Chapter 2

LITERATURE REVIEW AND OBJECTIVE OF THE PRESENT STUDY
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2.1. Oral Administration

Now a day’s oral administration have been used for the delivery of drugs in to the blood streams. However Controlled release drug delivery has also been applying in the pharmaceutical industry to get the therapeutic efficacy like easily administration of drugs to achieve the patient compliance (Garg and Gupta, 2008).

2.2. Controlled Release Drug Delivery Systems

To avoid the above mentioned limitations, the design of oral sustained-controlled (SR) release formulations is a major effort to discharge the medicaments gradually into the GIT and sustain an real medicament concentration in the systemic system for a extended period of time. After oral administration, such a dosage form will retain for longer time in the stomach region (Strebel et al., 2006). However, these developed drug delivery systems faces two problems viz the small gastric retention time and small gastric emptying time. The above sequence causes partial release of drugsto stomach or upper portion of small intestine region (Cheuh et al., 1995; Iannucelli et al., 1998).

2.3. Site Specific Drug Delivery Systems

To develop and design a site-specific orally CR dosage formulation, it is anticipated to attain prolonged gastric residence time (GRT) by the drug delivery system. Prolonged gastric retention improves oral bioavailability, increases the duration of action of medicament release, reduces wastage of medicament, and increases solubility of medicament that are fewer soluble in a elevated pH environment (Garg and Gupta, 2008; Iannucelli et al., 1998).
2.4. Gastro-retentive Drug Delivery Systems (GRDDS)

GRDDS is a method to extend gastric residence time (GRT). GRDDS goals drug release of medicament in the upper portion of GIT region for localized or systemic effects. These dosage formulations can stay buoyant in the GIT area for longer period of time and hence considerably prolong the GRT of medicaments (Desai and Bolton, 1993). Since the time drug delivery through gastro-retentive methods are being scientifically planned to develop GRDDS which include: sinking (high density) methods which can retain in the underside portion of the stomach region (Rouge et al., 1998; Davis et al., 1986), low density (floating) methods that causes buoyancy in gastric secretions fluid (Streubel et al., 2003; Goole et al., 2007), mucoadhesive methods that causes bioadhesion to mucosa lining of stomach region (Santus et al., 1997; Lehr. 1994), unfoldable, extendible or swellable methods which measures and controls the emptying of the dosage formulations via the pyloric sphincter of stomach region (Fix et al., 1993; Klausner et al., 2003a; Deshpande et al., 1997), superporous hydrogel methods (Park. 1988), magnetic methods and their delayed gastric emptying devices (Fujimori et al., 1994).

The following write-up covers with various gastrorentive have been used in the area of target-specific orally drug delivery methods (Sahu et al., 2011).

2.4.1. Factors Affecting Gastric Retention of Dosage Forms

It was found that various factors affecting gastric retention dosage form such as pyloric valve size which should be in the range between 1 to 2 mm. (Wilson and Washington. 1989). In addition size, shape of dosage form, food intake, gender, age, sex, body mass index and disease condition, administration of drugs also affect gastro intestinal transit time. (Streubel et al., 2006a). The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters (Larhed et al., 1997).

2.4.1.1. Density

The density of a formulation influences the GET and also decides the position of the formulation in the stomach. Formulations which have a density less than the gastric contents can buoyant. High density systems go down below to base region of the stomach. Both conditions could deal with it separately the dosage formulation from the pylorus
(Bardonnet et al., 2006; Dubernet. 2004). A density of less than 1.0 gm/cm$^3$ is essential to show floating ability (Arrora et al., 2005).

2.4.1.2. Size and shape of the formulation

Size and shape of the formulation are of value for developing single unit solid formulation (Bardonnet et al., 2006). The gastric residence times (GRT) of non-floating formulation are not consistent and depending on their size, that could small, medium and large subunits. In the majority of time, the greater the formulation the larger will be gastric residence time because of the bigger size of the formulation will not permit to rapidly passage from the pyloric antrum to the intestinal region (Garg and Gupta, 2008; El-Kamel et al., 2001). However, dosage formulation possess a diameter of more than 7.5 mm exhibit a satisfactory GRT in compare to that have 9.9 mm (Arrora et al., 2005). The devices of different shaped such as in shape of ring and in shape of tetrahedron showed good GRT when they compare to another different shapes (Garg and Sharma. 2003).

2.4.1.3. Nature and intake of food

Nature and intake of food showed a great influence to the gastric retention of formulation. In gastrointestinal tract (GIT), presence or absence of food stuffs in the gastric tract effects the GRT of the formulation. Generally by the occurrence of food in gastro tract enhances the GRT of the formulation. Boost in content of caloric value and acidity reduces gastric GET that can improve the gastric retention of formulation (Reilly et al., 1987; Khosla et al., 1989).

2.4.1.4. Age, posture and gender

So for as concern to the old aged personals, GET is dropped (Mojaverian et al., 1988). The influence of posture does not show drastic dissimilarity in the GRT for the persons in supine upright state. Mostly females shows slow GET in comparison to male.

2.4.2. Potential Drug Candidates for GRDDS

Many drugs are suitable for GRDDS. They are

1. Medicaments those are localized to the stomach region (e.g. antacids etc.).
2. Medicaments those show narrow therapeutic window in GIT (e.g. riboflavin etc.).
3. Medicaments those are found not stable in the area of intestine or environment of colon (e.g. ranitidine HCl etc.).

4. Medicaments which interfere the normal microbes of colon (e.g. antibiotics against the treatment of *H. pylori*).

5. Medicaments which show less solubility at higher pH values (e.g. verapamil HCl etc.).

### 2.4.3. Drugs Unsuitable for GRDDS

There are many medicaments that are not suitable for GRDDS such as medicaments which shows limited solubility in acid (e.g. phenytoin), medicaments which face unstability in the extensive gastric environment (e.g. erythromycin) and drugs which intend it’s selective release in the colon (e.g. corticosteroids and 5- amino salicylic acid).

### 2.4.4. Advantages of gastro-retentive drug delivery systems

The oral bioavailability of the therapeutic ingredients can be expressively increased which could get metabolized in the upper portion of GIT by these gastro-retentive drug delivery approaches in contrast to the administration of non-gastro-retentive drug delivery. Several different issues exist which relate to absorption and transit of the medicament in the gastric region, which act naturally to effect the extent of medicament absorption (Klusner et al., 2003c). For medicaments with short biological half life, sustained release (SR) action may turn out the flip- flop pharmacokinetics model. They inbuilt an advantage in compare to the conventional system that it can be utilized to sort out the problem of GRT along with the GET. These systems are supposed to continue floating on the gastric fluid secretions lacking affecting the intrinsic rate of emptying due to their bulk density which is less than of the gastric fluids. Gastro-retentive dosages formulations can bring forth prolong and sustain release of medicaments which can avail localized drug management in the region of stomach and small intestine. They can also be valuable in the management of various ailments associated to stomach and small intestine region. Gastro-retentive dosage forms can lessen the fluctuation in drug plasma concentrations. Therefore, adverse effect based on concentration that can associate with drug plasma concentrations could be accessible. This characteristic can be for distinctive significance for medicament with a narrow therapeutic index (Hoffman, 1998). Gastro-retentive drug delivery can curtail the counter activity of...
the physique which can lead to higher medicament efficacy. Lessening in fluctuation of the drug plasma concentration creates it thinkable to obtain developed selectivity in receptor activation. The prolonged mode of medicament release from Gastro-retentive doses form which permits extension of the time than a critical concentration and in this way increases the different pharmacological effects.

2.4.5. Approaches to Achieve Gastric Retention

Various approaches towards achieving extended gastric retention may be outlined as follows.

2.4.5.1. Sinking (High density) methods or non-floating (NF) methods

This methods incorporate formation of formulation with the density that should go above density of actual normal content of stomach (~1.004 g/cm\(^3\)). These dosage forms are formulated by coating the medicament by a weighty core material or mixing with some inert substances such as titanium oxide and iron powder (Vyas and Khar, 2006). The substances raises density by up to 1.5-2.4 gm/cm\(^3\). However, a density near to 2.5 gm/cm\(^3\) seems essential for considerable prolongation of GRT (Clarke et al., 1993). But, usefulness of this method in human beings was not established (Moes et al., 2003) and no such system has been marketed (Garg and Sharma, 2003).

2.4.5.2. Floating drug delivery systems

FDDS is considered as most essential methods to attain gastric retention for improving the oral bioavailability of medicament (Arrora et al., 2005; Sing and Kim, 2000). These delivery systems are anticipated for medicaments with an absorption window in the stomach or upper portion of small intestine (Sungthongjeen et al., 2006). These have bulk density less than the gastric fluids and so continue buoyant in the stomach in no way to affecting GET for a sustained period. Moreover, the drug is unconfined gradually as a anticipated rate from the system and after discharge of medicament, the remaining residual system can be moved out from the stomach. This causes an increased GRT and a improved management of the fluctuation in drug plasma concentration (Garg and Gupta, 2008). The inbuilt low density can be attained by air entrapment (Krogel and Bodmeier, 1999b) or by the merging of low density substances (Streubel et al., 2003; Sriumornnsak et al., 2005;
Streubel et al., 2002; Vyas and Khar. 2006).

The approaches utilized for the advancement of floating dosage forms are - single-unit floating system and multiple-unit floating system (Yang et al., 1996; Streubel et al., 2003; Streubel et al., 2006a; Arora et al., 2005; Sungthongjeen et al., 2006; Bechgard and Nielson, 1978; Vervaet et al., 1995; Iannucelli et al., 1998). Hollow microspheres (microballons) formulated by the method of solvent emulsion diffusion (Sato et al., 2003), microparticles dependent on low density powder (Streubel et al., 2003; Streubel et al., 2002) and beads formulated by emulsion gelatin method (Talukdar and Fassihi, 2004). Based on the mechanism of buoyancy, two various methods have been employed in the progress of floating drug delivery system. They are: non-effervescent systems and effervescent systems.

2.4.5.2.1. Non-effervescent methods

The air fascinated by the polymers indicates buoyancy of the formulations. Additives used most regularly in this method include hydroxypropyl methylcellulose (HPMC), polyacrylates and carbopol (Garg and Gupta, 2008; Hilton and Deasy, 1992). Further these systems can be classified into the sub-types: Hydro-dynamically balanced systems, Microballons / Hollow microspheres and Microporous Compartment system.

2.4.5.2.1.1. Hydro-dynamically balanced methods

Sheth and Tossounian first titled these ‘hydro-dynamically balanced systems (Seth and Tossounian, 1984). These systems comprises medicament with gel-forming hydrocolloids meant to continue buoyant on the content of stomach. These are single-unit dosage form, containing one or more hydrophilic gel-forming polymers. A frequently used additive to develop these systems includes NaCMC, HPMC, HEC, HPC, polycarbophil, agar (Reddy and Murthy, 2002; Hwang et al., 1998; Vyas and Khar, 2006). Nonstop erosion of the surface permits water permeation to the inner most layers that are responsible for surface hydration and buoyancy to dosage form (Bardonnet et al., 2006; Oth et al., 1992; Talukdar and Fassihi, 2004; Whiteland et al., 1996).
2.4.5.2.1.2. Microballons

The microballons are having the ability to float uninterruptedly over the surface of an acidic dissolution media which contain surfactant for at least more than 12 hours (Garg and Gupta, 2008). Hollow microspheres are deliberated to be one of the most capable buoyant systems just because of that they can combine the benefits of multiple-unit system and good floating ability (Mitra. 1984; Bardonnet et al., 2006; Kawashima et al., 1992; Reddy and Murthy. 2002).

2.4.5.2.1.3. Microporous Compartment methods

This methodology is established on the standards of the encapsulation of a medicament reservoir inside a microporous compartment with pores along its top and bottom walls (Harrigan. 1977). The exterior wall of the device was absolutely sealed to any direct interaction of the gastric contents with the undisolved medicament.

2.4.5.2.3. Effervescent (Gas generating) methods

In this system carbon dioxide is released and causes the formulation to float in the stomach. Other approaches and materials have also been reported include- a mixture of sodium bicarbonate and sodium alginate, multiple unit floating dosage forms which generate gas (carbon dioxide), floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with HPMC, and floating system based on ion exchange resin technology (Rubinstein et al., 1994; Harrigan. 1977; Garg and Sharma. 2003). Bilayer or multilayer system have also been designed (Bardonnet et al., 2006; Hilton and Deasy; 1992; Ingani et al., 1987; Krogel and Bodmeir. 1999a). (Krogel and Bodmeir. 1999). The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of the polymers (Bardonnet et al., 2006; Krogel and Bodmeir. 1999).

2.4.5.2.4. Bio-adhesive or Muco adhesive drug delivery methods

Methods for mucoadhesive drug delivery utilize the property of bioadhesion of certain polymers which become more adhesive on hydration and hence can be used for targeting a drug to a particular specific region of the body for extended periods of time. The mucosal layer lines a number of regions of the body including the gastrointestinal tract,
the urogenital tract, the airways, the ear, nose, eye and hence, the mucoadhesive drug delivery methods includes, buccal, oral, vaginal, rectal, nasal and ocular delivery systems(Moes. 1993; Faivre. 2004; Huang et al., 2000).

Materials most commonly used for bio-adhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxyl propyl methyl cellulose, sucralfate, tragacanth, dextrin, polyethylene glycol and polylactic acids. Even though some of these polymers are effective at producing bioadhesiveness, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the GIT. Furthermore, the stomach content is highly hydrated, decreasing the bioadhesiveness of polymers (Streubel et al., 2006; Bardonnet et al., 2006).

2.4.5.2.5. Expandable and unfoldable methods

Various configurations are small arrangement for oral intake, an expanded gastro-retentive form and a final small form enabling evacuation following drug release from the device. Thus gastro-retentivity could be improved and enhanced by the combination of dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach (Garg and Gupta, 2008; Bardonnet et al., 2006; Klusner et al., 2003a; Klusner et al., 2002; Caldwell et al., 1988; Mamajek and Moyer. 1980; Bardonnet et al., 2006; Hwang et al., 1998; Klusner et al., 2003b; Garg and Sharma. 2003).

2.4.5.2.6. Super porous hydrogel methods

In this method to enhance GRT porous hydrogels of average pore size more than 100 µm, bulge to equilibrium size within a fraction of time due to quick water uptake by capillary wetting through abundant interrelated open pores (Bardonnet et al., 2006; Chen et al., 2000).

2.4.5.2.7. Magnetic Systems

These also enhance the GRT which is based on the simple principle that the dosage form contains a small internal magnet, and the magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet should be positioned with a degree of precision that might not compromise patient compliance (Bardonnet et al., 2006; Dubernet. 2004; Hwang et al., 1998)
2.4.6. Literature review on some formulations containing floating drug delivery systems

Atybi et al., 1996 developed and designed floating drug delivery system (FDDS) based on the theory of ion exchange resins and their in vivo behavior was evaluated. This method actually depend on ion exchange resins that are loaded with bicarbonate that on contact with media containing hydrochloric acid causes to discharge carbon dioxide so that resin floats. Extension of the floating time can be attained by coating the bicarbonate loaded with particles of resin with a semi permeable membrane.

Desai and Bolton, 1993 Developed and formulated the floating controlled-release drug delivery system of theophylline tablet in an attempt to enhance the gastric retention time (GRT) of the dosage form and to control drug release profile. The floating was attributed to oil and air entrapped in the network of agar gel. The floating theophylline tablet maintained plasma constant level of theophylline for 24 hr.

Fabregas et al., 1994 used dynamic in vitro tests to study to buffering profile and environmental acidity under the simulated gastric conditions of formulations with the concept of prolonged gastric residence time (GRT) (Almagate Flot-CoatG). In comparison to antacid preparations the new formulation showed to high potency of antacid with a sustained GRT.

Ichiwaka et al., 1991 evaluated in vivo the ability of floating and the prolonged-release characteristics of the system in the gastrointestinal tract (GIT). In fed state of beagle dogs, the different type of floating pills which contain p-aminobenzoic acid (PABA) after dosing showed higher plasma levels of PABA at interval of 5 and 6 hrs.

Kawashima et al., 1992 prepared hollow microballoons loaded with drug in outer shells of polymer by a emulsion-solvent diffusion method. The ethanol: dichloromethane solution of drug (ibuprofen or tranilast) and an acrylic polymer were poured into an agitated aqueous solution of polyvinyl alcohol (PVA) that was thermally maintained at 40°C. The gas phase generated due to dispersed droplets of polymer by the evaporation of dichloromethane formed in the internal cavity in the microballoon of the polymer. The drugs incorporated were found partially or completely amorphous in the outer shell of the polymer. The packability and flow ability of the resultant microballoons were much enhanced in compare
to the raw forms of drug. The microballoons continuously floated throughout the surface of acidic dissolution media containing surfactant for more than 12 h. The drug release pattern behavior of the microballoons was evaluated.

Mazer et al., 1988 investigated prolonged gastric residence time (GRT) can be deciding element for the slow absorption of a floating modified-release capsule of is radipine from measurements of different levels of drug in both gastric juice and plasma. The release profile and absorption of a lipophilic drug from a modified floating release capsule may be interfered and affected by intragastric interaction of the lipid phase in the meal. The main portion of medicament release profile occurred in colon from the modified-release capsule than stomach.

Nur and Zhang, 2000 Formulated floating tablets of captopril using HPMC and Carbopol 934P. In vitro drug dissolution study was carried out in simulated gastric fluid at 37 degrees C using the USP apparatus 2 basket method. In compare to conventional tablets, release of captopril from floating tablets was prolonged and 24-hr controlled-release dosage form for captopril was attained. Drug release kinetics fitted best both the Higuchi model and the Korsmeyer and Peppas equation, followed by first-order kinetics. While stirring rate and tablet hardness did not showed its impact on the release kinetics, tablets hardness was considered as a deciding factor in relation to the floating properties of the tablets.

Patel and Amiji, 1996 developed novel drug delivery systems with drug release properties and pH-sensitive swelling for localized delivery of antibiotic in the stomach. The drug delivery systems (DDS) were triggered by poly(ethylene oxide) (PEO) and crosslinking chitosan to form blend semi-interpenetrating network of polymer (semi-IPN). More than 59% of metronidazole and 65% of the entrapped amoxicillin were unconfined from the freeze-dried chitosan-PEO semi-IPN after 2 h in SGF. The results of this study suggested that freeze-dried chitosan-PEO semi-IPN could be better useful for localized delivery of antibiotics in the acidic media of the gastric fluid.

Srivastava et al., 2005 prepared matrix tablets of atenolol were prepared to prolong gastric residence time (GRT) and for increasing the bioavailability of drug. Atenolol was selected as a model drug because it is poorly absorbed from the lower gastrointestinal tract (GIT). The tablets were manufactured by direct compression method, using synthetic and natural
polymers such as hydroxypropyl methylcellulose (HPMC K15M, K4M), guar gum (GG), sodium carboxy methyl cellulose (SCMC), alone or in combination, and other excipients. Tablets were evaluated for physical characteristics viz. hardness, thickness, swelling ratio, floating ability, and weight variation test. Tablets were also evaluated for in vitro release profile for 8 hrs. The effect of effervescent on drug release profile and buoyancy was studied. In vitro release kinetics was evaluated by linear regression method. GG and SCMC based matrix tablets showed greater swelling indices in compare to other batches. The tablets showed prolonged and controlled drug release pattern while floating over the dissolution media.

**Yang et al., 1999** anticipated a new approach for the triple drug management (tetracycline, metronidazole and bismuth salt) of *H. pylori* induced peptic ulcers and designed the FDDS based on the asymmetric swellable triple layer tablet approach, with floating quality in order to prolong the gastric retention time (GRT) of the delivery system. HPMC and PEO were used as the chief rate-controlling polymers. Tetracycline and metronidazole were incorporated for controlled delivery in the core matrix, while bismuth salt was incorporated in the outer most layers for immediate release. The delivery system showed the potential to improve the efficacy of the management and enhanced patient compliance.

**Zhenphing and Zhanfeng, 2001** Prepared concept for new tablet of cisapride as two-layered tablets of floating for gastric retention (TFTGR). Curve between time-buoyancy and resultant buoyancy were plotted. The in vitro drug profile of dosage form was managed by quantity of hydroxypropylmethylcellulose in the medicament-loaded layer. Mostly, the more HPMC, the retard the medicament profile. The innovative idea for development of any other tablets used for gastric retention can be used.

**Amin et al., 2016** Prepared alginate microspheres of metronidazole by method of ionic gelation for sustained drug release profile at the gastric mucosa using Eudragit L100 as release modifier, guar gum as mucoadhesive natural polymer and using sodium bicarbonate as gas creation agent. The microspheres were evaluated for in vitro buoyancy, swelling studies, encapsulation efficiency and characterized by scanning electron microscopy.

**Khatri and Awasthi, 2016** Prepared acyclovir loaded floating microspheres by method of emulsification solvent evaporation. The microspheres were evaluated for size, shape, drug
entrapment efficiency, in vitro drug release profile, and in vivo pharmacokinetic parameters. The percentage drug release was decreased at higher concentrations of polymer. The preliminary results of study revealed that the developed acyclovir microspheres could increase entrapment efficiency, decrease initial burst release, and prolong the medicament release profile with improved bioavailability.

**Goswami et al., 2012** Prepared multiple unit of Valacyclovir hydrochloride by W/O emulsification solvent evaporation method using ethylcellulose as polymer to localise the drug for improvement of absorption at upper part of GIT. He proved that floating microspheres could be an appropriate alternative to the conventional formulation.

**Shadab et al., 2011** Prepared alginate mucoadhesive microspheres of acyclovir by emulsification phase separation method. The particle size of formulations was measured by SEM method and the particle size distribution was determined by an optical microscope. The results revealed that the mean particle size of the mucoadhesive microspheres increased with an increase in polymer concentration and decreased with increase in speed of stirring. In Gamma scintigraphy method, the section of GIT was critically examined. The study indicated that the optimized prepared formulation demonstrated gastroretention in vivo for more than 4 h, that indicated that optimized formulation could be a good and suitable choice of gastroretentive systems.

**Chordiva et al., 2011** Developed gastroretentive multiple units of famotidine by solvent emulsion diffusion method in four various ratio of drug to polymer, to retaining the drug concentration in the upper gastrointestinal tract resulting in increased absorption and improved bioavailability. Microspheres were characterized by particle size using optical microscopy.

### 2.5. Drug Profile

#### 2.5.1. Ranitidine Hydrochloride (RH)

RH is orally used H₂-receptor antagonist for the management of active duodenal and gastric ulcer, it is also used for the management of various other disorders such as endoscopically diagnosed erosive esophagitis, gastro-esophageal reflux disease. Orally it is also used for the management of pathological GI hyper-secretory conditions. Through
parenteral (IV) route, it is used in admitted patients in hospitals with intractable ulcers or pathological GI hyper-secretory conditions when oral therapy is not feasible (Debas and Mullholland, 1986).

**Molecular weight:** 314.4 g/mol

**Molecular formula:** C₁₃H₂₂N₄O₃S

**Melting point:** 140°C

**Physical state:** White to pale yellow, granular substance.

**Solubility:** Highly soluble in water, methanol and ethanol (95%) very slightly soluble in dichloromethane, chloroform.

### 2.5.2. Mechanism of action

Histamine is a biochemical compound which causes stimulation of the stomach cells to produce acid. RH belongs to a class of medicament known as H₂-blockers. Medications belonging to this class block the effect of histamine on stomach cells, which causes decreased production of acid in stomach.

### 2.5.3. Pharmacokinetics

#### 2.5.3.1. Absorption:

After oral administration this medicament is partly absorbed from the GI tract and undergoes least first-pass metabolism. Its oral bioavailability in adults is about 40–50%. Various clinical studies in a limited number of children (11–15 years of age) indicate a similar oral bioavailability of Ranitidine HCl (mean bioavailability: 50%). The oral suspension, film-coated tablets, and orally disintegrating tablets of Ranitidine HCl reportedly are bioequivalent.

#### 2.5.3.2. Distribution:

Distribution of this medicament into various human body tissues and biological fluids was not characterized. However, in adults, apparent volume of distribution is reported between the 1.1–1.4 L/kg and subsequently altered substantially in patients with
renal dysfunction. In children it was found between 1–15 of the age group. Moreover, It was also noticed that that volume of distribution between 1.6–2.07 L/kg has been noticed. Experimental studies in rats after oral or IV administration has shown that the drug have a wide distribution and achieves highest concentrations in the various organs like kidney, liver, pancreas, and submandibular gland. It is approximately 15–20% the total were protein bound.

2.5.3.3. Elimination:

The elimination half-life of RH averages 2.5–4 hours in adults with normal renal function and 2.3–3.38 hours in children of 1 to 15 years age group. The elimination of this medication does not appear to be affected substantially by age in adults. The elimination is prolonged in patients with renal impairment so it is necessary adjustment of dosage or dosing interval may be necessary to avoid extra deposition of the drug in moderate or severe renal impairment patients (Goodman and Gilman, 2006).

2.5.4. Dose

- In the treatment of benign gastric and duodenal ulceration, In night 40 mg for 4 to 8 weeks; 20 mg at night for maintenance therapy of duodenal ulceration.

- 20–40 mg two times in a day for 6 to 12 weeks for Reflux oesophagitis and 20 mg two times in a day for maintenance

- 20 mg every 6 hours (higher dose in those who have previously been receiving another H₂-receptor antagonist) for Zollinger–Ellison syndrome (Murakami et al., 1999).

2.5.5. Adverse effects

Hypertension, Fever, flushing, arthralgia, musculo-skeletal pain, and tinnitus have been reported in 1% or less of patients receiving Ranitidine HCl, but a causal relationship to the drug has not been established in many cases. An acute episode of gout occurred in one patient during therapy with the drug.
2.5.6. Literature Review on some sustained/ controlled release formulations of Ranitidine hydrochloride

**Abdul and Larry, 2001** Investigated the stability of ranitidine in vitro. Batch culture fermentation method was used in this process. With the help of UV and mass spectrometry it was found that metabolism occurred via cleavage of an N-oxide bond within the molecule. Such metabolism can be responsible for the poor bioavailability of ranitidine from the colon.

**Coffine et al., 1995** Described a bi-layer tablet. Tablet has one layer figured for the fast release of ranitidine and second layer designed for sustained release of ranitidine. Developed tablet formulation have proportion of ranitidine in the IR layer to that in the SR in the range of from about 30:70 to about 60:40.

**Dave et al., 2004** Prepared a delivery system for gastroretention (GRDDS) of RH. Xanthan gum, guar gum and hydroxypropyl methylcellulose have been used in delivery system because of gel-forming properties. For gas-creation purpose NaCO₃ was incorporated. The effects of stearic acid and citric acid on medicament release pattern and buoyancy properties were investigated. The existence of stearic acid in formulation decreases the medicament dissolution due to hydrophobic nature. The study pointed out that the appropriate balance between a release rate retardant and a release rate enhancer can generate a drug dissolution pattern like to a theoretical dissolution pattern.

**Davis et al., 1997** Figured the compositions for oral drug delivery for the management of gastric disorders embodying histamine H₂-receptor antagonist, and neutralization of acid, optimally buffered to enhance the local absorption of H₂-receptor antagonist, wherein the quantity of H₂-receptor antagonist per unit dosage form is under 25 mg.

**Mody et al., 1998** Developed an oral pharmaceutical formulation of Ranitidine Hydrochloride (RH) in capsule form, formulation containing a therapeutically effective amount of Ranitidine Hydrochloride (RH) in combination with a specific polymer which are coated with a coating comprising a specific polymer and specified polymer in coating and granules being selected from the group consisting of alkyl celluloses, Hydroxymethylcellulose (HMC), hydroxyl propylcellulose (HPC), hydroxyl propylmethylcellulose (HPMC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG)
and polymer being included in granules taken in quantity equivalent to about 0.2 to 1.2 times the weight of RH. Oral pharmaceutical formulations provided a MEC of RH for a sustained period of at least 12 hrs.

**Quirck et al., 1995** Invented pharmaceutical composition for use in veterinary medicine or human which contain ranitidine or a physiologically acceptable salt, thereof, bicarbonate or a physiologically acceptable salt thereof, or alginic acid and a bicarbonate or carbonate. The composition preferably contains 1.25% to 10% w/w ranitidine hydrochloride, 2% to 15% w/w sodium bicarbonate and 5% to 35% w/w alginic acid and is in the form of a tablet or capsule. The compositions are suitable for the treatment of reflux oesophagitis and gastrointestinal disorders.

### 2.6. Polysaccharides

Polysaccharides represent a structurally diverse class of natural originated biological polymeric materials. The formation of Polysaccharides occurs by the linkages between glycosides and monosaccharides. Polysaccharides posses linear or branched structure which is based on type of the monosaccharide sub units. The possibility for chemical modification in polysaccharides may be due to the nature of structural diversity and a large number of highly reactive groups, such as hydroxyl groups, carboxylic acid and amino acid. Molecular weight of polysaccharide may in the range of hundreds to thousands of Daltons units (Darekar et al., 2013).

The derivatives of naturally originated polysaccharides belong to a group of biopolymers which are utilized for the controlled drug delivery systems. These controlled drug release formulations have various advantages such as-

- They achieve the optimum concentration for prolong period of the time.
- They can enhance the activity of labile medicaments.
- They minimize the various toxic effects because of the reduction of higher initial blood plasma concentrations.

**Advantages of natural polysaccharides**-

- Local availability:
❑ Low cost:
❑ Biodegradable:
❑ Biocompatible and Nontoxic:
❑ Environmental friendly processing:
❑ Improved patient compliance and better acceptability in public.
❑ Freely available, compared to their synthetic counterparts (Avachat et al., 2011).

Disadvantages of natural polysaccharides:
❑ High variation in batch to batches.
❑ Reduced viscosity on storage.
❑ Microbial contamination
❑ Uncontrolled rate of hydration (Reddy and Manjunath., 2013; Kulkarni U et al., 2011).

Extraction and purification of natural polysaccharides (gums/mucilages)

The various materials of plant were dried preferably in presence of the sun light for retaining its own properties. Before extracting the mucilage, mostly pigments or chlorophylls should be removed. Different materials of plant must be treated with chloroform and petroleum and then double distilled water to remove chlorophyll and pigments. Final isolated/extracted mucilage should be dried carefully. It must be dried at a very less temperature range (not more than 45°C) or vacuum. The dried plant material is then kept and stored very carefully in desiccators so that it can be prevented from further moisture degradation or uptake.

2.6.1. Fenugreek (Trigonella foenum-graceum)

Trigonella foenum-graceum is commonly known as Fenugreek. It is an herbaceous plant belonging to leguminous family (Dharmendra et al., 2012). The seeds of Trigonella foenum graecum L. are also known as fenugreek seed or Methi, Methi Dana, in Hindi. The seeds of Trigonella foenum graecum L. are also used for various purposes such as vegetables and preservative (added to pickles).
The ripe seeds of fenugreek have medicinal values and are used in the management of: dyspepsia, dysentery, enlargement of liver, chronic cough, and diabetes (Abdul-barry et al., 1997). Fenugreek seeds possess high percentage of mucilage which does not dissolve in the water but it forms a viscous tacky mass when exposed to other fluids (Dharmendra et al., 2012).

Fenugreek gum is at great demand currently due to its considerable amount of applications in the industries. It is an annual legume plant which is native to the Mediterranean region but is also grown in Africa and Central East Asia. India is a chief and an important exporter of Fenugreek seeds. Fenugreek seeds are used as spice and also in various natural medicines in India.

2.6.1.1. Extraction of Trigonella foenum graecum L. Seed Mucilage

Hot water extraction method is used for extraction of mucilage in which seeds are washed with water and dried at room temperature. The clean and dried seeds are further placed in water to boil for 12 hours at 45°C for release of mucilage into water. Further the material is squeezed through a muslin cloth to remove the marc from the filtrate and the filtrate is allowed to cool in a refrigerator and the mucilage is precipitated using ethanol.

2.6.1.2. Pharmaceutical applications:

**Controlled release polymer:** Fenugreek gum was explored as an emulsifying agent and hydrophilic polymer in drug delivery systems of a drug simvastatin and the drug is low soluble in water and poor biocompatibility. The study confirmed the improved solubility and dissolution profile due to better wetting (Sav et al., 2013).

**Binder in tablets:** Fenugreek gum was used as a tablet binder in three model drugs of ibuprofen, calcium acetate, and theophylline. The study confirmed that fenugreek gum can be used as a binding agent for sustaining the dissolution profile of the drugs that are water soluble (Tavakoli et al., 2012).

**Gelling agent:** Different batches of Diclofenac gel were prepared using different concentration of gum or mucilage. The gels were evaluated using various quality parameters such as viscosity determination, drug content, skin permeation test, and irritation etc. The prepared gel formulations did not showed any allergic reactions in mice.
formulations were established stable by various means of like physical appearance, drug content and viscosity at all different temperature conditions for continuous three weeks. The Study described that the extracted mucilage can be utilized as a better gelling agent in formulations (Mundhe et al., 2012).

**Disintegrating agent:**

Fenugreek seeds powder was used as disintegrating agent in tablets, formulated by wet granulation method. Tablets were evaluated using different quality controls like weight variation test, hardness test, friability test, disintegration time, wetting time and stability study. Results described that fast dissolving tablets prepared from powder of fenugreek seed can be made at any level of super disintegrants and can cause to better efficiency and better patient compliance (Kulkarni U et al., 2011).

**2.6.2. Tamarindus Indica**

Polysaccharide of Tamarind seed is basically a natural polysaccharide. Tamarind (Tamarindus indica) obtained from the evergreen tree belongs to the family Fabaceae and is called as "Indian date". They grow well in the presence of full sunlight and clay that is having medium growth and long lived, bushy tree. It is also known as Galactoxyloglucan.

Polysaccharide of Tamarind seed was evaluated for the study of toxicity in its parts, and there was no carcinogenicity. Tamarind seed polysaccharide contains monomers of galactose, xylose and glucose sugars present in a molar ratio of 3:1:2, which constitutes about 65% of the seed components. Xylose is considered as very important sugar of tamarind seed and it could be used for the production of xylitol (pentahydric alcohol formed by a five carbon chain). Tamarind seed polysaccharide has significantly improved bioavailability of some drug (Ganesan et al., 2013; Hernandez et al., 2012; Satle and Agrawal, 2013).

The fruits were present in the formation of pods (6-11cm long and 2cm broad). It has shape of oblong, curved or straight, with rounded ends. The color of pod was light brown gray or light brown. Brittle pod was thick, soft pulp and scaly that was coupled to an outer epicarp. The pulp is traversed by formed seed cavities, which contains the seeds (Sahoo et al., 2010; Rasala et al., 2011; Singh et al., 2011; Caluwe et al., 2010).
Seed of Tamarind contain endosperm or kernel (71-76%) and testa or seed coat (10-30%). Tamarind seed can be utilized as a source of raw material for the preparation of polysaccharide (jellose), tamarind seed kernel powder, tannin and adhesive. The seeds can also be used for different purposes such as an alternative source of protein, rich in some essential amino acids. Unlike the pulp the seed is a good source of protein and oil. Seed and kernels are found as rich source of protein and the seed coats contain a large quantity of tannins (20%) and fiber (20%) (Sahoo et al., 2010; Rasala et al., 2011; Singh et al., 2011).

2.6.2.1. Composition of Tamarind Seed Polysaccharide

Pulp of Tamarind contains 3.1% protein, 20.6% water, 70.8% carbohydrates, 0.4% fat, 3.0% fiber and 2.1% ash. The pulp has high level of protein, carbohydrates and low water content minerals (Rasala et al., 2011, Singh et al., 2011, Caluwe et al., 2010).

2.6.2.2. Properties of Tamarind Seed Polysaccharide

It is insoluble in organic solvents and similar to ethanol, methanol, acetone, ether and cold water. It yields a viscous gel or viscous colloidal solution at above 86°C temperatures that can be dissolved in heated water. It has the properties such as high adhesivity, viscosity, broad pH tolerance and non-carcinogenicity. It is non-irritant agent having haemostatic activity. It is also a potential emulsifier, nontoxic, includes high capacity of drug, high swelling index and high thermal stability consider it a suitable excipient for drug delivery system. Seed polysaccharide woks as a good viscosity enhancer and shows mucomorphic, mucoadhesive and bioadhesive activities. Tamarind kernel seed also have the property of forming films with high tensile strength and flexibility, making it a good excipient for ocular preparations (Sahoo et al., 2010, Singh et al., 2011, Caluwe et al., 2010, Singh et al., 2007, Isha et al., 2010).

2.6.2.3. Pharmaceutical Application of Tamarind Seed Polysaccharide

Tamarind kernel powder can be used as a thickening, gelling, stabilizing and binding agent in pharmaceutical and food industries and as a thickening agent and a sizing agent in paper industry and textile industries. Tamarind Seed Polysaccharide can be utilized as a carrier for number of medicaments for controlled release applications. It is used as an emulsifying and suspending agent in oral liquid and also acts as a binding agent in solid...
dosage form (Caluwe et al., 2010; Singh et al., 2007; Chandramouli et al., 2012; Manchanda et al., 2014).

2.6.2.4. Uses of Tamarind Seed Polysaccharide

Pulp of Tamarind is used for preparing spiced sauces, making beverages and wine. Its juice is also used for preservation of fish for six months. Tamarind kernels used as a mayonnaise, cheese and stabilizing agent in ice-cream, also used as in making jams and jellies. Tamarind extract is utilized as anti-fungal and anti-viral agent and replacement of citric acid, phosphoric acid, and other type of acids added to soft beverages. Leaves and flowers are used to make salads, curries and soups. Fruits and its extract is used as fungicidal, bactericidal and anti-bacterial agent. Dyes and ink is prepared by Bark containing tannin component. Fresh bark and stem are used as to get relieve from abdominal. Leaf juice or Fruit pulp and with milk or lemon can be used for treatment diarrheal and dysentry (Singh et al., 2011; Isha et al., 2012; Chandramouli et al., 2012; Manchanda et al., 2014).

2.7. Eudragit RS100

Commercial form

Eudragit RS 100

Chemical structure: It is a copolymer of methyl methacrylate, ethyl acrylate and a less content of ester of methyl acrylic acid with the presence of quaternary ammonium groups. The presence ammonium groups of as a salt causes permeability. The avg molecular weight is approx. 31800 gram/mol.

Description: no color, transparent to hazy granules with a slightly odor similar to amine.

Solubility: 1 gram of the substance dissolved in 8 gram ethanol aqueous, IPA (containing approximately 4 % H2O), methanol, ethyl acetate, acetone and methylene chloride give transparent to hazysolutions. The substance is found insoluble in 1 N sodium hydroxide, petroleum ether and water.

Storage: Protect from moisture and high temperatures. It should be stored at the any temperature between 8°C and 25 °C.
2.8. Objectives of the Present Study

The objectives of the present study are:

- To formulate and evaluate the floating muco-adhesive microspheres loaded with RH.
- To utilize the novel natural polysaccharides extracted from plant sources.
- To estimate the effect of polysaccharides on the floating and drug release.
- To evaluate the floating microspheres using physicochemical and in vitro parameters.
- To utilize the dissolution data and gain insight into the mechanism of drug release from floating microspheres.
- To treat dissolution data with different kinetic models.
- To conduct the drug stability studies for best formulations as per ICH guidelines.
- To determine shelf life of dosage forms.
- To improve the bioavailability of the drug through floatation.
- To increase the effectiveness in therapy.
- To reduce the dosing frequency.
- To maintain plasma concentration of drug in therapeutic range for longer time by enhancing GRT and minimizing plasma drug level fluctuation.
- To improve patient compliance.

2.9. Plan of work

The stages involved as follows

- Extraction of natural polysaccharides from natural plant sources.
- Characterization and standardization of extracted polysaccharides.
- Drug-excipient compatibility studies by FT IR spectroscopy and XRD.
- Construction of calibration curve.
- Formulation of floating mucoadhesive microspheres using extracted natural polymers.
- Physicochemical evaluation of formulated floating microspheres.
- In vitro buoyancy study.
- In vitro dissolution study.
- Treatment of dissolution data with different dissolution kinetic equations.
- The stability studies for the shelf life determination and to determine the best formulations.