Review of Literature

Amit B et al., (2012) has prepared and evaluate mucoadhesive capsule enclosing microspheres of drugs clarithromycin and omeprazole to treat H. pylori infection. Drug entrapment efficiency, swelling and adhesion property and in-vitro drug release of microspheres were evaluated. The result of the study showed that the capsule containing microspheres of drugs clarithromycin and omeprazole can be targeted to the stomach; hence drugs residence time at absorption site was increased. So drug remains at absorption site for prolonged period of time which is most beneficial to treat H. Pylori infection.

Arya RKK et al., (2010) has prepared and characterized mucoadhesive microspheres of famotidine for prolongation of gastric residence time. The w/o emulsification solvent evaporation method was used for the preparation of microspheres. Sodium Carboxy Methyl Cellulose (Sodium CMC) was used as a mucoadhesive polymers, and sodium alginate as a release controlling polymer. Good muchoadhesion and good entrapment efficiency was achieved by using hydrophilic polymer, Sodium CMC. The prepared microspheres exhibited prolonged drug release for 8h. As the concentration of sodium alginate increased, the mean particle size also increased but rate of the drug release decreased. The mucoadhesion increased, as the sodium CMC polymer concentration increases.

Patel JK et al., (2009) formulated and evaluated in-vitro and in-vivo performances mucoadhesive microspheres of amoxicillin for the potential use in the treatment of Helicobacter pylori. Carbopol-934P was used as mucoadhesive polymer and ethyl cellulose as carrier polymer for the preparation of mucoadhesive microspheres. Screening of the emulsifying agent, time for stirring, drug-to-polymers ratio and speed of rotation was carried out. An in-vitro mucoadhesive test showed that microspheres adhered more strongly to the gastric mucous layer for an extended period of time. A sustained drug release was obtained for more than 12 h. In- vitro release test showed that amoxicillin released slightly faster in acidic medium than in alkaline medium. In-vivo H. pylori clearance tests were also carried out by administering amoxicillin powder and mucoadhesive microspheres to H. pylori infectious wistar rats. The results showed that
amoxicillin mucoadhesive microspheres had a better clearance effect than amoxicillin powder.

**Thong-Ngam D and Chatsuwan T, (2007)** assess the *in-vitro* potential of selected herbal plants, namely *Aloe vera*, curcumin, garlic, and plau-noi against *H. pylori*. A standard strain (NCTC 11637) and 9 clinical isolates of *H. pylori* were used to assess antibacterial activity of four herbal substances, employing an agar dilution and disk diffusion method. The disk diffusion was tested using varying amounts of herbal substance at 20, 50, 100, 200 and 400µg. The minimum inhibitory concentrations (MICs) of *Aloe vera*, curcumin, garlic, and plau-noi were >512, 64, >512, >512µg /mL, respectively. They conclude that curcumin exhibited potential of *in-vitro* antibacterial activity against *H. pylori*, which suggests that it may be useful for the treatment of *H. pylori* infection. However, *Aloe vera*, garlic, and plau-noi did not show any antibacterial activity against *H. pylori*.

**Ronita D et al., (2009)** examined the *in-vitro* and *in-vivo* antibacterial potential of curcumin. The *in-vitro* antibacterial activity of curcumin was performed against 65 clinical isolates of Indian *H. pylori* strains. *In-vivo*, the antimicrobial effect of curcumin in *H. pylori*-infected C57BL/6 mice was examined. Apart from anti-*H. pylori* activity, its efficacy in reducing the gastric damage due to infection were also examined histologically. The MIC of curcumin against *H. pylori* growth was found to be in ranges from 5µg/ml to 50 µg/ml. This study provides novel insights into the therapeutic effect of curcumin against *H. pylori* infection, suggesting its utility as an alternative therapy against *H. pylori* infection.

**Pant P et al., (2011)** has formulated mucoadhesive microspheres of clarithromycin as a gastroretentive drug delivery system to target the *H. pylori* in ulcer patients. The microspheres were prepared using sodium alginate and hydroxypropyl methylcellulose (HPMC) as polymer by ionic gelation technique. HPMC used as a mucoadhesive polymer and sodium alginate used to control the release rate. The study revealed that both the polymers (HPMC and sodium alginate) used in the formulation of microspheres have a significant effect on the mucoadhesion, drug entrapment efficiency and *in-vitro* drug release. After evaluating all the formulations, the formulation which has
the higher percentage of HPMC showed good entrapment efficiency (63%), mucoadhesion about 79.6% as well as good release profile in 8 hrs.

Liu Z et al., (2005) has formulated amoxicillin mucoadhesive microspheres using ethyl cellulose as matrix and carbopol 934P as mucoadhesive polymer for the potential use of treating gastric and duodenal ulcers, which were associated with H. pylori. In vitro and in vivo mucoadhesive tests showed that Amo-ad-ms adhered more strongly to gastric mucous layer than non adhesive amoxicillin microspheres and retained in gastrointestinal tract for an extended period of time. In vivo activity against H. pylori was also carried out by administering amoxicillin powder and mucoadhesive microspheres, to H. pylori infectious BALB/c mice under fed conditions at single or multiple dose(s). They conclude that the prolonged gastrointestinal residence time resulting from the mucoadhesive microspheres of amoxicillin might make contribution to H. pylori clearance.

Rajinikanth PS et al., (2008) developed a stomach-specific drug delivery system for controlled release of clarithromycin for eradication of H. pylori. Bio-adhesive microspheres of clarithromycin were prepared by emulsification-solvent evaporation method using ethyl cellulose as matrix polymer and carbopol 934P as mucoadhesive polymer. The in-vivo H. pylori clearance efficiency of clarithromycin microspheres in comparison to clarithromycin suspension was examined. Mucoadhesive microspheres showed a significant anti-H. pylori effect in the in vivo gerbil model. The required amount of clarithromycin for eradication of H. pylori was significantly less in mucoadhesive microspheres than from corresponding clarithromycin suspension.

Kundu P et al., (2011) have shown that curcumin is capable of eradicating H. pylori infection in mice. They examined the mechanism by which curcumin protects H. pylori infection in cultured cells and mice. They investigated the role of curcumin on inflammatory matrix metalloproteinases (MMPs) as well as proinflammatory molecules. Since, MMP-3 and MMP-9 are inflammatory molecules associated to the pathogenesis of H. pylori infection. Curcumin dose dependently suppressed MMP-3 and -9 expression in H. pylori infected human gastric epithelial (AGS) cells. Consistently, H. pylori eradication by curcumin-therapy involved significant downregulation of MMP-3 and -9.
activities and expression in both cytotoxic associated gene (cag)\textsuperscript{+ve} and cag\textsuperscript{−ve} H. pylori infected mouse gastric tissues. Both curcumin and triple therapy were associated with MMP-3 and -9 downregulation during H. pylori eradication, but unlike triple therapy, curcumin enhanced peroxisome proliferator activated receptor-\(\gamma\) and inhibitor of kappa B-\(\alpha\). The result indicated that curcumin-mediated healing of H. pylori infection involves regulation of MMP-3 and -9 activities.

Hardenia SS et al., (2011) have prepared mucoadhesive microspheres containing ciprofloxacin. The surface morphological characteristics of ethyl cellulose microspheres were investigated using scanning electron microscopy. The Mucoadhesive property of the ethylcellulose microspheres was evaluated by in-vitro wash off test. The microspheres exhibited 75\% mucoadhesion and showed good drug entrapment efficiency. It was investigated that on increasing the concentration of polymer the particle size increases and it was concluded that ethyl cellulose microspheres showed good mucoadhesive properties and good surface morphology.

Yadav VK et al., (2011) designed the gastro retentive dosage forms of repaglinide as controlled-release drug delivery systems to increase its residence time in the stomach. The dosage form was achieved through the preparation of mucoadhesive microspheres by the emulsion solvent evaporation technique consisting of chitosan as a mucoadhesive polymer and Eudragit RS-100 as rate controlling polymer. The drug release was also found to be slow and extended for 24 h. In-vivo testing of the mucoadhesive microspheres in diabetic albino rats demonstrated significant antidiabetic effect of repaglinide. The hypoglycemic effect obtained by mucoadhesive microspheres was for more than 16 h whereas repaglinide produced an antidiabetic effect for only 10 h suggesting that mucoadhesive microspheres are a valuable system for the long term delivery of repaglinide.

Patel JK et al., (2005) formulated mucoadhesive microspheres of glipizide containing chitosan by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Results of preliminary trials indicate that volume of cross-linking agent, time for cross-linking, polymer-to-drug ratio, and speed of rotation affected characteristics of microspheres. A \(3^2\) full factorial design was employed to study
the effect of independent variables, polymer-to-drug ratio (X1), and stirring speed (X2) on dependent variables percentage mucoadhesion, drug entrapment efficiency, and swelling index. The best batch exhibited a high drug entrapment efficiency of 75% and percentage mucoadhesion after 1 h was 78%. The drug release was also sustained for more than 12 h. The polymer- to-drug ratio had a more significant effect on the dependent variables. In vivo testing of the mucoadhesive microspheres to albino wistar rats demonstrated significant hypoglycemic effect of glipizide.

Deshmukh T et al., (2012) have prepared sustained release mucoadhesive microspheres of ziprasidone HCl using sodium alginate as a shell forming polymer and HPMC-E5 as a mucoadhesive polymer for the potential use of treating schizophrenia. The microspheres exhibited good mucoadhesive properties and slow drug release depending on the composition of sodium alginate coat. The drug was found to be compatible with the polymer, however the crystallinity of drug was found to be reduced in prepared microspheres, which were confirmed by DSC and PXRD studies. The time to release 90% of drug in the optimized batch M1 was 10 h.

Dhaliwal S et al., (2008) investigated the use of mucoadhesive microspheres for gastroretentive delivery of acyclovir. Chitosan, thiolated chitosan, carbopol 71G and methocel K15M were used as mucoadhesive polymers. Gelatin capsules containing drug powder showed complete dissolution (90.5±3.6%) in 1 h. The release of drug from the mucoadhesive microspheres was prolonged to 12 h (78.8±3.9). The poor bioavailability of acyclovir is attributed to short retention of its dosage form at the absorption sites (in upper gastrointestinal tract to duodenum and jejunum). The results showed better retention of thiolated chitosan microspheres (8.0±0.8 h) in duodenal and jejunum regions of intestine. Pharmacokinetic study revealed that administration of mucoadhesive microspheres could maintain measurable plasma concentration of acyclovir through 24 h. Thiolated chitosan microsphere showed superiority over the other formulations as observed with nearly 4.0 fold higher in comparison to drug solution.

Gaba P et al., (2011) formulated galactomannan coated mucoadhesive microspheres of glipizide and systematically evaluated its in-vitro characteristics and in vivo performance for sustained glucose lowering effect and improvement in diabetic
condition as compared to immediate release of glipizide. Since, the site of absorption of glipizide is from stomach thus dosage forms that are retained in stomach by mucoadhesion; would increase absorption, improve drug efficiency and decrease dose requirements. From this study they concluded that release of glipizide drug was slow and extended over a longer period of time depending upon the composition of polymers and drug. In vivo evaluation carried out using Male Sprague–Dawley rats and diabetic swiss albino mice showed sustained glucose lowering effect of glipizide microspheres and improvement in various diabetic parameters as compared to immediate release formulation of glipizide.

Khan R et al. (2010) have prepared mucoadhesive microspheres of flurbiprofen by w/o solvent evaporation. Sodium carboxy methyl cellulose, hydroxy propyl methyl cellulose, and carbopol 934 were used as mucoadhesive polymers. The particle size of the prepared microspheres was in the range of 29.20 to 38.45μm. Flurbiprofen release from these microspheres was slow and extended over longer period of time and depended on the type of polymer used. In-vivo studies conducted on male albino rats. In comparison to marketed tablets of flurbiprofen, the result indicated that the microspheres not only decreased the inflammation to larger extent, but also sustained this magnitude for longer period of time.

Dhawan S et al. (2004) have evaluated the mucoadhesive properties of chitosan microspheres prepared by different methods by studying the interaction between mucin and microspheres in aqueous solution. The interaction was determined by the measurement of mucin adsorbed on the microspheres. Method of preparation of microspheres and the amount of mucin play an important role in the intensity of the interaction. The amount of mucus adsorption was proportional to the absolute values of the positive zeta potential of microspheres. The adsorption of a suspension of chitosan microspheres in the rat small intestine indicated that chitosan microspheres prepared by tripolyphosphate cross-linking and emulsification ionotropic gelation can be used as an excellent mucoadhesive delivery system. Good stability was found to be in microspheres prepared by glutaraldehyde and thermal cross-linking as compared with microspheres prepared by tripolyphosphate and emulsification ionotropic gelation.
Belgamwar V et al., (2009) prepared mucoadhesive microspheres of metoprolol tararate for oral drug delivery using ionic gelation technique. Different grades of HPMC (K4M, K15M, K100M, E50LV), Carbopol (971P, 974P) and polycarbophil were used for the preparation of microspheres. The prepared microspheres were discrete, bulky, free flowing in nature. The drug entrapment efficiency was found to be in the range of 50-60%. Particle size of the microspheres was found to be between 400-650µm. In-vitro drug release from the multiparticulate system was in a controlled manner and extended until 12 h. The stability studies indicated no significant change in the physicochemical properties after performing on the optimized batches at 40°C/ 75% RH for 90 days.

Sambathkumar R. et al., (2011) discussed about H. pylori infection and related chronic active gastritis and duodenal ulcer (DU). Triple therapy (proton pump inhibitor [PPI], amoxicillin and clarithromycin), is most successful and universal treatment. These three drugs prescribed twice a day for 1 week. However, some clinical trials and reports indicate that combination therapies cannot bring out complete eradication of H. pylori. Probably short residence time of anti-H. pylori agents in the stomach is one of the main reason for incomplete eradication. Due to short residence time the effective antimicrobial concentrations cannot be achieved in the gastric mucous layer or epithelial cell surfaces where H. pylori exists. To overcome this problem or to improve the efficacy in eradicating the infection is to deliver the antibiotic locally in the stomach. Considering above issue, they prepared mucoadhesive microspheres of clarithromycin for the treatment of H. pylori infection. The microspheres have prepared by emulsification internal gelation technique, using sodium alginate alone and in combination with HPMC K4M and Carbopol 974 P. The maximum incorporation efficiency was found to be 93%. Microspheres were spherical in shape examined by the scanning electron microscope. The in-vitro bioadhesion study indicated the good mucoadhesive properties of microspheres. Thus, gastroretentive drug delivery approach show great promise in the treatment of H. Pylori infection.

Rasala TM et al., (2010) discussed the formulation of mucoadhesive multiparticulates of Diltiazem HCl prepared by orifice-ionic and emulsification-ionic gelation technique and the results of both techniques were compared. Mucoadhesive
polymers HPMC K15 and carbopol 934 were used in combination with sodium alginate which provides gastric retention for prolonged time. The entrapment efficiency of drug was improved (46% - 61%) in emulsification-ionic gelation technique, as compared to orifice-ionic gelation technique (<15%). Thus it was concluded that emulsification-ionic gelation technique is superior to orifice-ionic gelation technique to entrap water soluble drug diltiazem HCl.

Muzaffar F et al., (2010) formulated mucoadhesive microspheres of amoxicillin trihydrates by using Eudragit RS 100 as matrix polymer. A $2^3$ full factorial design was performed to study the effect of formulation variables (concentration of polymer) on the release properties by applying optimization techniques. They observed that the polymer concentration is a major factor affecting the release and mucoadhesion strength of the prepared microspheres.

Shanthi CN et al., (2010) discussed about uses of particulate drug delivery systems covers all areas of medicine such as cardiology, endocrinology, gynecology, immunology, pain management, oncology and molecular biology. Microsphere is already having an impact on products as diverse as novel foods, medical devices, chemical coatings, personal health testing kits, sensors for security systems, water purification units for manned space craft, and high throughput screening techniques. Most of the advanced drug delivery systems utilize microspheres or microcapsules for the encapsulation of drugs and proteins.

Surini S et al., (2009): studied the application of pregelatinized cassava starch succinate (PCSS), in combinations with carbopol 974P and hydroxyl propyl methyl cellulose (HPMC) for preparing mucoadhesive microspheres of propanolol by the spray-drying technique. On gastric mucosa, the microspheres of PCSS, HPMC and PCSS-HPMC were more mucoadhesive than the microspheres of Carbopol 974P and PCSS-Carbopol 974P. On the other hand, all kinds of the microspheres show good mucoadhesive properties on intestinal mucosa. During 8 h in-vitro release study, the release of drug from the microspheres of PCSS-HPMC and PCSS-Carbopol 974P in pH 7.2 was slower than that in pH 1.2. The obtained result revealed that PCSS microspheres have good mucoadhesive property on both of gastric and intestinal mucosa. Moreover,
the addition of HPMC and Carbopol 974P to PCSS hydrophilic matrix significantly extended the drug release.

Rout PK et al., (2009): formulated the microspheres by solvent evaporation and w/o emulsion solvent evaporation methods followed by in-vitro characterization of microspheres to evaluate the effect of method of preparation on physical properties and drug release profile of microspheres. The yield was found to be maximum in case of solvent evaporation method. The mean geometric particle size of microspheres prepared by solvent evaporation method was found in the ranges of 40-50 µm and the microspheres prepared by w/o emulsion solvent evaporation method was found in a ranges of 126-150 µm, respectively. The microspheres formulation prepared by solvent evaporation method has shown greater encapsulation efficiency than w/o emulsion solvent evaporation method. In-vitro drug release rate for microspheres was found to be sustained over 8 hours. Hence, it can be concluded that the formulation prepared by solvent evaporation method, has potential to deliver Losartan potassium in a controlled manner in a regular fashion over extended period of time in comparison to all other formulations and can be adopted for a successful oral delivery of Losartan potassium for safe management of hypertension.
DRUG PROFILE

CURCUMIN

Synonym: Diferuloylmethane

Structural Formula:

![Structural formula of curcumin]

Molecular formula: \( C_{21}H_{20}O_{6} \).

Chemical name: [1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-Dione]

Molecular weight: 368.38 g/mol

Description:

Colour: orange–yellow crystalline powder

Odor: Practically odorless

Melting point: 179–183 °C

Solubility

Curcumin is readily soluble in dimethylsulfoxide (DMSO), ethanol or acetone, but it is sparingly soluble in water.

Biological activity of curcumin

Curcumin is the major constituent of the yellow pigments isolated from rhizome of Curcuma longa (turmeric). The root of this plant has been used in India as preservative, colorant, flavoring agent in meals (curry) and as a traditional medicine. It has also been used as an essential ingredient in medicine as a carminative, anthelmintic, laxative and as a cure for some liver ailments. Curcumin has been reported to have a wide spectrum of biological actions such as antibacterial, antiprotozoan, antiviral, hypolipemic, hypoglycemic, antiulcer, hypotensive, antidiabetic, anticoagulant, antioxidant, antitumour, anticarcinogenic (Chattopadhyay et al., 2004). Furthermore, antibacterial activity of curcumin has widely been reported. The mechanism of action of
phenolic compounds is involved in the interaction of the their hydroxyl groups with the cell membrane resulting in cell leakage, alteration of fatty acids and phospholipid profiles and a damage of the energy metabolism and synthesis of genetic materials (Donsi et al., 2011).

The presence of a diene ketone system provides lipophilicity to the compounds and thus probably better skin penetration. Structure–activity relationship studies suggest that a hydroxy group at the para-position is most critical for the expression of biological activity (Kim et al., 2001)

**Curcumin Safety and Toxicity**

Curcumin was given to Wistar rats, guinea pigs and monkeys of both sexes at a dose of 300mg/kg body wt. No pathological, behavioural abnormalities or lethality was observed. No adverse effects were observed on both growth and the level of erythrocytes, leucocytes, blood constitutes such as haemoglobin, total serum protein, alkaline phosphatase, etc. human clinical trials also indicate that curcumin has no toxicity when administered at doses of 1-8g/kg and 10g/day (Chattopadhyay et al., 2004).

**POLYMER PROFILE**

**ETHYL CELLULOSE**

*Formula:*

- **Empirical:** $C_{12}H_{23}O_6(C_{12}H_{22}O_5)_n \cdot C_{12}H_{23}O_5$
- **Structural**

*Synonyms:* Aquacoat ECD; Aqualon; Ethocel; Surelease.

*Chemical Name:* Cellulose ethyl ether
Functional Category: Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

Description

Ethylcellulose is a tasteless, free-flowing, and white to light tan-colored powder.

Moisture content

Ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Solubility

Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material and should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat.

Incompatibilities

Incompatible with paraffin wax and microcrystalline wax.

Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is generally regarded as a nontoxic, nonallergenic, and nonirritating material.

CARBOPOL 934P (Raymond, et.al. 2003)

Synonyms

Carboxy polymethylen; carboxyvinyl polymer; acrylic acid polymer, carbopol.

Chemical name

Carboxy polymethylene.
Description

A white, fluffy, acidic, hygroscopic powder with a slight characteristic odor.

Functional category

Bioadhesive, suspending and/or viscosity-increasing agent, release-modifying agent, tablet binder.

Typical properties

Carbopol is soluble in water, alcohol and glycerin. Agents that can neutralize carbopol include sodium hydroxide; potassium hydroxide; sodium bicarbonate; borax; amino acids; polar organic amines.

Specific gravity: 1.41
Density (bulk): 5 g/cm$^3$
Density (tapped): 1.4 g/cm$^3$

Viscosity (0.2%): 20.5-54.5 poise and (0.5%): 305-394 poise.

Acidity/ alkalinity: pH = 2.7-3.5 for a 0.5 % w/v aqueous dispersion, pH = 2.5-3.0 for a 1 % w/v aqueous dispersion.

Glass transition temperature: 100-105 °C.

Moisture content: normal water content is up to 2 % w/w. Carbomers are hygroscopic and typical equilibrium moisture content at 25 oC and 50 % relative humidity is 8-10 % w/w.

Applications in pharmaceutical formulation or technology

Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Formulations include creams, gels and ointments for use in ophthalmic, rectal and topical preparations. Carbomer having low residuals only of ethyl acetate, such as carbomer 971P or 974P, may be used in oral preparations, in suspensions, tablets or sustain release tablet formulation. Carbomer resins have also been investigated in the preparation of sustained-release matrix beads as enzyme inhibitors of intestinal proteases in peptide containing dosage forms, as a bioadhesive for a cervical patch and for intranasally administrated microspheres and magnetic granules for site specific drug delivery to the esophagus.
Stability and storage conditions

Dry powder forms of carbopol do not support the growth of molds and fungi; however, microorganisms grow well in unpreserved aqueous dispersions. Dispersions maintain their viscosity on storage during prolonged periods at room temperature or elevated temperature when stored away from light or with the addition of an antioxidant. Store in an airtight or well-closed container.

Incompatibilities

Carbopol is incompatible with phenol, cationic polymers, strong acids and high concentrations of electrolytes, and is discolored by resorcinol. Exposure to light causes oxidation, which is reflected in a decrease in viscosity.

Safety

Acute oral doses of carbopol-934P to rats, mice and guinea pigs produce LD$_{50}$ values of 4.3, 4.6 and 2.5 g/kg, respectively. In dogs, no fatalities were noted with doses as high as 8g/kg. No primary irritation or any evidence of sensitivity or allergic reaction in humans following topical application of dispersions containing carbopol-934P has been observed. Carbopol-934P in contact with the eye is very irritating.