Gastric emptying of dosage forms is an extremely variable process. It is a complex procedure and is subject to many variables. These include the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. Thus; small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastric retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion,\(^2\) flotation,\(^4\) sedimentation,\(^5,6\) or by the simultaneous administration of pharmaceutical agents\(^11,12\) that delay gastric emptying. The gastroretentive drug-delivery system can be retained in the stomach and assists in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GI tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Several approaches are currently used to prolong gastric retention time. These include floating drug-delivery systems, swelling and expanding systems, polymeric bioadhesive systems, high-density systems, and other delayed-gastric-emptying devices.\(^13\) The principal of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for dosage form and sustained drug release.\(^14\)

TH is centrally acting oral analgesic that blocks pain through opioid receptor binding and inhibition of nor epinephrine and serotonin uptake. TH is having short plasma half life (6h)\(^15\) which is suitable for developing gastro retentive floating drug delivery system. The present system of preparing floating drug is that, it will remain in gastric region for longer duration causing increase in gastric residence time, which may cause improve bioavailability & reduces drug waste.

**INTRODUCTION**

**MATERIALS & METHODS**

**Materials**

TH was procured from Matrix Laboratories, Bangalore. HPMC K 15M, HPMC 100 LV were procured from Merck Chemicals Ltd. Germany. Other ingredients like Sodium bicarbonate, gum tragacanth, starch, talc, magnesium stearate were procured from S.D. Fine chemicals, Mumbai.

**Method**

**Preparation of gastro retentive controlled release tablets**

Floating hydrophilic matrix tablet were prepared by direct compression technique using different grades of polymer with varying concentration as well as different concentrations of sodium bicarbonate and varying amount of starch, gum tragacanth. All the ingredients (Table 1) except magnesium stearate were shifted and blended in mixer uniformly. After the sufficient mixing of drug as well as other components, magnesium stearate were added and further mixed for additional 2-3 minutes. The tablets were compressed using 12 mm concave punch on a single stroke punching machine, the weight of tablets was kept constant for tablets of all batches, i.e. 420 mg with hardness about 5 kg/cm\(^2\).

**Characterization of tablets**

**Pre compression parameters**

**Fourier Transform Infrared (FTIR) studies**

FTIR studies of formulation along with pure drug (TH) were carried out at room temperature by FTIR spectrophotometer (FTIR, Paragon-500) using KBr pellet. All the spectra were recorded in the range of 400–4000 cm\(^{-1}\).

**Bulk density**

The power sample under test was screened through sieve no.18 and the sample equivalent to 25 gm was weighed and filled in a 100 ml graduated cylinder and the power was leveled and the unsettled volume, \(V_s\) was noted.
The time taken for dosage form to emerge on surface medium called floating lag time (FLT) and duration of time by which it constantly remain on surface of medium were noted.

**Swelling behavior study of the Tablets**

Swelling of tablet involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in swelling of particles. The extent of swelling can be measured in terms of %weight gain by the tablet. For each formulation batch, tablets were weighed and placed in a beaker containing 200 ml 0.1 N HCl of pH 1.2. After each hour the tablets were removed from beaker and weighed again up to 12 hours. The swelling study was not performed for batch F1, F2 and F3 as the tablet of these batches did not float. The % weight gain by the tablet was calculated by the formula,

\[
\text{Swelling Index (SI)} = \left( \frac{W_f - W_0}{W_0 \times 100} \right)
\]

where \( W_f \) being the total of all the tablet weight after swelling, and \( W_0 \) representing the weight of tablet before immersion.

**In-vitro dissolution studies**

Dissolution of tablets of each batch was carried out using USP type II dissolution apparatus (Disso 2000, Labindia) using paddle. 900 ml of 0.1 N HCl (pH 1.2) was filled in a dissolution vessel and the temperature of medium were set at 37±0.5°C. Tablets were placed in dissolution vessel and the rotational speed of paddle was set at rpm 100. The 10 ml of sample was withdrawn at predetermined time interval and same volume of fresh medium was replaced. The samples were analyzed for drug content using 0.1 N HCl as a blank at wavelength of 272 nm using double beam UV-Visible spectrophotometer (Genesis-2,USA). The content of drug was calculated using the equation generated from standard curve. The %cumulative drug release was calculated.

**Kinetics of drug release**

Different mathematical models may be applied for describing the kinetics of the drug release process from the formulation matrix; the most suited being the one which best fits the experimental results. The kinetics of TH release from tablets was determined by finding the best fit of the dissolution data (drug release vs. time) to distinct models: Zero order[eq.1], first-order [eq.2] and Higuchi [eq.3].

\[
Q_t = k_0 t \quad [1]
\]

\[
Q_t = Q_\infty (1 – e^{–k_1 t}) \quad [2]
\]

\[
Q_t = Q_\infty t^{1/2} \quad [3]
\]

where \( Q_t \) being the total amount of drug in the matrix, \( k_0 \) the zero order kinetic constant, \( k_1 \) the first order kinetic constant and \( k_{H} \) representing the Higuchi rate constant.

**RESULTS AND DISCUSSION**

FTIR studies of the pure drug (TH) and the formulation (F5) were carried out to study the interaction between drug and excipients in the formulation. From the study, major peaks of drug (TH) were found to be at 3460, 2910,1601,1575, 1284,1238,1042,702 cm⁻¹ (Fig.1a). In the F5 formulation, major peaks of TH were found to be at 3406,2912,1600, 1565,1280, 1040, 702 cm⁻¹ (Fig.1b). Other peaks were due to presence of excipients. So no interactions were found between drug and excipients in the formulation.

The flow properties of the granules were studied and formulation F5 was found to have comparatively good compressibility index and Hausner ratio than other formulations (Table 2). From the results of floating properties it was shown that all tablets except of batch F1, F2, F3 had good floating properties, which might be due to absence of sodium bicarbonate in these three formulations (Fig 2). From the results of swelling study it was concluded that swelling index increases as time passes because the polymer gradually absorbed water due to hydrophilic in nature and swell. The swelling index increases with time up to 2 hours in some batches which might due to low viscosity of polymer and after 2 hours, the polymer chain relaxation was dominating phenomenon as swelling reaches
thresholds resulting in lowering of swelling index. Thus the viscosity of polymer had a major role on swelling process, matrix integrity as well as floating capability. The higher swelling index was found for tablets which are due to HPMC K 15 M which is having nominal viscosity of 15000 cps. Thus it was concluded that linear relationship may be there in between swelling process and viscosity of polymer. From the swelling study of the formulations, formulation F5 was found to have good swelling properties.

The in vitro dissolution was carried out for all batches except F 1, F2, and F3 as the tablets of these had no floating properties. From the dissolution studies of the formulations, formulation F5 was found to have better drug release profile than other formulations (Fig.4).

Formulation F5 was also found to have better swelling capacity and floating time than other formulations. The drug release was extended upto 12 hours from the floating drug delivery formulations.

To determine the mechanism of drug release from floating tablet matrices, different kinetic models like zero order kinetic, first order kinetic, Higuchi model were used. Regression coefficient ($R^2$) values of each kinetic models were compared to find out the best fit model. By comparing the $R^2$ values of different models, Higuchi model was found to be best fit (Table 3). So it could be predicted that release of TH from the floating drug delivery formulations were of diffusion type.

![Fig. 1a: FTIR spectra of pure drug (TH)](image1a)

![Fig. 1b: FTIR spectra of formulation F5 containing TH](image1b)

![Fig. 2: Stepwise floating of formulation F5](image2)
CONCLUSION

Floating delivery system of TH was prepared using different grades of HPMC as drug release retarding polymer and sodium bicarbonate as source for carbon dioxide which helps tablets to float. From FTIR studies no interactions were found between TH and polymers. The flow properties of the granules were studied and formulation F5 was found to have comparatively good compressibility index and Hausner ratio than other formulations. From the swelling study of the formulations, formulation F5 was found to have good swelling properties. From the dissolution studies of the formulations, formulation F5 was found to have better drug release profile than other formulations.

From the drug release kinetic study, Higuchi model was found to be best fit. So it could be predicted that release of TH from the floating drug delivery formulations were of diffusion type.

REFERENCES


