CHAPTER-2

Literature Review

2.1 Anatomy of colon

Human gastrointestinal tract (GIT) is divided into two parts, upper GIT and lower GIT.The upper part comprises of mouth, pharynx, oesophagus and stomach whereas lower part consist of small intestine, large intestine and anus [Singh et al., 2014]. Colon is a part of the large intestine which is approximately 1.5 m long and further subdivided in proximodistal sequence including ascending, transverse, descending and sigmoid colon(Figure 2.1).

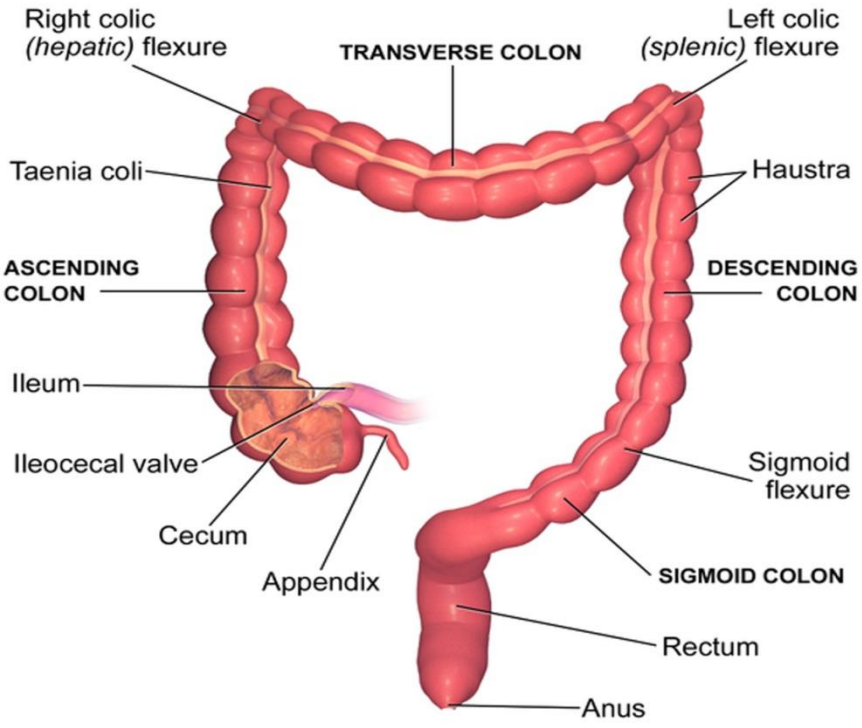

Figure 2.1 Parts of Large Intestine (obtained from teachanatomy.info/abdomen/gi-tract/colon)

The ascending colon is approximately 15 cm long and extends vertically from the ileocaecal junction to the hepatic flexure (the turn of the colon by the liver) before continuation with transverse colon.

Transverse colon covers colonic part involving hepatic flexure to the splenic flexure (the turn of the colon by the spleen). It is approximately 45 cm in length and regarded as the most mobile segment. It hangs off the stomach through a wide band of tissues called as greater omentum.

Descending colon is an extension of splenic flexure to the iliac fossa that endsin continuation with sigmoid colon. It measures about 25 cm in length.

The sigmoid colonis about 35-40 cm in length. Walls of the colonare muscular that contracts and enhance the pressure causing stool to move into rectum[Jorge and Habr-Gama, 2007, Mahadevan, 2017].

Functionally colon can be divided into two divisions, the right and the left colon. Right colon comprises cecum and ascending colon that serves in the absorption of water and electrolyte and fermentation of undigested carbohydrates whereas left colon consist of descending colon, sigmoid colon and rectum that primarily stores and evacuate faecal matter[Thomson, 1994].

2.2 Colon cancer

The colon and the rectum (colorectal) part together in the combination forms the large intestine[Compton et al., 2012]. The initial risk of developing colorectal cancer is 5% that could further increase with an increase in age. Generally two-third of all colorectal cancer occurs in the colonic region and one third in the rectal region [Ghanipour, 2014]. Colon cancer develops gradually over a period of 10-15 years[Kelloff et al., 2004]. Initially, it appears as a non-cancerous polyp, an outgrowth of tissue and develops on the lining of colon or rectum. With the passage of time, this polyp turns into cancer [Byrne, 2008]. Polyps can either be benign or malignant among which the possibility of the benign polyp to turn into adenomatous polyp is maximum. About 96% of colorectal cancers are adenocarcinomas commonly evolve from glandular tissue [Stewart et al., 2006]. Once the cancer forms in the large intestine it progresses through the lining and the wall of colon and rectum. The cancer

cells that have penetrated the walls can also enter the blood vessel and lymph vessel and through metastasis can spread further to the liver or lungs [Perdue et al., 2008](Figure 2.2).

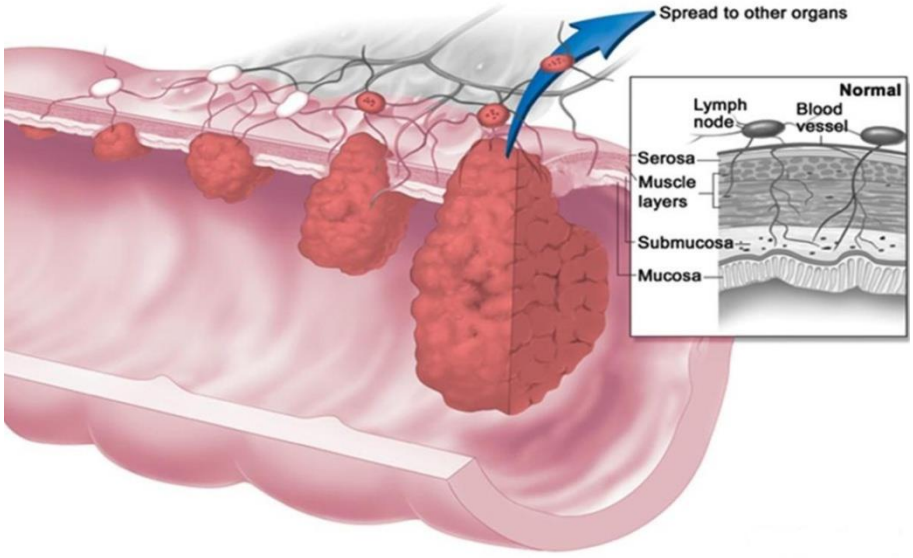

Figure 2.2 Progress of colon cancer cells in the large intestine (Adapted from Colorectal Cancer Facts & Figures 2017-2019)

2.3 Stages of colon cancer

The extent to which cancer has spread towards the organ is measured during diagnosis is termed as staging. The differentsystem used for staging the cancer isthe TNM system; SEER system and Duke system[Akkoca et al., 2014].

2.3.1 TNM system

This system classifies cancer based on [Wood, 1971].

Grade I (T): This kind of carcinomas appears microscopically similar to the adenomas. This system describes how far the adenoma has spread to the intestinal wall and to the nearby tissues.

Grade II (N): The neoplasm under this grade appears considerably irregular in shape with slight tubular structure. This system describes how far cancer has spread to the lymph nodes.

Grade III (M): The carcinoma falling under this grade is devoid of tubular structure. This kind of carcinoma starts to metastasize especially to the lung and the liver.

2.3.2 SEER System

According to this, staging can be defined as

In situ: These cancers are non-invading in nature and remains at the colonic wall.

Local: They are likely to be spread to the wall of the colon and also spread to the colonic wall as well to the nearby tissues.

Regional: They spread to the colonic wall, nearby tissues and to the lymph nodes.

Distant: These cancers spread to the major organ such as the liver and lungs.

2.3.3 Duke System[Petersen et al., 2002]

This system is now no longer in use and is of historical interest only. The system is replaced by TNM and SEER system.

2.4 Risk factors of colon cancer

Age: As the age advances the risk of colon cancer increases. According to the survey 2017, the occurrence of colon cancer is maximum at the median age. It is recorded as 68 in men and 72 in women[Haggar and Boushey, 2009]. People between the age of 65-85 are more likely to be suffering from colon cancer than the people at the age of 50 [Church, 2005].

Gender: The role of gender for colon cancer is ambiguous. However, it has been observed that the risk of approximately 30-40% is higher in men than women [Kim, 2009].

Race: The incidence of advanced adenomas is highest in blacks than the whites and Hispanics possess lower risk than non-Hispanics [Strum, 2016].

Obesity & metabolic syndrome: The risk of colon cancer is getting increased in obese person especially in men than women. Patients with metabolic syndrome such as diabetes and lung diseases are at higher risk of adenoma detected during colonoscopy [Chiu et al., 2015].

Family history: People with a family history of colon cancer are at risk of developing cancer. Generally,it occurs by following the genetic mutation that results as familial adenomatous polyposis [Byrne, 2008].

Physical activity: People who do not exercise daily or lack any physical activity are found to be at greater risk of colon cancer. Through studies, physically active people have 25% less chance of colon cancer than the least active people [Macfarlane and Lowenfels, 1994].

Diet: Intake of processed or red meat enhancesthe chance of colon cancer [Chan et al., 2011]. It may be due to the formation of cancer-causing substance while cooking it at the high temperature [Kim et al., 2013].

Smoking: As per the survey of the International Agency for Research on Cancer, tobacco smoking is sufficient to cause colon cancer. However, with this risk factor, the incidence of rectal is more than the colon cancer [Botteri et al., 2008].

Alcohol intake: Occurrence of colon canceris high with moderate and heavy use of alcohol [Giovannucci et al., 1994]. People who take more than three drinks per day are ata 40% risk of having colon cancer.

2.5 Screening of colon cancer

Prevention of colorectal cancer can be done through various examinations if done at an early stage [Rex et al., 2017]. As per the guidelines of United States, screening of the colorectal cancer must be started for the patients who are at the age of 50 (both men and women) and at average risk [Winawer et al., 1976]. The screening method involves usually two types of

examinations i.e. visual examination or endoscopic screening and faecal test [Knudsen et al., 2016]. The methods for screening of colon cancer are summarized in Table 2.1.

Table 2.1 Different screening method for the detection of colon cancer

Screening test	Advantages	Disadvantages
Endoscopic screening		
Flexible sigmoidoscopy	Involves a proper check of rectum and colon; simple and quick; reduces the incidence of colorectal cancer especially in the distal part.	The tube can be inserted only to the lower third of the colon.
Colonoscopy	Involves an entire check of colon and rectum; allows biopsy; removes polyp; can detect other diseases.	Expensive; risk of infection and bowel tears.
Computed or virtual colonoscopy	Quick; examines entire colon; non-invasive; recommended for large polyp.	Does not allow biopsy; use of X-rays.
Barium enema using air contrast	Quickly examines the entire colon with few complications.	Less sensitive than colonoscopy and sigmoidoscopy.
Faecal test		
Guaiac-based Faecal occult blood test (gFOBT)	Uses chemical guaiac to detect blood in the faecal matter; more effective in combination with flexible sigmoidoscopy; can be performed at home; non-invasive and inexpensive	Requires repetition and limited sensitivity.
Faecal Immunochemical test	Uses antibodies for the detection of blood in the stool. It is performed in a similar way as gFOBT.	Expensive;Requires multiple faecal samples; more technical and complicated than gFOBT.
Stool DNA test	Requires only single faecal sample; non-invasive;	Highly expensive; sometimes require colonoscopy;

2.6 Treatment strategy/plan

The treatment plan of colon cancer is based on the stage of the disease and the functional status of the patient. If cancer is diagnosed at a very early stage then surgery can be preferred and if it has metastasized to the near and the distant organs then, in that case,proper medical

care with chemo and radiation therapies are preferred. In between these two therapies, chemotherapy is used mostly as most of the cancers are detected at the last stage [Mustafa et al.].

2.6.1 Chemotherapy

Chemotherapy involves the use of chemotherapeutics or cytotoxic anticancer agents given to the patients through the intravenous route of administration. Chemotherapeutic drugs are cell cycle specific and depending upon their specificity the schedule of the therapy plan is decided[Harrington and Smith, 2008]. Use of only one chemotherapeutic agent causes the incidence of toxicity to the patient however in a combination of various agents they reduce the toxicity to the healthy cell by blocking the replication of cell[Seiwert et al., 2007]. Chemotherapy, given after surgery increases the profusion of blood and also increases the effectiveness of adjuvant therapy. But it cannot always be a perfect treatment plan for preventing cancer, as a common problem with this therapy is the ‘drug resistance’ resulting in the reoccurrence of cancer[Gottesman, 2002]. The intravenous route of administration is the current choice of administering the cytotoxic agents because of the poor solubility of anticancer agents into the aqueous solution. Due to the delivery of drug directly into the systemic circulation leads to the common adverse effects such as mucositis, myelosuppression and alopecia. No doubt, that chemotherapy cannot be ignored while treating cancer but still there is a requirement of improved delivery methods of cytotoxic agents especially the oral route of delivery for patient concerning their care and comfort in reduced healthcare cost [DeVita and Chu, 2008].

2.7 Formulation specific review of the literature

2.7.1 Multi-particulate drug delivery system (MDDS)

Multi-particulate drug delivery systems (MDDS) are meant mainly for the oral dosage form and contains multiple small discrete units each showing desired properties. In thistype of dosage form, the drug is divided into numerous subunit comprising thousands of spherical particles with a diameter of 50 µm-2000 µm. Thus, these are the pharmaceutical formulations where the active pharmaceutical ingredient is present in numerous small independent subunits that can be further packed into a sachetor encapsulated or compressed in tablets[Dey et al., 2008].Despite of major advancement in drug delivery system MDDS as an oral dosage form has secured a centre stage in the area of pharmaceutical research and development for achieving an extended release of drug from the formulations (Table 2.2) [Jeevana and Jyosna, 2010]. They offer several advantages over single unit systems, for instance,less inter and intrasubject variability because of less dependency on the gastric emptying, lower risk of local irritation and systemic toxicity [Asghar and Chandran, 2006].The system shows better and reproducible results of a pharmacokinetic study in comparison to the conventional formulations. Being micron in size and especially if the diameter is less than 2mm they show fast disintegration and vacate the stomach continuously even if the pylorus is closed resulting in decreased inter and intraindividual variability in plasma level and bioavailability [Dey et al., 2008].

2.7.1.1 Advantages of MDDS [Patwekar and Baramade, 2012]

- Improved bioavailability
- Less inter and intra patient variability
- Limited risk of local irritation and less adverse effect
- Less possibility of dose dumping

- Flexibility in design
- Improved stability and patient compliance and comfort
- Exhibits unique release pattern

2.7.1.2Disadvantages of MDDS [Patwekar and Baramade, 2012]

- Requires a number of excipients during preparation
- Requires numerous number of process variables
- Multiple formulation steps

Table 2.2 Marketedmultiparticulate based drug delivery system

Product	**Brand**	**Drug**	**Dosage form**
Coreg CR	GSK	Carvedilol phosphate	Polymer coated beads in capsule
Luvox CR	Jazz	Fluvoxamine maleate	Polymer coated beads in capsule
Pentasa	Shire	Mesalamine	Controlled release beads in capsule
Metadate CD	UCD,Inc.	Methylphenidate	SR coated beads
Amrix	Cephalon	Cyclobenzaprine HCl	Polymer coated beads in capsule
Equetro ER	Validus	Carbamazepine	IR + SR beads in capsule
Losec MUPS	AstraZenaca	Omeprazole magnesium	Delayed release pellets in tablet
Toprol XL	AstraZeneca	Esomeprazole magnesium	Delayed release pellets in tablet
SoluTab	Takeda	Lansoprazole	Enteric coated micro-granule in tablet

2.7.2Interpenetrating polymeric network

Oral multiparticulate controlled release dosage forms, for instance, microbeads, micro-particles, are becoming more acceptable than single unit dosage form. These multi-unit dosage form easily spreads and retain over a large area of absorbing mucosa and release the drug in a controlled/ sustained manner[Ekici and Saraydin, 2007]. Generally for the preparation of multi-unit oral controlled release dosage forms natural polymers are preferred due to their non –toxic, biodegradable and biocompatible nature[Debotton and Dahan, 2017]. Though, they are gaining importance day by day but few limitations are still associated with it such as mechanical instability and their rapid disintegration into the gel form [Şolpan and Torun, 2005]. To overcome the problem of instability and to improve its biological performance the technique of formulating Interpenetrating Polymeric Network (IPN) would be an ideal approach.IPN through their denser polymeric network can control the drugrelease behaviour[Burugapalli et al., 2001].IPNs are the part of a broad class of polymeric blends. They are formed by combining two or more than two polymers in a network form where at least one polymer is polymerized or cross-linked in the immediate presence of each other [Sperling and Mishra, 1996]. Each polymer network associated with IPN shows the synergistic effect and forms an advanced multicomponent polymeric system thus, improves and enhances both the mechanical stability and biological performance [Kim et al., 2004, Kulkarni et al., 2013]. Few examples of IPN based dosage forms and drugs that have been delivered through IPN are illustrated in Table 2.3 and 2.4 respectively.

Table 2.3 IPN based Drug Delivery systems

S.No.	Title	Drug/ Therapeutic	Dosage form	Reference
1	Novel interpenetrating polymeric network hydrogel microspheres of chitosan and Poly (acrylamide) grafted guar gum for controlled release of ciprofloxacin	Ciprofloxacin	Microsphere	[Kajjari et al., 2011]
2	Novel interpenetrating polymer network mucoadhesive microspheres of gum ghatti and poly (vinyl alcohol) for the delivery of ranitidine HCl	Ranitidine HCl	Microsphere	[Jain and Banik, 2013]
3	Novel interpenetrating polymer network microspheres of chitosan and methylcellulose for controlled release of theophylline	Theophylline	Microsphere	[Rokhade et al., 2007b]
4	Controlled Release of an Antihypertensive Drug through Interpenetrating Polymer Network Hydrogel Tablets of Tamarind Seed Polysaccharide and Sodium Alginate	Propranolol HCl	Tablet	[Kulkarni et al., 2013]
5	Biodegradable interpenetrating polymer network hydrogel membranes for controlled release of an anticancer drug	5-FU	Hydrogel membrane	[Subha, 2015]
6	Curcumin encapsulated pH sensitive gelatin based interpenetrating polymeric network nanogels for anticancer drug delivery	Curcumin	Nanogel	[Rao et al., 2015]
7	Amphiphilic interpenetrating polymer networks for the oral delivery of chemotherapeutics	Doxorubicin	Microbeads	[Schoener et al., 2013]

Table 2.4 Drugs delivered through IPN

S. No.	Drug	Therapeutic category	Formulation	Reference
1	Acyclovir	Anti-viral	Micro-particle	[Jana et al., 2016]
2	Ketoprofen	NSAIDs	Microbeads	[Boppana et al., 2015]
3	5-FU	Anticancer	Hydrogel	[Mallikarjuna Reddy et al., 2008]
4	5-FU	Anticancer	Hydrogel membrane	[Mallikarjuna et al., 2015]
5	Insulin	Antidiabetic	Superporous hydrogel	[Yin et al., 2008]
6	Curcumin	Anticancer	Nanogel	[Rao et al., 2015]
7	Acyclovir	Antiviral	Microsphere	[Rokhade et al., 2007a]
8	Cefadroxil	Cephalosporin	Microgel	[Rao et al., 2006]
9	Ciprofloxacin	β- lactam antibiotic	Microsphere	[Kajjari et al., 2011]
10	Diclofenac sodium	Anti inflammatory	Microgel	[Kurkuri and Aminabhavi, 2004]

2.7.2.1Classification of IPN

2.7.2.1.1On basis of chemical bonding

- **Covalent Semi IPN:** When two individual polymers are cross-linked to form a single polymeric network.
- **Non-covalent Semi IPN:**It is formed between two individual polymers, involving only one polymer is cross-linked.
- **Non-covalent Full IPN:** When two individual polymers are cross-linked separately.

2.7.2.1.2 On basis of synthesis

- **Sequential IPN:** Here the first cross-linked polymer is swelled in the presence of monomer of the second polymer which is either polymerized or cross-linked later [Sperling, 2004].
- **Simultaneous IPN**: It involves the formation by polymerizing the two different polymers with two different monomers and two different cross-linker in one step [Lohani et al., 2014].
- **Latex IPN**: Also known as an interpenetrating elastomeric network. In this type of IPN, both polymers are mixed to form single latex by polymerization of the second monomer in combination with cross-linker and activatorin the original seed latex of the first cross-linked monomer [Zhang et al., 2014].
- **Thermoplastic IPN:** This type of IPNs involves the use of physical cross-linkers instead of chemical cross-linkers. The physical cross-linkers thatare used for thesynthesis are of ionic and crystalline nature thus these materials flow at high temperature same as thermoplastic elastomers [Siegfried et al., 1981].
- **Gradient IPN:** This type of IPN is formed as a result of swelling of first monomer network present in the network of the second monomer. During preparation,a stage occurs where swelling is terminated and polymerization is done to produce the IPN [Karabanova et al., 2005].

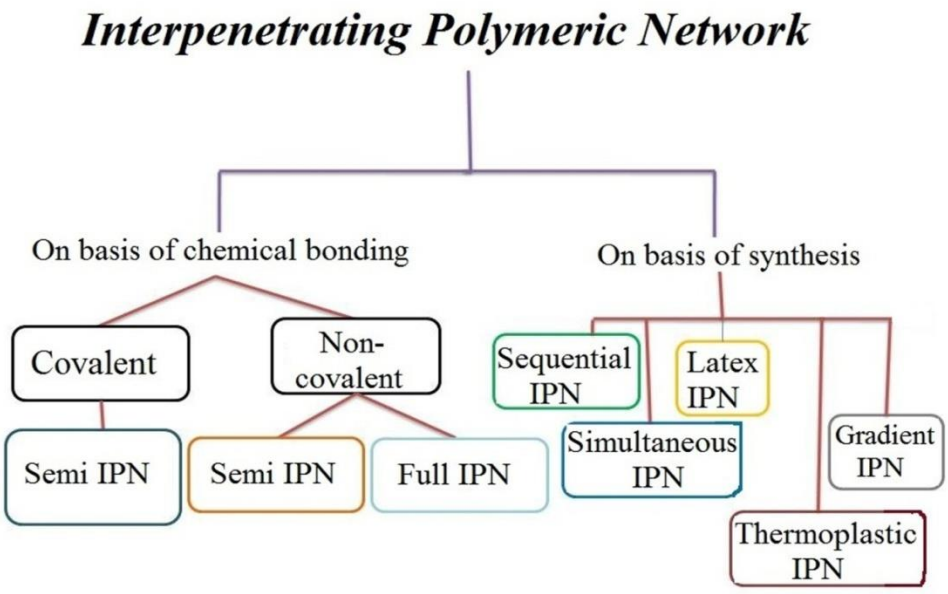

Figure 2.3 Classification of Interpenetrating Polymeric Network

2.7.2.2 Method of preparation of IPN[Lohani et al., 2014]

Casting evaporation method: This method is widely used to prepare cross-link polymeric network especially sequential IPN. It involves heating of each polymeric solution separately thenthe addition of polymeric solution I in the cross-linker solution followed by the addition of polymeric solution II leaving the entire solution to mix well. Finally, the solution is casted and dried.

Emulsification cross-linking method: The method is based on the principle of phase separation. It involves preparation of IPN in two ways i.e. w/o and w/w emulsion method. In w/o emulsification method water-soluble materials are dissolved in the water phase which is further poured drop-wise to the non- aqueous phase[Banerjee et al., 2010]. The second method w/w emulsification method the aqueous solution of the hydrophilic polymer is emulsified as a dispersed phase in an aqueous solution of another aqueous polymeric solution that acts as the continuous phase.

Ionotropic gelation method: This method is mainly used to prepare polymeric hydrogel beads of water-soluble drugs.Generally, the polymers that are used are polysaccharides. It is based on the principle where polyelectrolyte solution containing sodium alginate, xanthan gum, chitosan, pectin etc. get cross-linked in presence of counter ions such as calcium chloride, zinc chloride, barium chloride, aluminium chloride etc. and forms spherical hydrogel microbeads[Patil et al., 2012].

Miniemulsion technique: This technique involves the preparation of IPN beads by applying high shear stress in the continuous phase that crates small stable droplets [Landfester, 2006].

Inverse Miniemulsion technique: It involves polymerization of aqueous monomers. The monomeric solution is miniemulsified in the continuous oil phase. The process of polymerization starts either from the continuous phase or from the droplet [Koul et al., 2011].Delivery of the active pharmaceuticals through a suitable carrier system has always been a challenge in the field of drug delivery. Numerous approaches have been studied for the extended release of the drugs such as micro-particles, nanoparticles, hydrogels, tablet, capsules and films etc. examples of few drug delivery systems and drugs delivered through IPN based carrier are illustrated in Table 2.3 and 2.4 respectively.

2.7.3Buoyant and mucoadhesive interpenetrating polymeric network system

Recently, floating interpenetrating polymeric network has gained increased importance as novel dosage formulation [Balamuralidhara et al., 2013]. They act as a multiparticulategastro retentive drug delivery system (GRDDS) and extend the gastric residence time of drug in the stomach by combining the principle of swelling,mucoadhesive and floating [Bera et al., 2015b]. The multiple unit grdds evenly distributes and retained in the stomach region, thus, releases the drug slowly in a controlled manner with plausibility in the reduction of dose dumping [Guru et al., 2013]. The property of swelling and mucoadhesion is generally

imparted by the hydrophilic polymers[Vasir et al., 2003]such as alginate [Singh et al., 2010], tamarind gum [Mali, 2016], locust bean gum [Jagdale et al., 2013], xanthan gum [Patil and Talele, 2015], guar gum [Dave et al., 2004]etc. and the floating or buoyancy by effervescent agents such as calcium carbonate, sodium bicarbonate etc. [Sungthongjeen et al., 2008]. Once upon reaching the stomach region these polymers when in contact with gastric fluid swells anduse of effervescent agent or gas generating agents initially enable the system to float rather than adhere to the wall of the membrane. However with the passage of time and during stomach empting the buoyant system will no more in floating condition thus at that time property of mucoadhesion will help the formulation to adhere with biological membrane due to their mechanical and mucoadhesive property imparted by polymers[Siepmann and Peppas, 2001, Thirawong et al., 2007]. Behavior of buoyant and mucoadhesive IPN is presented in Figure 2.4.

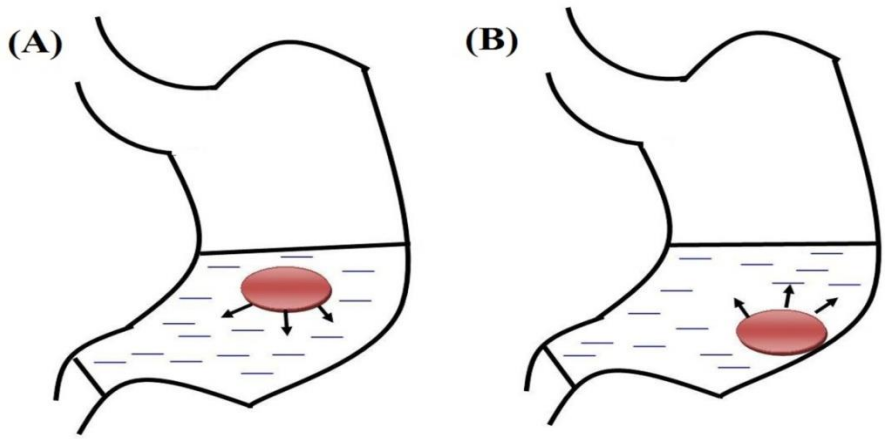

Figure 2.4Buoyant IPN initially in stomach region (A); with the passage of time drug release through property of mucoadhesion (B)

2.7.3.1Mechanism of the floating

For a system to float the density of the gastric content must be below 1.004 g/cm^3[Lopes et al., 2016]. This propertymakes the system to remain float for an extended period and release the drug with the desired rate during gastric residence time [Jiménez-Martínez et al., 2008]. The buoyancy of the system in the stomach region is maintained by two mechanisms which are differentiated by the gas production, i.e. non- effervescent and effervescent system.

Non-effervescent system: This system makes the system buoyant in two ways. In first approach combination of high swelling polymers for examples polysaccharides and matrix forming polymers are used. On reaching the gastric fluid system swells and becomes viscous and entrapped air around the core of the system that controls the drug release. The entrapped air imparts floating capacity to the system [Singh and Kim, 2000].Another type of non-effervescent system is called a Hydrodynamically Balanced System (HBS). They are prepared by using gel-forminga hydrophilic polymer in whichthe drug is incorporated. Finally, the entire mixture is filled in a gelatin capsule. The gelatin capsule when comes in contact with gastric fluid it degrades and the polymers swell and forms a surrounded layer that exhibits the controlled drug release by diffusion and erosion [Sheth and Tossounian, 1984].

Effervescent system: This system makes the system to float either by the use of gas generating salts such as carbonates and bicarbonates or using volatile liquid for instance ether or cyclopentane. When carbonates or bicarbonates mix with gastric fluid CO_2 is generated a resulting increase in the hydration volume of the dosage form and superficial area of drug diffusion [Streubel et al., 2006]. In case of volatile liquid system,volatile liquids are introduced in the inflatable chamber of the hydrophilic polymers that volatilize at the body temperature and allows the inflation of the chamber in the stomach thus, the system remains

buoyant [Talukder and Fassihi, 2004]. A diagrammatic illustration of the mechanism of the effervescentnon effervescent system is shown in Figure 2.5.

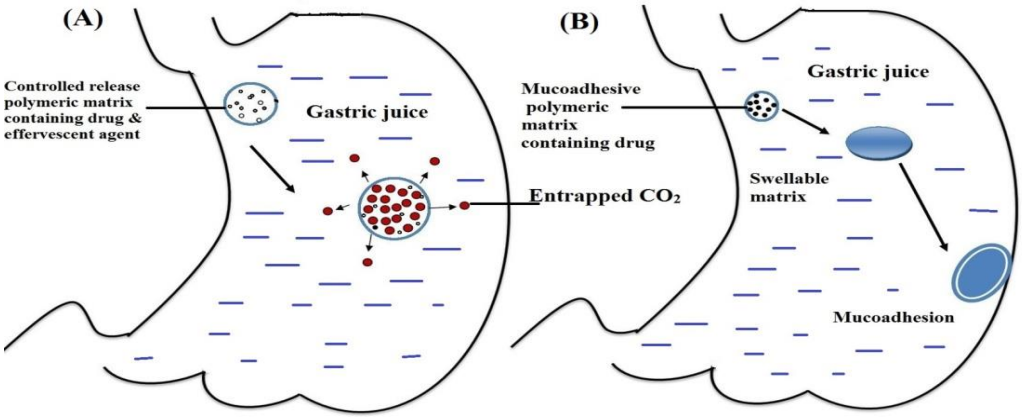

Figure 2.5 Mechanism of buoyancy shown by (A) Effervescent system and (B) Non-effervescent system

Drugs usually with shorthalf-life, high toxicity, quick metabolism, narrow absorption window, low solubility at alkaline pH, plasma fluctuations are preferred to be deliveredthrough this system. Examples of the drugs that are delivered through gastroretentive IPNs are listed below.

Table 2.5 Drugs delivered through Buoyant and mucoadhesive IPN drug delivery system

S.No	Title	Drug	Therapeutics	Reference
1	Alginate gel coated oil entrapped tamarind gum magnesium state buoyant beads of risperidone	Risperidone	Bipolar disorder and Schizophrenia	[Bera et al., 2015a]
2	HPMC based gastrorete-ntive dual working matrices coated with Ca^{2+} ion cross-linked alginate fenugreek gum gel membrane.	Quetiapinef umarate	Bipolar disorder Schizophrenia	[Bera et al., 2016]

3	Core-shell alginate ghatti gum modified montmorrilonitecomposite matrices for stomach specific flurbiprofen delivery.	Flurbiprofen	Inflammation	[Bera et al., 2017]
4	Oil entrapped sterculia gum buoyant systems of aceclofenac: Development and in vitro evaluation	Aceclofenac	Inflammation	[Guru et al., 2013]
5	Mucoadhesive floating zinc pectinatesterculia gum interpenetrating polymer network beads encapsulating ziprasidoneHCl	Ziprasidone HCl	Bipolar disorder, Schizophrenia	[Bera et al., 2015b]
6	QbD enabled development of novel stimuli-responsivegastro-retentive systems of acyclovir for improved patient compliance and biopharmaceutical performance	Acyclovir	Anti-viral	[Singh et al., 2016]
7	Development of sustained release gastro-retentive tablet formulation of nicardipine hydrochloride using quality by design (QbD) approach	Nicardipine HCl	High blood pressure and angina	[Chudiwal et al., 2018]
8	Floating microspheres of carvedilol as gastro-retentive drug delivery system: 3^2 full factorial design and in vitro evaluation	Carvedilol	Congestive heart failure	[Nila et al., 2014]
9	In vitro and in vivo evaluation of gastroretentive floating drug delivery system of ofloxacin	Ofloxacin	Bacterial infection	[Shakya et al., 2013]
10	Development and evaluation of new sustained release floating microsphere	DiltiazemHCl	Angina pectoris and hypertension	[Ma et al., 2008]
11	Interpenetrating polymeric network hydrogel for stomach specific drug delivery of clarithromycin: preparation and evaluation	Clarithromycin	Throat and skin infection	[Gupta et al., 2010]

2.8 Drug-specific review of the literature

2.8.1 Capecitabine

Capecitabine is an oral chemotherapeutic fluoropyrimidine prodrug of 5-Fluorouracil (5-FU) approved by USFDA on June 15th 2005 [Sharma and Saltz, 2000]. It is used in various types of cancer such as colon, bladder, prostate, breast and cervical. If one observes from the patient point of view, the oral administration of Capecitabine can be considered the most convenient way to be taken at home by the patient in comparison to the infusional therapy that requires proper care and assistance [Sternberg et al., 2004]. The detailed description of the drug capecitabine including its physical, chemical, toxicology, pharmacology, mechanism of action and pharmacokinetic profile are mentioned below:

Chemical structure:

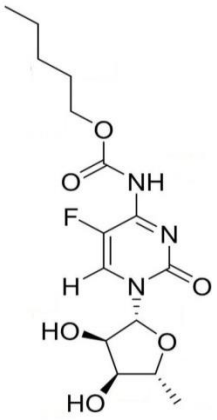

Figure 2.6 Chemical structure of Capecitabine

Molecular weight: 359.35 g/mol

Chemical formula: $C_{15}H_{22}FN_3O_6$

Colour: white to off white crystalline powder.

Half-life: 0.5-1 h

Log P: 0.4

pK_a: 8.8

Melting point: 110-121°C

Solubility: soluble in water, ethanol, dimethylsulfoxide, dimethylformamide

Pharmacokinetic

Absorption: CAP shows complete absorption from the GI tract

Protein binding: binds mainly to albumin approximately 54%

Metabolism: primarily three metabolites are formed 5'-DFCR; 5'-DFUR and finally to 5-FU. The site of metabolism isthe liver and tumour respectively.

Elimination: eliminated through urine

Trade name: Xeloda

Dosage form: Tablet (150 and 500 mg)

Clinical use: 1250 mg/m^2 twice daily for two weeks followed by one week of the rest period to complete a full 21-day cycle.

Side effects: Diarrhoea, dermatitis, stomatitis, hand and foot syndrome, myelosuppression,bone marrow depression, cardiotoxicity, nausea and vomiting.

Administration: must be taken with food (usually after half an hour)

Mechanism of action: It converts into 5-FU enzymatically following sequential three-way step. Capecitabine when administered convert into 5'-fluorodeoxycytidine (5'-DFCR) in liver by the enzyme carboxylesterase; than 5'-DFCR then convert to Doxifluridine or 5'-

fluorouridine (5'DFUR) by cytidinedeaminase present in liver and tumor tissue; and finally 5'DFUR changes into 5-FU by thymidine phosphorylase principally up regulated in tumors.

Table 2.6 Examples of Capecitabine loaded multiparticulate carrier based drug delivery

S. No.	Title	Carrier	Reference
1	Development and in vitro characterization of capecitabine loaded alginate pectinate chitosan beads for colon targeting	Alginate, chitosan, pectin	[Patel et al., 2016]
2	Design, optimization and evaluation of capecitabine loaded chitosan microsphere for colon targeting	Chitosan	[Jena, 2017].
3	Novel interpenetrating network chitosan-poly (ethylene oxide –g-acrylamide) hydrogel microspheres for the controlled release of capecitabine	Chitosan and poly (ethylene oxide –g-acrylamide)	[Agnihotri and Aminabhavi, 2006]
4	Formulation and characterization of colon targeted pH dependent microspheres of capecitabine for colon cancer	Eudragit S-100 and L-100	[Agarwal et al., 2014]
5	Formulation and in vitro evaluation of microspheres embedded with capecitabine	Guar gum and xanthum gum	[Shivani et al.]
6	Preparation and development of capecitabine microspheres for colorectal cancer	Hydroxy propyl methyl cellulose and ethyl cellulose	[Reddy and Reddy, 2017]
7	Formulation and development of colon specific multiparticulate system of capecitabine	Chitosan	[Dilip, 2016]

2.9 Excipient specific review of the literature

2.9.1 Locust bean gum

Locust bean gum, botanically known as *Ceratoniasiliqua*L. and commonly known as algarroba, carob gum, and St. John's bread is an evergreen tree of Mediterranean region belongs to the family Leguminosae [Yousif and Alghzawi, 2000]. It is a high molecular weight polysaccharide and chemically composed of *β*-(1-4)-D-mannopyranosyl as a backbone and *α*-(1-6)-D-galactopyranosyl simple units are linked as a side chain [Azero et al., 1997]. It is a non-ionic hydrocolloid witha molecular weight ranging between 300,000 and 1200,000 Dalton. It is slightly soluble in water hence, requires heating to dissolve. Being neutral in nature locust bean gum can be used over a wide range of pH [Silveira and Bresolin, 2011]. Locust bean gum possesses M/G ratio 4:1 which is reported as second highest gum mannose content among all the commercially available galactomannans[Dea and Morrison, 1975]. Due to non-ionic nature, locust bean gum is unaffected by the ionic strength of the liquid media and holds good water holding capacity that makes it suitable to be used widely in the pharmaceutical and cosmetic industry [Rizzo et al., 2004, Wu et al., 2012]. Recently in the pharmaceutical industry, it is popularly used as thickener and gel strengthening agent due to its ability to form a viscous solution at relatively low concentration (≤0.02%) [Richardson and Norton, 1998]. A general description of locust bean gum is mentioned below

Chemical structure:

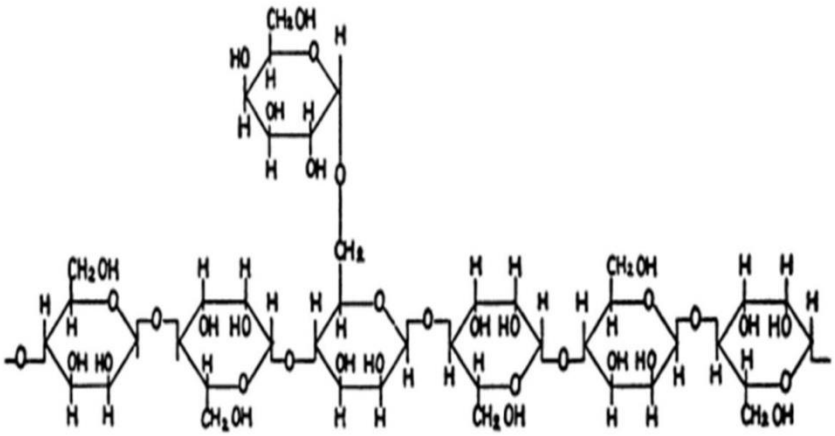

Figure 2.7 Chemical structure of locust bean gum [Deuel and NEUKOM, 1954]

Nature: Non-ionic

Molecular weight: 300 K- 1200 K Dalton

Solubility: Practically insoluble in organic solvents, aggregates in cold water and soluble in hot water.

Viscosity: capacity to form a viscous solution at low concentration that is unaffected by salt, pH or temperature.

Storage condition: stable in dry powder state at room temperature.

Table 2.7 Locust bean gum based IPN drug delivery system

S.No.	Drug	Title	Reference
1	Buflomedilhydrochloride	LBG and PVA based IPN microspheres exhibited controlled release of highly water-soluble drug buflomedil. The polymers used showed no incompatibility while formulating the IPN device.	[Kaity et al., 2013]
2.	Aceclofenac	Chitosan – Locust bean gum interpenetrating polymeric network nanocomposites for delivery of aceclofenac.	[Jana and Sen, 2017]
3.	Famotidine	Novel interpenetrating polymer network mucoadhesive microspheres of locust bean gum and poly(vinyl alcohol) for the delivery of Famotidine	[Jain and Banik, 2013]
4.	Aceclofenac	Formulation and optimization of natural polysaccharide hydrogel microbeads of aceclofenac sodium for the oral controlled drug delivery	[Manjanna et al., 2013]
5.	Buflomedilhydrochloride	Carboxymethylation of Locust Bean Gum: Application in Interpenetrating Polymer Network Microspheres for Controlled Drug Delivery	[Kaity and Ghosh, 2013]
6	Ibuprofen	Development and characterization of pH-sensitive locust bean gum-alginate microspheres for controlled release of ibuprofen	[Bulut and Dilek, 2014]
7	Diclofenac sodium	Al^{3+} ion cross-linked interpenetrating polymeric network microbeads from tailored natural polysaccharides	[Bhattacharya et al., 2012]
8	Aceclofenac	Metal ion-induced alginate–locust bean gum IPN microspheres for sustained oral delivery of aceclofenac	[Jana et al., 2015]
9	Glipizide	Novel etherified locust bean gum-alginate hydrogels for controlled release of glipizide	[Dey et al., 2013]

2.9.2 Sodium alginate

Sodium alginate is a natural occurring polysaccharide obtained from brown algae. It is the most widely used polymer in control drug release application due to its excellent gel-forming

property [Kumar et al., 2017]. Structurally it is a linear polyanionic polymer containing mannose (M unit) i.e. 1,4-linked β-D- mannuronic acid and galactose (G unit) 1,4- linked α-L guluronic acid [Jiao et al., 2016]. The mechanism of gel formation in the polymer involves the exchange of sodium ion (Na^+) from G unit with counter divalent (Ca^{2+}) or trivalent (Al^{3+}) cation leading to the formation of three dimensional "egg box" dimer or an immobile network that dimerized to form gel [Fang et al., 2007]. A general description of the polymer is given below:

Chemical structure

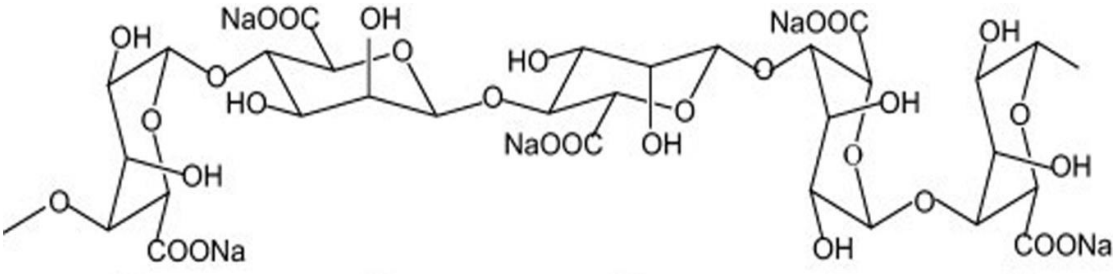

Figure 2.8 Chemical structure of sodium alginate [Yang et al., 2011].

Nature & type: Anionic, linear

Appearance: white to yellowish brown, grainy or powdered.

Molecular weight: 216.121 g/mol

pK_a : 3.4

Solubility: soluble in water, forming a viscous solution. Practically insoluble in ether and ethanol.

Table 2.8Sodium alginate based IPN drug delivery system

S.No.	Drug	Title	Reference
1	Oxcarbazepine	Development and optimization of modified release IPNmacro-molecules of oxcarbazepine using natural polymers	[Prajapati et al., 2015]
2.	Glipizide	Impact of gelation period on modified locust bean-alginate interpenetrating beads for oral glipizide delivery	[Dey et al., 2015]
3.	Tramadol HCl	Alginate-polyvinyl alcohol based interpenetrating polymer networkfor prolonged drug therapy, Optimization and in-vitro characterization	[Anwar et al., 2017]
4.	Acetaminophen	Synthesis, characterization, swelling and drug release behaviour of semi-interpenetrating network hydrogels of sodium alginate and polyacrylamide.	[Samanta and Ray, 2014]
5.	Acyclovir	Interpenetrating hydrogels of O-carboxymethyl Tamarind gum andalginate for monitoring delivery of acyclovir	[Jana et al., 2016]
6.	Cefadroxil	In-vitro release kinetics of cefadroxil-loaded sodium alginate interpenetrating network beads	[Kulkarni et al., 2001]
7.	Aceclofenac	Oil entrapped sterculia gum- alginate buoyant systems of aceclofenac: Development and in vitro evaluation.	[Guru et al., 2013]
8.	Diclofenac sodium	Development and optimization of interpenetrating network beads of Delonixregia gum and sodium alginate using response surface methodology	[Dias et al., 2015]
9.	Diltiazem	Novel interpenetrated	[Kulkarni et al., 2012]

	hydrochloride	polymer network microbeads of natural polysaccharides for modified release of water soluble drug: an in-vitro and in-vivo evaluation.	
10.	Propranolol HCl	Controlled Release of an Antihypertensive Drug through Interpenetrating Polymer Network Hydrogel Tablets of Tamarind Seed Polysaccharide and Sodium Alginate	[Kulkarni et al., 2013]
11	Propranolol	Interpenetrating Polymer Network Matrices of Sodium Alginate and Carrageenan for Controlled Drug Delivery Application	[Kulkarni et al., 2011]