Chapter 1

INTRODUCTION
INTRODUCTION

A large numbers of novel drug delivery systems are investigating day by day for drug administration through various routes. Administration of drugs by oral route is well-thought-out as appropriate and ideal route of drug delivery for increased patient compliance as compared to other drug delivery system by any other route. However, oral administration of some of the drugs suffers from short term limitations such as their less oral bioavailability because of partial absorption. Degradation of drug in the gastrointestinal tract (GIT) is one of the most important cause of less oral bioavailability. Various medicaments exhibit a narrow therapeutic window in the upper portion of the GIT because of proximal part of the small intestine shows prolonged absorption properties (including larger gaps between the tight junctions and dense active transporters). The extent of absorption is limited at these sites as the drug passage is rapid through these regions despite the higher absorption properties at the jejunum and duodenum. The net absorption of the drugs exhibiting narrow therapeutic window can significantly be improved by increasing the gastric residence time (GRT) of the medicament (Alexander et al., 2006).

Ranitidine hydrochloride (RH), an H₂ receptor antagonist competitively inhibits the interaction of histamine with its receptors, is commonly known for the management of gastric ulcer and Zollinger-Ellison syndrome. It shows maximum absorption at upper part of GIT. Effective management using conventional immediate release solid dosage forms can be achieved by administration of 150 mg of RH, two to three times a day, which may lead to patient incompliance. Moreover, it shows less bioavailability(50%) when administered as oral traditional dosage forms due to decreased absorption (short half life - 2.2 hrs) and colonic metabolism (Maslarska ,2014; Abdul and Larry 2001; Yu-meng and Ling 2008).
Local drug delivery to the receptor of parietal cell wall is promoted by RH oral drug delivery. This local delivery in turn improves the receptor site on stomach wall bioavailability and value to decrease acid secretion. Hence, prolonged gastro retention can improve systemic and localized effect of RH to efficiently reduce gastric acid secretion (Mohamed and Dehghan, 2009). In order to improve therapeutic action and patient compliance it is required to design a formulation which can increased the retention of drug into upper part of along with sustain release action upto 10 h (Abdul and Larry, 2001).

In order to minimize these limitations, a large numbers of innovative smart formulation are coming into accounts with improves drug features such as efficacy, bioavailability and safety into the systemic circulation. Various approaches have been proposed to retain the dosage form in the stomach such as gastro-retentive floating drug delivery systems were developed dependent on the principle of generation of carbon dioxide effervescence by various researchers (Dettmar and Lloyd-Jones, 1994; Deshpande et al., 1997 & Yang et al., 1999) ; hollow microspheres called microballoons capable of floating in the gastric fluid were reported (Umamaheshwari et al., 2002) and mucoadhesive drug delivery systems were developed by many scientists produced longer gastric residence time and better efficacy (Ponchel and Irache, 1998, Nagahara et al., 1998, Katayama et al., 1999) or by the simultaneous co-administration of pharmacological therapeutic additives that prolong gastric emptying (Groning and Heun, 1989). Cross linked chitosan microspheres also exhibited prolonged gastric retention (Hejazi and Amiji, 2002; Naisbett and Woodley, 1995).

Many difficulties and problems are continuously faced by researchers in development and design of the controlled release systems for increased absorption and thus improved bioavailability. Researchers have made attempts to prolong the retention time of dosage forms in the stomach. The preparation of a dosage forms that remain buoyant in the stomach due to its lower density than that of the gastric fluids is one of the several approaches (Desai and Bolton, 1993). Floating drug delivery systems (FDDS) are basically low-density based systems which have enough buoyancy to float over the gastric contents and thereby remain floating in the stomach region for a prolonged period of time without affecting the gastric emptying rate. While the system is buoyant over the gastric contents, the drug is released slowly at the pre-desired rate
from the delivery system and results in an increased GRT and reduced plasma drug level fluctuations. Prolonged gastric retention would extend the absorption phase of the medicaments with narrow absorption window. FDDS would be retained in the stomach and proximal part of small intestine while the drug would be release in a controlled and prolonged manner to its absorption sites and thereby improving oral bioavailability, reducing drug wastage and enhancing solubility of poorly soluble drugs at a higher pH values (Hoffman and Strepsensky, 1999; Sawicki, 2002). Single-unit preparations are associated with various problems such as sticking together or being obstructed in the gastro-intestinal tract which have significant problem of causing gastric irritation. While a floating system is made of multiple unit forms and has relative advantages in comparison to a single unit formulations. The gastric emptying of a multi-unit floating system would happen in a controlled and regular manner with less different drug-plasma level differences. On subsequent gastric emptying, the sunk particles of the floating formulations will spread over a huge area of absorption positions in the stomach and thus increasing the changing the medicament release pattern and absorption in a more efficient anticipated way (Tanwar et al., 2007). Furthermore, since each individual dose is made up of many subunits, the danger of dose dumping would be condensed (Iannuccelli et al., 1998; Kawashima et al., 1992).

FDDS have also exhibited there utility in the delivery of medicaments which are not stable in the intestine or colonic environment (Dave et al., 2004) and in the effective management of eradication of *H. pylori*, that is considered to be the connective agent for peptic ulcer and chronic gastritis (Hejazi and Amiji, 2002). Thus, gastro-retention using FDDS may provide better bioavailability of existing drugs with new therapeutic promises and extensive patient compliance.

The objective of such formulations has been achieved by using increased number of natural originated and synthesized polymer. The synthetic polymers suffer from certain demerits such as expensive, not easy to process, produce toxic and side effect, release of acidic degradation products, not environmental friendly, poor bio compatibility, loses its mechanical properties and poor patient acceptability. They may also produce eye irritation, skin irritation and mild inflammatory reactions during handling and
manufacturing of some synthetic polymers (Rangari, 2006; Kokate et al., 2006; Kottke and Edward, 2002; Aslam and Parrott, 1971).

On the other hand naturally obtained polymers are considered to be safe and equally effective due to their biocompatible or at least biodegradable nature. A broad range of natural originated polymers are available such as chitosan and alginate etc. and they are extensively used as excipients in formulations. The plant based natural gums and mucilages have number of advantages such as inert, inexpensive, readily and easily available, biodegradable and bio-acceptable, non toxic and non irritant, environmental friendly, better patient and public acceptance. (Robbins, 1988).

Today, there are a wide range of mucilages and gums of natural origin such as agar, alginates, gelatine, starch, pectin and acacia, as pharmaceutical polymers/ excipients. These plant based polymers are generally employed in the pharmaceutical formulations as diluents, binder, disintegrating agents in tablets and capsules, gelling agent in gels, thickening agents in oral liquids, bases in suppository. These also find applications in cosmetics, paints, food, paper and textile industry (Kulkarni et al., 2011).

Mucilages are basically composed of heterogenous polysaccharide complexes formed from the sugars such as mannose, xylose, arabinose, galactose, uronic acid and glucose units. They have numerous pharmaceutical properties and play important role in design of formulations, which make them useful as additives in pharmaceutical preparations and in present investigations (Aulton, 2002; Avachat and Kotwal, 2007; Banker and Anderson, 1990; Banker and Rhodes, 1996; Jain et al., 2008; Sheng-Fang et al., 2003; Sravani et al., 2011).

It is proposed that as there will be an increased understanding of polymer behavior in future the research work in the drug delivery systems will be aimed on the usage of plant based natural polymers for the optimization of pharmacokinetic and toxicological profiles of drugs.

In the field of FDDS, it was observed that there are many problems and obstacles which are needed to be overcome in order to prove proper gastric retention. Considering significant improved delivery of medicaments through FDDS, some researchers have took the challengeable work for the development of these types of
dosage forms but because of the unpredictability in the human GI tract, some have succeeded and some others have not succeeded.

To overcome above discussed problems associated with RH and FDDS, a floating drug delivery system of RH loaded floating microspheres using noval natural polysaccharides was proposed to develop in the present study. The focus in the present study was mainly on some of the unanswered, important issues of FDDS like the role of buoyancy in increasing GRT. Moreover developed formulation of an perfect and suitable dosage formulation that can dispersed by orally by proper utilization of natural originated polymers. Moreover, the role of novel polysaccharides was investigated in development of floating muco-adhesive microspheres for localized drug delivery of RH specifically into upper parts of GIT to achieve the required floating characteristics of the dosage form and to effectively check the gastro-retentive properties.

In the present study, some novel plant polysaccharides were investigated for their application in the floating drug delivery system. The plant polysaccharides were isolated from the traditional Indian plants such as tamarind and fenugreek.

Polysaccharides, extracted from the seeds of tamarind (Tamarindus indica, TI), are un-ionic, neutral in nature, densely branched structure consist of cellulose like backbone having xylose and galactoxylose subunits. These polysaccharides have been investigated by many researchers for many applications such as gelling agent, tablet binder, stabilizer and thickening agent. However, so far, these polysaccharides are not evaluated in floating drug delivery system yet.

Polysaccharides from seed of tamarind are being obtained from the kernels of Tamarindus indica (Family: Leguminosae). It exhibits elevated adhesive property, higher viscosity and stable at wide pH (Rao et al., 1946). Moreover, it is reported as mucoadhesive, biocompatible, (Burgalassi et al., 1996), thermally stable (Saettone et al., 1997), high drug loading capacity (Kulkarni et al., 2011) as well as no carcinogenic, (Sano et al., 1996). Due to above mentioned properties, They are being utilized as stabilizing agent, thickening agent, gelling additives and binding agent in food business. Tamarind gum is also used for as a bioadhesive tablet (Kulkarni et al., 2011). But, its utilization and application in pharmaceutical developed formulations has not been tested and evaluated so
Polysaccharide was also obtained from the seeds of *Trigonella foenum-graecum* (TFG, Family: Fabaceae). Chemically this polysaccharide consist of five components such as kaempferol 7-O-glucoside, kaempferol 3-O-β-d-glucopyranoside, kaempferol 3-O-α-L-rhamnosyl (1→2) β-d-xyloside, kaempferol 3-O-β-glucosyl (1→2) (6′-O-acetyl)-β-d-galactoside and kaempferol 7-O-β-D-glucopyranosyl (1→4) β-D-glucopyranoside (Faten et al., 2014).