosity had significant impact on the drug release from the prepared HBS. Among the three viscosity grades of HPMC (K4M, K15M, K100M), HPMC K4M along with lactose as diluents was found to be beneficial in improving the drug release rate and floating properties.
**Shinde S. et al., 2010** formulated the floating matrix tablets of Salbutamol sulphate by wet granulation method. Hydroxypropyl methylcellulose was used as a release retardant material and sodium bicarbonate and Citric acid was incorporated as a gas-generating agent. The effects of citric acid on drug release profile, floating properties and matrix integrity of tablet were investigated. Addition of high level of HPMC K100M didn't significantly retard the burst effect and tablet disintegration produced by citric acid but addition of stearic acid was necessary to retard the same. The in vitro drug release followed Korsemeyer-Peppas kinetics and the drug release mechanism was found to be of anomalous type.

**Sivabalan M. et al., 2011** formulated and evaluated the hydrodynamically balanced controlled drug delivery system of Glipizide using different formulae of floating tablet consisting of various polymers like HPMC, MC and EC. Dissolution study was carried out in simulated gastric fluid using USP dissolution test apparatus employing paddle stirrer. The variation in weight was within the range of ±3% complying with pharmacopoeial specifications (±7.5%). The drug content varied between 9.127±0.1317mg and 9.923±0.0183mg in different formulations indicating content uniformity. The buoyancy of the tablets was ranged between 10.917±0.4403hrs and 16.237±0.1217 hrs, the maximum buoyancy was seen in G8, which has a high level of drug to polymer ratio.

**Streubelet al., 2000** developed single unit of floating controlled drug delivery systems consisting of polypropylene foam powder, matrix-forming polymers, drug, and filler. All foam powder-containing tablets remained floating for at least 8 h in 0.1 N HCl at 37°C. Different types of matrix-forming polymers were also studied for example hydroxypropyl methylcellulose (HPMC), polyacrylates, sodium alginate, corn starch, carrageenan, gum guar and gum arabic. The tablets eroded upon contact with the release medium, and the relative importance of drug diffusion, polymer swelling and tablet erosion for the resulting release patterns varied significantly with the type of matrix former. The release rate could effectively be modified by varying the “matrix-forming polymer/foam powder” ratio, initial drug loading, tablet geometry (radius and height), matrix-forming polymer, polymer blends and the addition of water-soluble or water-insoluble fillers (such as lactose or microcrystalline cellulose).
Wei C. et al., 2009 developed floating tablet for gastric retention of cisapride as a model drug. The in vitro drug release was determined, and the resultant buoyancy and the time-buoyancy curve were plotted. Because of the sodium bicarbonate added to the floating layer, when immersed in simulated gastric fluid (SGF) the tablet expands and rises to the surface, where the drug is gradually released. The in vitro drug release of this kind of two-layer dosage was controlled by the amount of hydroxyl propyl methyl cellulose (HPMC) in the drug-loading layer.

Wieslaw S. et al., 2002 work on pharmacokinetics of verapamil (V) in a dose of 40 mg and its metabolite norverapamil (N) from the new oral drug formulation in a form of capsule filled with floating pellets. Conventional 40-mg tablets used in a medical practice served as a reference. Bioavailability studies were carried out in 12 healthy volunteers including six men and six women. In an in vitro test the pellets floated on the surface of the extraction fluid for 6 h. mean value of maximum plasma concentration ($C_{max}$) of V for floating pellets was 28.27 ng ml$^{-1}$ and $t_{max}$ 3.75h. The value of the area under the concentrations versus time; $AUC_{o-\infty}$ was calculated as 364.65 ng ml$^{-1}$h, biological half-lives of the absorption and elimination ($T_{1/2a}$) phase were 0.5h and 10.68h, respectively. For the reference conventional tablets those values were 33.07 ng ml$^{-1}$, 1.21 h, 224.22 ng ml$^{-1}$ h, 0.36h and 6.17h, respectively.

7.4. Experimental Methods

Ca-Na$_2$EDTA Floating hydrophilic matrix tablets were prepared by direct compression technique using different grades of polymer of varying concentrations as well as different concentration of sodium bicarbonate and varying ratios of MCC. All the ingredients except magnesium stearate and talc were blended in glass mortar pestle uniformly. After sufficient mixing of the chelating agent as well as other components, magnesium stearate and talc was added and further mixed for additional 2-3 minutes. The Tablets were compressed using 12mm punches on a 10 station rotary tablet punching machine (Lab Press, CIP Machineries Pvt. Ltd, Ahmedabad India). The weight of tablets was kept constant for tablets of all formulation, which were 650mg for formulation F1 to formulation F13. The compositions of all the formulations are tabulated in table 7.1.
Table 7.1: Optimization of tablet formula at different composition

<table>
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<tr>
<th>Exp. No.</th>
<th>Tablet code</th>
<th>Amount of Ca-Na2EDTA (g)</th>
<th>Amount of Carbopol (g)</th>
<th>Amount of Avicel (g)</th>
<th>Amount of citric acid (g)</th>
<th>Amount of NaHCO₃ (g)</th>
<th>Amount of NaCl (g)</th>
<th>Amount of HPMC (g)</th>
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<tr>
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</tr>
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<td>100</td>
<td>55</td>
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</tr>
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<td>F10</td>
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<td>100</td>
<td>55</td>
<td>30</td>
<td>70</td>
<td>130</td>
<td>65</td>
</tr>
<tr>
<td>13</td>
<td>F13</td>
<td>200</td>
<td>100</td>
<td>55</td>
<td>30</td>
<td>70</td>
<td>65</td>
<td>130</td>
</tr>
</tbody>
</table>

7.4.1. In process quality control of floating tablets (TP-2007, USP 30-NF-25):

All prepared floating tablets were evaluated for its uniformity of weight, hardness, friability and thickness according Indian Pharmacopoeia.

7.4.1.1. Hardness

The tablet crushing strength was tested by commonly used Monsanto type tablet hardness tester (IEC, Mumbai, India). A tablet was placed between the anvils and the crushing strength, which causes the tablet to break, is recorded.

7.4.1.2. Friability

This test is applicable to compressed tablets and is intended to determine the physical strength of tablets. Dedusting was done carefully of the tablets and weighs twenty tablets and placed in the drum of Electrolab friabilator. The apparatus was rotated at 25rpm for 4mins. After 4 minutes the tablets were dedusted and weighed again. The percentage friability was measured using the formula maximum loss of weight (from a single test or from the mean of the three tests) not greater than 1.0 per cent is acceptable for most tablets. Obviously cracked, chipped or broken tablets present in the sample after tumbling, the sample fails the test.
If the size or shape of the tablet causes irregular tumbling, adjust the drum base so that it forms an angle of about 10° with the horizontal and the tablets do not bind together when lying next to each other, which prevents them from falling freely.

\[
% F = \left( \frac{W_f - W_i}{W_f} \right) \times 100
\]

Where, \( % F \) = Friability in percentage
\( W_0 \) = Initial weight of tablets; \( W \) = Final Weight of tablets after 4 minutes.

7.4.1.3. **Weight variation**

Weigh individually 20 units selected at random or, for single dose preparations in individual containers, the contents of 20 units, and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage.

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Average weight</th>
<th>Percentage deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>tablets</td>
<td>80 mg or less</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>More than 80 mg but less than 250 mg</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>250 mg or more</td>
<td>5</td>
</tr>
</tbody>
</table>

7.4.1.4. **Thickness**

It was accomplished on 20 tablets by measuring thickness using venire caliper.

7.4.1.5. **In-vitro buoyancy**

*In-vitro* buoyancy studies were performed for all preparations as per the method described by Rosa *et al.*, 1994. The randomly selected tablets from each formulation were kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time. The overall floating time was calculated during the dissolution studies.

7.4.1.6. **Drug uniformity**

The test for uniformity of content of single-dose preparations is based on the assay of the individual contents of active substance(s) of a number of single-dose units to determine
whether the individual contents are within limits set with reference to the average content of the sample. Ca-Na₂EDTA content in the tablets was estimated by using UV spectrophotometric method based on the measurement of absorbance at λ<sub>max</sub> = 246 nm in phosphate buffer 7.4. Tablet complies with the test, if individual content is between 85 to 115 per cent of the average content (label claim). The preparation fails to comply with the test, if more than one tablet content is outside these limits or if any individual content is outside the limits of 75 to 125 per cent of the average content. If one individual’s content is outside the limits of 85 to 115 per cent of the average content but within the limits of 75 to 125 percent, repeat the determination using another 20 tablets. The preparation complies with the test if not more than one of the individual contents of the total sample of 30 dosage units is outside 85 to 115 per cent of the average content and none is outside the limits of 75 to 125 per cent of the average content.

7.4.2. Dissolution/Drug release

In-vitro drug release studies of F1 to F13 formulations and one conventional tablet of Ca-Na₂EDTA (Developed at INMAS) were carried out in the dissolution test apparatus (USP Type II). The tests were carried out in 900 ml of dissolution media 7.4 pH buffers for 24 h at 50 rpm at 37±0.5°C, 10ml of the aliquot was withdrawn at different predetermined time intervals (0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 hr) and filtered. 5ml of sample was replaced in the vessel after each withdrawal to maintain sink condition. The required dilutions were made and the solution was analyzed for the drug content by using UV-spectrophotometer detecting at λ<sub>max</sub> 246nm. From this percentage drug release was calculated and it was plotted against function of time to study the pattern of drug release. The in-vitro drug release profiles of tablet from each batch (F1 to F13) was done and tabulated. The plot of cumulative percentage drug release versus time (hr) was plotted and depicted.

7.4.3. Swelling Index

Swelling index of individual batch was carried out using USP dissolution apparatus-II (rotating paddle), in 900 ml of 0.1NHC1 which is maintained at 37±0.5°C, rotated at 50 rpm. Weight of individual tablet was taken prior to the swelling study (W<sub>i</sub>). The tablet was
kept in a basket. The tablet was removed after every one hour time interval up to 12 hour and excess water was removed carefully using filter paper. The swollen tablets were re-weighed (Wf); Percentage hydration (swelling index) was calculated as shown in table below using following formula,

\[
\% \text{Swelling Index} = \left( \frac{W_f - W_i}{W_i} \right) \times 1000
\]

Where \( W_i \) = initial weight of tablet, \( W_f \) = Final weight of the swollen tablet.

7.4.4. Analysis of release mechanism

Dissolution test was designed to determine compliance with the dissolution requirements for solid dosage forms administered orally. In order to examine the release mechanism of Ca-Na\textsubscript{2}EDTA from the prepared floating tablets of the optimized formulation (F8), the results of the dissolution study was examined in accordance to the kinetic models. The regression coefficient \( R^2 \) value nearer to 1 indicated the model fitting of the release mechanism. The commonly adopted models for understanding the release of drugs from matrices are zero-order equation, first-order equation (Gibaldi, Feldman, 1967; Wagner, 1969), Higuchi equation (Higuchi, 1963) and Korsmeyer-Peppas simple exponential equation (Korsmeyer et al., 1983; Peppas, 1985) models. These simple exponential equation models have been used to elucidate the mode of release.

Comparison with conventional tablet

The promising formulation (F8) as found by evaluation studies was compared with conventional tablet for in-vivo compression. The evaluation parameters tested and compared in-vitro dissolution profile. The values of comparative in-vitro dissolution study of optimized formulation (F8) and conventional tablet product are recorded, followed by in-vivo performance in animal and human studies.

7.4.5. In-vivo studies

The in-vivo test was performed as per approved protocol by institutional ethical comities. Six healthy New Zealand white rabbit, weighing approximately 2-2.5kg, were used throughout the study. In each experiment an un-anaesthetized animal was fasted for at least 24h. One radiolabelled tablet of optimized formulation containing (200\muCi of 99m\textsuperscript{T}Technetium pertechnetate) was given to New Zealand white rabbit orally followed by
100 ml of water. During the experiment the rabbit were not allowed to eat, but water was available ad libitum. For Scintigraphy imaging the animal was positioned in right lateral or ventrodorsal recumbency. At different time intervals (30min, 2h, 4h and 6h) scintigraphy images of abdomen area were acquired by gamma camera (GE electronics, USA). Experimental condition was kept the same for all experiments. It allowed us to visualize the tablet in the stomach, antrum or pyloric part of the stomach; so that observation of tablet movements could be made.

7.4.6. Phase zero clinical studies

In vivo gamma scintigraphy

A total of six healthy volunteers were recruited after giving informed written consent for gastric emptying studies (mean age 35 years, 22–54 years). The clinical protocol was approved by the institutional Human Ethics Committee (Reg. No. INM/TS/IEC). Vital parameters were recorded before and 30 min after each dose and before discharging the subject from the study centre. Adverse events were monitored throughout the study. The studies were conducted on a dual head gamma camera system (Symbia T2, Siemens, Erlangen, Germany). The investigational radiolabelled formulation contained 200 mg of radiolabelled Ca-Na₂EDTA (1-2Bq), given to the subject (on fasting) in sitting position with 200 ml of water at room temperature. The activity was followed by mouth to assess compliance to dosing. Subjects were instructed not to lie down for the first two hours after dosing except during gamma imaging. Thereafter the subjects were allowed to engage only in normal activities while avoiding severe physical exertion. Dynamic scintigraphy imaging was performed for first 15-30 minutes at appropriate frame rate immediately after swallowing the formulation, followed by sequential static imaging every hour’s intervals till six hours. Imaging was done from both camera heads, placed anteriorly and posteriorly over abdomen. All images were recorded on a computer system assisted with the software EntegraVersion-2. Additional images of the chest were taken between 2h and 4 h. This was done to observe the movement of radioactivity, if any.

For comparison, the same volunteers was called for conventional tablet of Ca-Na₂EDTA (200mg) containing Tc-99m labelled Ca-Na₂EDTA (1.5-2MBq) on another day and the scintigraphy procedure was repeated as described above.
Scan analysis

Images acquired on the same time scale ensured that the count statistics comparison between different scans were valid. Region-of-Interest was drawn around the tablet area and whole stomach for obtaining count statistics. Since transfer of food from stomach to intestine release radioactivity continuously from stomach to intestine, counts deposited in these two organs were integrated to represent a single compartment. Gastric emptying was calculated in the initial and delayed images. Visual comparison between the floating behaviour of tablet in stomach images was done to record movement of the drug release from the tablet matrix with respect to time from one compartment to another.

7.4.7. Efficacy studies

A total of six healthy male volunteers were recruited for efficacy studies (mean age 35 years, 22-54 years). Vital parameters were recorded before and 30min after each dose and before discharging the subject from the study centre similarly as mention in Phase zero trials. Adverse events were monitored throughout the study. The studies were conducted on a dual head gamma camera system (Symbia T2, Siemens, Erlangen, Germany). The investigational formulation contains 200mg Ca-Na$_2$EDTA was orally administered to the subject (on fasting) in a sitting position with 200ml of water at room temperature followed by oral administration of 99m- technetium pertechnetate (1-5MBq). Subjects were instructed not to lie down for the first two hours after dosing except during gamma imaging. Thereafter the subjects were allowed to engage only in normal activities while avoiding severe physical exertion. Dynamic scintigraphy imaging was performed for first 15-30 min at appropriate frame rate immediately after swallowing the formulation, followed by sequential static imaging every hour’s intervals till six hours. Imaging was done from both camera heads, placed anteriorly and posteriorly over abdomen. All images were recorded on a computer system assisted with the software EntegraVersion-2. Additional images of the stomach and intestinal area were also taken between 2 and 4 h. This was done to observe the movement of radioactivity, if any.

For comparison, the same volunteer was called for oral administration of technetium pertechnetate only on another day and the scintigraphy procedure was repeated similarly as described above.
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7.4.8. Stability studies

As per ICH guidelines

The physical stability of floating tablet was evaluated after storage for 6 months. Hundred tablet of Ca-Na$_2$EDTA was stored in closed close container at 25±0.5°C (room temperature). Ten tablet of the formulation was withdrawn at 0, 1, 2, 4 and 6 month time intervals and crush to make up the volume up to 10 ml with solvent to measure drug content. For quantitative analysis, UPLC was performed using a Waters Acquity system equipped with a binary solvent delivery pump, an auto-sampler, and a tunable UV detector (Waters, USA). The chromatographic separation was performed using a Waters Acquity HSS T-3 (100 × 9.12.1) mm; 5μm RP 18(C$_{18}$), LiChrospher®100,(250×4.6mm), C18 column. A mixture of ammonium acetate and acetonitrile solution (10mM, pH 3.00 ± 0.05 adjusted with 85% phosphoric acid) at pH=3 in the ratio 60:40 (v/v) with a trace of triethyl amine as mobile phase at a flow rate of 1.0 mL min$^{-1}$. UV detection was performed at 246nm.

Accelerated stability as per conventional method by Arrhenius equation

Floating tablet is intended to be stored at room temperature (25°C) conditions and away from moisture. For the determination of shelf life by conventional method, ophthalmic formulation was kept at 40± 0.5 °C; 50 ± 0.5 °C and 60 ± 0.5 °C for three months. Samples were withdrawn after specified time intervals (0, 30, 60, 90 and 180days) and the remaining drug content was determined using stability indicating UPTLC method at 246nm as described in previous section. Zero time samples were used as controls. All the samples were passed through 0.22μm filter before being injected into the UPTLC system. Logarithm of percent drug remaining versus time (in days) was plotted. The degradation rate constant ‘k’ was determined from the slope of the lines at each elevated temperature using the equation-

$$\text{Slope} = -\frac{k}{2.303}$$

Plot of the logarithm of k values at various elevated temperatures against the reciprocal of absolute temperature was drawn (Arrhenius plot). From the plot, k value at 5 °C was determined and was used to calculate shelf life by substituting in the equation

$$T_{0.9} = \left(-\frac{0.1052}{k}\right)$$
Where, $T_{0.9}$ is the time required for 10% degradation of the drug and is referred to as shelf life.

7.5. Result and Discussion

As we have discussed in previous chapters, Ca-Na$_2$EDTA is commonly used as a chelating agent for the chelation therapy against heavy metal exposure and also suitable in the radiation poisoning cause due to internalization of radio-isotopes. Ca-Na$_2$EDTA has good aqueous solubility. Ca-Na$_2$EDTA has some adverse effect on renal function at higher dose. Prolonged gastric retention improves local bioavailability, reduces drug waste and improves chelation efficiency against heavy metal/radio-isotopes present in gastric environment.

As mentioned above, exposure of heavy metal due to ingestion leads to significant absorption from stomach and intestinal region hence efficacy of product depends on local bioavailability as well and chelation of heavy metal with in stomach. Effervescence production decreases the several local GIT side effects, such as gastric irritation, nausea and gastritis. Various techniques for optimization of tablets are well understood and reported in literature (Ceshel et al., 1999). The objective behind the optimization is to establish best formulation from pharmaceutical and consumer point of view and to understand the relationship between independent and dependent variables. Optimization has now become popular day by day in pharmaceutical research, since best result was obtained in limited number of laboratory experiments.

The floating tablets of Ca-Na$_2$EDTA were formulated through effervescent technique in thirteen different batches from F1 to F13 by using hydrophilic polymers HPMC K100M, sodium chloride and hydrophobic polymer carbopol 934 along with effervescing agent sodium bicarbonate and citric acid. The magnesium stearate was used as lubricant and talc was used as glidant. It was found that carbopol has negative effect on floating behavior but it was used only for the drug release retardant characteristics. All the formulations were prepared by direct compression method. The prepared tablets of all the formulations were evaluated for physical characters like tablet hardness, friability, weight variation buoyancy lag time, total floating time, assay, in-vitro drug release. These results of the physicochemical characterization are given in table below. The main aim was to optimize
the Ca-Na\textsubscript{2}EDTA floating formulation for controlled release and total floating time up to 24 hours.

7.5.1 In process quality control

The results of physicochemical characterizations are shown in Tables 7.2. The thicknesses of floating tablets were measured by vernier caliper and were ranged between 6.11 ± 0.38 to 6.30 ± 0.48 mm. The hardness of the floating tablets was measured by Monsanto tester and was controlled between 3.52 ± 0.18 to 5.21 ± 0.26 kg/cm\textsuperscript{2}. The friability was below 1% for all the formulations. Weight variation in different formulations was found to be 648 ± 4.4 to 655 ± 3.6 mg. The percentage of drug content for F1 to F13 was found to be in between 97.01 ± 1.8 to 97.01 ± 1.8 % of Ca-Na\textsubscript{2}EDTA. The combination of sodium bicarbonate and citric acid provides desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (Avicel), thus decreasing the density of the tablet below one and tablet becomes buoyant. The tablet swelled radially and axially during in vitro buoyancy studies. Prepared formulations were also tested for Buoyancy lag time (BLT) and total floating time (TFT) of different formulation were noted and tabulated below. All the formulations ensuring that the tablets were mechanically stable and also passed weight variation test as the % weight variation was within the Indian Pharmacopoeia limits of ±5% of the weight.

7.5.2 Dissolution/ drug release

All the batches of tablets were found to exhibit shorter floating lag times due to presence of Carbopol, sodium bicarbonate and citric acid. In presence of citric acid the floating lag time and tablets were found to float for longer duration (up to 24 hrs). The pH of the stomach (1-3) is elevated under fed condition (~3.8), therefore citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate; more over citric acid has an stabilizing effect formulation. The data obtained from \textit{in-vitro} dissolution studies and plot a graph time vs. % drug release. Release of Ca-Na\textsubscript{2}EDTA from the effervescent floating tablets was studied in phosphate 0.1 N HCl.
Table 7.2: In-vitro characterization of different formulations

<table>
<thead>
<tr>
<th>Exp No.</th>
<th>Tablet Code</th>
<th>Drug content (Percentage)</th>
<th>Weight (mg)</th>
<th>Percent Friability (n=10)</th>
<th>Hardness (Kg/Cm²) (n=5)</th>
<th>Thickness (mm) (n=6)</th>
<th>Leg time (Sec)</th>
<th>Total Floating time (Sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>97.01 ± 1.20</td>
<td>648 ± 2.5</td>
<td>0.53 ± 0.08</td>
<td>5.49 ± 0.24</td>
<td>6.28 ± 0.22</td>
<td>35 ± 2</td>
<td>&gt; 8h</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>99.51 ± 2.40</td>
<td>651 ± 2.8</td>
<td>0.42 ± 0.10</td>
<td>3.00 ± 0.16</td>
<td>6.18 ± 0.13</td>
<td>44 ± 4</td>
<td>&gt; 18h</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>98.01 ± 2.54</td>
<td>652 ± 3.5</td>
<td>0.48 ± 0.05</td>
<td>5.13 ± 0.22</td>
<td>6.10 ± 0.18</td>
<td>50 ± 3</td>
<td>&gt; 18h</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>98.21 ± 2.02</td>
<td>654 ± 2.8</td>
<td>0.54 ± 0.05</td>
<td>5.02 ± 0.25</td>
<td>6.11 ± 0.38</td>
<td>19 ± 2</td>
<td>&gt; 24h</td>
</tr>
<tr>
<td>5</td>
<td>F5</td>
<td>99.03 ± 1.98</td>
<td>654 ± 2.8</td>
<td>0.64 ± 0.09</td>
<td>4.02 ± 0.25</td>
<td>6.22 ± 0.12</td>
<td>22 ± 3</td>
<td>&gt; 24h</td>
</tr>
<tr>
<td>6</td>
<td>F6</td>
<td>97.42 ± 2.65</td>
<td>652 ± 3.8</td>
<td>0.60 ± 0.07</td>
<td>5.54 ± 0.22</td>
<td>6.30 ± 0.48</td>
<td>25 ± 4</td>
<td>&gt; 24h</td>
</tr>
<tr>
<td>7</td>
<td>F7</td>
<td>91.41 ± 2.23</td>
<td>655 ± 3.0</td>
<td>0.55 ± 0.04</td>
<td>4.08 ± 0.20</td>
<td>6.14 ± 0.32</td>
<td>19 ± 3</td>
<td>&gt; 24h</td>
</tr>
<tr>
<td>8</td>
<td>F8</td>
<td>99.25 ± 2.53</td>
<td>650 ± 3.0</td>
<td>0.41 ± 0.05</td>
<td>3.90 ± 0.32</td>
<td>6.23 ± 0.36</td>
<td>19 ± 4</td>
<td>&gt; 24h</td>
</tr>
<tr>
<td>9</td>
<td>F9</td>
<td>99.95 ± 2.08</td>
<td>652 ± 3.8</td>
<td>0.55 ± 0.07</td>
<td>3.52 ± 0.20</td>
<td>6.24 ± 0.32</td>
<td>11 ± 4</td>
<td>&gt; 24h</td>
</tr>
<tr>
<td>10</td>
<td>F10</td>
<td>98.46 ± 2.12</td>
<td>650 ± 3.9</td>
<td>0.52 ± 0.07</td>
<td>3.88 ± 0.21</td>
<td>6.23 ± 0.18</td>
<td>12 ± 4</td>
<td>&gt; 24h</td>
</tr>
<tr>
<td>11</td>
<td>F11</td>
<td>99.83 ± 1.82</td>
<td>653 ± 4.5</td>
<td>0.51 ± 0.02</td>
<td>2.22 ± 0.21</td>
<td>6.26 ± 0.24</td>
<td>18 ± 4</td>
<td>&gt; 24h</td>
</tr>
<tr>
<td>12</td>
<td>F12</td>
<td>98.45 ± 2.34</td>
<td>648 ± 4.4</td>
<td>0.46 ± 0.08</td>
<td>2.99 ± 0.19</td>
<td>6.29 ± 0.25</td>
<td>19 ± 3</td>
<td>&gt; 24h</td>
</tr>
<tr>
<td>13</td>
<td>F13</td>
<td>98.75 ± 2.71</td>
<td>652 ± 4.8</td>
<td>0.53 ± 0.05</td>
<td>4.11 ± 0.21</td>
<td>6.30 ± 0.11</td>
<td>24 ± 3</td>
<td>&gt; 24h</td>
</tr>
</tbody>
</table>

The release profile of various formulations are shown in table no. and Figure no. on the bases of release pattern obtained for various formulation we can said that F8 formulation was said to be optimized formulation. Comparison study with conventional tablet (control) containing 200mg showed that the optimized formulation F8 has better control over release rate in-comparison to the conventional product. The conventional tablet released the drug 99.28% in 4 hours whereas the optimized formulation F8 released the drug 44.41% in 4hours and optimized formulation F8 remained floatable in the stomach for long duration and gives controlled and prolong released up to 24 hours.

Table 7.3: Dissolution profile of different batches of effervescent and control (conventional) Ca-Na₂EDTA tablets.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
<th>F11</th>
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<th>F13</th>
<th>control</th>
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<tr>
<td>0.25</td>
<td>6.23</td>
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<td>7.21</td>
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<td>5.52</td>
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<td>1.00</td>
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<td>15.34</td>
<td>16.28</td>
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<td>19.20</td>
<td>18.30</td>
<td>18.24</td>
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<td>20.20</td>
<td>19.42</td>
<td>22.28</td>
<td>42.22</td>
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<tr>
<td>2.00</td>
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<td>24.20</td>
<td>20.12</td>
<td>32.28</td>
<td>38.42</td>
<td>32.54</td>
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<td>28.28</td>
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<td>49.57</td>
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<td>58.32</td>
<td>62.24</td>
<td>60.23</td>
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<td>68.23</td>
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<td>70.65</td>
<td>67.25</td>
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<td>10.00</td>
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<td>90.28</td>
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<td>90.60</td>
<td>92.05</td>
<td>83.23</td>
<td>87.11</td>
<td>90.22</td>
<td>92.16</td>
<td>91.48</td>
<td>93.40</td>
<td>99.91</td>
</tr>
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</table>

The release profile of various formulations are shown in table no. and Figure no. on the bases of release pattern obtained for various formulation we can said that F8 formulation was said to be optimized formulation. Comparison study with conventional tablet (control) containing 200mg showed that the optimized formulation F8 has better control over release rate in-comparison to the conventional product. The conventional tablet released the drug 99.28% in 4 hours whereas the optimized formulation F8 released the drug 44.41% in 4hours and optimized formulation F8 remained floatable in the stomach for long duration and gives controlled and prolong released up to 24 hours.
Figure 7.1: Plot of comparative dissolution profile of different batches of effervescent tablet and control tablet.

Figure 7.2: Comparative dissolution profile of optimized formulation (F8) and conventional (control) formulation

7.5.3. Swelling Index

Swelling ratio describes the amount of water that is contained within the hydrogel at equilibrium and is a function of the network structure, hydrophobicity and ionization of the functional groups. Swelling study was performed on F6, F8, F10 batches up to 12hrs,
which swelling increases as the time passes because the polymer gradually absorbed water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier were formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form. In the swelling index study, the higher swelling index was found for tablets of batch F80 (figure 7.3). Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer.

![Bar graph showing swelling index of F6, F8, and F10 formulations.](image)

Figure 7.3: Swelling index of F6, F8 and F10 formulations

7.5.4. Analysis of release mechanism

Optimized formulation F8 was subjected to curve fitting analysis, zero order, and first order, Higuchi Kinetics, Korsmeyer and Peppas model. The slope and $R^2$ are shown in table 7.4 and graphs in Figure 7.4 to 7.7. Optimized formulation F8 fitted best for Korsmeyer – Peppas equation with $R^2$ value of 0.9930.
Figure 7.4: Plot of cumulative percentage drug released vs. time of optimized formulation (F8) [Zero Order]

Figure 7.5: Plot of log cumulative percentage drug retained vs. time of optimized formulation (F8) [First order]

Figure 7.6: Plot of cumulative percentage drug released vs. root time of optimized Formulation (F8) [Higuchi Matrix]
In-vivo studies

The behavior of optimized tablet (F8) in the rabbit was observed in real time using non-invasive Pharmaco-scintigraphy techniques. Scintigraphy images were taken at 5 min, 15 min, 30 min, 1h, 2h, 4h and six hours after the oral administration of radiolabelled Ca-Na$_2$EDTA effervescent tablet. Tablet impression and significant changes were observed in rabbit stomach as hot spot. The tablet had altered its position and turned round. This indicates that tablet did not adhere to gastric mucous but, on the contrary, floated on the gastric fluid. The major limitation to the upper gastrointestinal residence time of solid single unit dosage forms administered in the fasted state or non-caloric fluids constitutes third phase of myoelectric complex, since it occurs approximately every 2h in humans (Hwang et al., 1998) and approximately every one hour in animals (Cunningham, 1997).

For this phase the intense activity that empties large, non-disintegrating particles including dosage form the stomach to the small intestine is characteristic, but the result has shown that mean gastric residence time for the optimized formulation was 4h(n=3), in later images position and shape of tablet was disturbed and a broad mass was appear in intestinal
position. It was seen that mean residence time in rabbit was about four hours for optimized Ca-Na2EDTA tablet.

7.5.6. **Phase zero Clinical studies**

In all cases, the tablet, whether effervescent floating tablet (F8) or reference (conventional control) tablet was clearly observed to maintain its integrity in the stomach. Not in single case it broke down into pieces on swallowing. The following four sequential steps were visualized in all cases though the time of happening was different. On entering the stomach, the conventional tablets settled down in the lower half of the stomach, mostly in proximity of the pylorus and lower greater curvature and with time they start releasing radioactivity into the medium but the tablet maintained its integrity up to 1h. The released radioactivity slowly tricked into the upper small intestine through the duodenum. Finally, the tablet lost its identity and disintegrated completely, soon followed by emptying of the stomach.

![Image](image_url)

**Figure 7.8:** Intragastric behavior of radiolabelled Ca-Na2EDTA effervescent tablet (F8) represented by scintigraphy image at different time intervals (tablet is pointed by an arrow) in rabbit. In 6h images of rabbit appearance of tablet was disturbed and it reached...
While in case of optimized effervescent tablet (F8), when tablet enters after oral administration, initially tablet settled down in the lower half of the stomach. Tablet starts moving in upward direction (within 20-30 seconds) in stomach due to initiation of floating behavior, due to which full clear position of tablet images were not recorded in first image. Using ROI (region of interest), individual parameters were defined and integrated. Tablet integrity is maintained up to 4 h in stomach, which gives clear indication of floating nature of tablet inhuman stomach, which was not observed in case of conventional tablet. Figure shows the comparative scintigraphy images at different time intervals in same volunteer. It is clear that tablet appears more or less at the same position in stomach for first four hours, but there is complete dissolution in conventional tablet images. It could be related to its floating nature, later on the tablet slightly releases significant activity from its matrix’s and this activity moves toward large intestine area. Hence mean gastric retention period of effervescent floating tablet was 6 hours.

7.5.7. **Efficacy studies**

Efficacy study was done for Ca-Na$_2$EDTA (effervescent floating tablet = f8) against heavy metal (Technetium-99m) exposure by ingestion route. Deposition of heavy metal/ radioisotopes in different organ/ tissue of the body after absorption through stomach are considered as prime source of heavy/radio isotope toxicity, which leads to hazardous effect normal functions of organ or tissue. Hence fewer uptakes by the organ or fast excretion of
heavy metal/ radio-isotope from body is considered as efficacy parameter of formulated tablet. Efficacy study involved change in uptake pattern of radio-isotope (technetium-pertechnetate) through salivary gland and thyroid in presence and absence of prepared formulations. Significant fall in uptake of technetium pertechnetate by salivary gland and thyroid was seen which indicates in effectiveness of prepared formulation against technetium pertechnetate exposure. Increase in counts in kidney and bladder confirms the formation of $^{99mTc}$-Technetium-EDIT complex which was not present or present in less quantities in case of pure technetium pertechnetate exposure. Appearance of activity in intestine indicates non-dissolved technetium-EDIT complex.

### Table 7.5: $^{99mTc}$-Technetium uptake in presence and absence of Ca-Na$_2$EDTA floating tablet

<table>
<thead>
<tr>
<th>Organ</th>
<th>$^{99mTc}$ Technetium exposure</th>
<th>$^{99mTc}$ Technetium exposure in presence of F8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 min</td>
<td>1h</td>
</tr>
<tr>
<td>S. Gland</td>
<td>0.91</td>
<td>6.62</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.37</td>
<td>2.97</td>
</tr>
<tr>
<td>Heart</td>
<td>0.60</td>
<td>1.64</td>
</tr>
<tr>
<td>Stomach</td>
<td>50.82</td>
<td>16.35</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.41</td>
<td>5.65</td>
</tr>
</tbody>
</table>

#### 7.5.1 Stability studies

The stability studies of optimized effervescent Ca-Na$_2$EDTA were performed for six months as mentioned in section above. Statistical analysis of results before and after conducting the stability studies for six months was carried out using paired student test. No significant difference was observed in the tablet hardness or friability. Similarly, there was very little/ or no effect on the total floating duration or matrix integrity of the tablets. The batches were analyzed at time intervals of 0, 1, 2, 4 and 6 months to determine any change in physical appearance, pH and drug content of optimized formulation (F8) and the results are as shown in table 7.6. Shelf life was determined as the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion of 90% percentage label claim (drug remaining). The data was evaluated using Sigmaplot TM 10 software (Cranes Software International, Bangalore, India). Percentage label claim (% drug remaining) was plotted against time in months to determine the shelf life (Figure 7.11)
Figure 7.10: Efficacy studies of Ca-Na$_2$EDTA in healthy human volunteers

Table 7.6: Percent drug remaining for Ca-Na$_2$EDTA effervescent floating tablet at 25 ± 2°C and 60 ± 5% RH

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Mean Area ± S.D. (n=3)</th>
<th>Drug concentration (ug/ml)</th>
<th>Drug amount$^t$ (mg/ml)</th>
<th>% Drug remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3768366.670</td>
<td>200.00</td>
<td>200.00</td>
<td>100.00</td>
</tr>
<tr>
<td>1</td>
<td>3763087.270</td>
<td>199.72</td>
<td>199.72</td>
<td>99.86</td>
</tr>
<tr>
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<td>3757430.770</td>
<td>199.42</td>
<td>199.42</td>
<td>99.71</td>
</tr>
<tr>
<td>4</td>
<td>3744232.270</td>
<td>198.72</td>
<td>198.72</td>
<td>99.36</td>
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<tr>
<td>6</td>
<td>3728016.970</td>
<td>197.86</td>
<td>197.86</td>
<td>98.93</td>
</tr>
</tbody>
</table>

$^t$ Dilution factor = 1000
The changes in the observed parameters were not found to be statistically significant (p>0.05) which indicated that the optimized formulations were stable. Stability studies as per ICH guidelines at 25 ± 0.5°C and 60 ± 5% RH predicted a Ca-Na\textsubscript{2}EDTA degradation of 1.07%, in the optimize floating tablet at the end of 6 months. From the plot obtained using the software, the shelf life of Ca-Na\textsubscript{2}EDTA floating formulation was found to be 56.30 months.

![Graph showing shelf life determination of Ca-Na\textsubscript{2}EDTA floating tablet (F8)]

**Figure 7.11:** Shelf life determination of Ca-Na\textsubscript{2}EDTA floating tablet (F8)

<table>
<thead>
<tr>
<th>Time (Day)</th>
<th>Storage condition</th>
<th>Mean Area (ng/ml)</th>
<th>Drug concentration (µg/ml)</th>
<th>Drug amount (mg/ml)</th>
<th>% Drug remaining</th>
<th>log % Drug Remaining</th>
</tr>
</thead>
<tbody>
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<td>3768366.67</td>
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<td>200.00</td>
<td>100.00</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>50 ± 0.5 °C</td>
<td>3758939.17</td>
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<td>199.50</td>
<td>99.75</td>
<td>1.9989</td>
</tr>
<tr>
<td>60</td>
<td>60 ± 5% RH</td>
<td>3748757.47</td>
<td>198.96</td>
<td>198.96</td>
<td>99.48</td>
<td>1.9977</td>
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<tr>
<td>180</td>
<td>3736690.27</td>
<td>198.32</td>
<td>198.32</td>
<td>198.32</td>
<td>99.16</td>
<td>1.9963</td>
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<tr>
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<td>199.32</td>
<td>199.32</td>
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<td>1.9985</td>
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<td>60 ± 5% RH</td>
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<td>198.64</td>
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<td>197.94</td>
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<td>194.46</td>
<td>194.46</td>
<td>97.23</td>
<td>1.98777</td>
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</table>
Accelerated stability as per conventional method using Arrhenius equation:

The accelerated stability studies were determined by method reported in previous section to determine the percentage drug remaining in the optimized formulation when stored for 3 months at elevated temperatures of 40 ± 2°C; 50 ± 2°C; 60 ± 2°C at 60 ± 5% RH as shown in Table 7.7.

Shelf life = $t_{0.9} = \frac{0.1052}{k_{25}}$

Shelf life of Ca-Na$_2$EDTA floating tablet formulation = $\frac{0.1052}{5.496 \times 10^{-5}} = 1913.79$ days = 62.91 months = 5.24 years

The order of degradation of Ca-Na$_2$EDTA floating tablet was determined as shown in Table 7.7 above and was found to follow first order kinetics showed in Figure 7.12. The reaction rate constant 'k' for the degradation was measured. Plot of the logarithm of k values for floating tablet 7.8 at each elevated temperature against the reciprocal of absolute temperature was drawn (Arrhenius plot) as shown in Figure 7.13. From the plot, k value at 25°C (room temperature) was determined and was used to calculate shelf life. The shelf life
of the Ca-Na$_2$EDTA floating tablet at 25°C (room temperature) was calculated to be 5.2 years.

7.6. Conclusion

The present study was aimed to develop the high retention formulation in the stomach for longer period of time, gastro retentive dosage form was designed, to release the chelating agent (Ca-Na$_2$EDTA) in sustained manner in gastric fluid for neutralization of ingested heavy metal. Floating matrix tablets containing Ca-Na$_2$EDTA can be prepared successfully by using direct compression technique. The Ca-Na$_2$EDTA floating tablets were white, smooth, and round shaped in appearance. According to table 7.2, hardness and friability were an indication of good mechanical resistance of the tablets. The weight variation test showing satisfactory results as per Indian Pharmacopoeia (IP) limit. Good uniformity in drug content was found among different formulation of the tablets. For buoyancy gas generating agent plays important role, the gas generating agents immediately evolves carbon dioxide in presence of HCl solution generating sufficient porosity which helped the dosage unit to float. Formulation F8 started floating after 19 seconds and remains buoyant for more than 24hr till they were completely eroded. It is evident from the in-vitro dissolution data that formulation F8 has good floating and control release property. Comparative dissolution profile is represented in figure 7.3. Tablets of batch F8 have
considerable in vitro drug release, and also showing good floating lag time and total floating time was more than 24 hours. The drug release kinetics follows Korsmeyer and Peppas model and the mechanism was found to be non Fickian/anomalous. The stability studies were carried out according to ICH guideline which indicates that the selected formulation was stable up to 5.2 years.