7. SUMMARY AND CONCLUSION

7.1 Summery and Conclusion for preparation of Metformin – Glimepiride bilayer floating tablets

7.1.1 Summary for preparation of Metformin – Glimepiride bilayer floating tablets

Among the various gastro retentive systems, gastric floating drug delivery systems (GFDDS) offer numerous advantages over the gastric retentive systems. These systems have a density lower than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.

In humans, metformin is incompletely absorbed and predominantly excreted in urine with a half life of 4-6 hours. Metformin absorption after oral absorption is therefore likely to be site specific.

Glimepride is one of the third generation sulfonylurea drug useful for control of diabetes mellitus, type 2. A Glimepride and Metformin HCl combination is used to treat high blood sugar levels that are caused by type 2 diabetes. Normally, the pancreas release insulin after eating to help the body store excess sugar for later use. Immediate action of Glimepride will be helpful to control excess sugar, which will be maintained by Metformin HCl action later on. Thus, the developed single tablet will be sufficient instead of two to three tablets of both drugs per day, and it will also increase patient compliance and therapeutic efficacy.

7.1.2 Development and characterization of Metformin – Glimepiride bilayer floating tablets

- The present investigation was carried out to develop bilayer bilayer tablets of Metformin HCl and Glimepiride.
- The drug release from tablets is controlled by various polymer like HPMC K4M, HPMC K100M, various release retarding agent like Guar gum, sodium alginate, Sodium carboxymethyl cellulose, various release retarding agent like stearic acid, Carbopol.
- The drug release study was carried out by performing dissolution.
- For immediate release glimepiride layer dissolution carried out for 45 minutes in 900 ml 0.1 N HCl with 0.1 w/v Sodium lauryl sulphate, Basket, 100 RPM.
• For sustained release Metformin layer dissolution carried out for 1, 4 and 8 Hrs in 900 ml pH 6.8 phosphate buffer, Basket, 100 RPM.

• The floating property is aimed to be achieved by various gas forming agents like Sodium bicarbonate, Sodium carbonate, Calcium carbonate, Potassium carbonate. (B.No. B1, B2, B3, B4)

• The floating property was studied by observing floating lag time.

• Floating lag time carried out in 500 ml 0.1 N HCl.

• The ratio of drug and polymer, gas generating agent, release retarding agent is optimized.

• Trial were initiated with HPMC K4M and HPMC K100M with drug polymer ratio 4:1 and 4:2. No floating observed as no gas generating agent incorporated in formulation. (B.No. A1, A2, A3, A4)

• Formulation with Sodium bicarbonate i.e. B1 shows less floating lag time so decided to optimize the % w/w of Sodium bicarbonate. Concentration of sodium bicarbonate with 5%, 7.5% and 10% (B.No. C1, C2, C3) trial were taken and there is no major difference with 7.5% and 10% but floating lag time increased up to 10 minutes for 5%.

• By including various gel forming agents like Guar gum, sodium alginate, Sodium carboxymethyl cellulose erosion and bursting observed with sodium alginate and Sodium carboxymethyl cellulose and initially fast dissolution and increase in floating lag time observed with Guar gum. (B.No. D1, D2, D3)

• By adding stearic acid at different concentration i.e. 1%, 2%, 3% (B.No. E1, E2, E3) as release retarding agent in the formulation there is retardation of dissolution at 8 hrs. and no complete release observed with 8 hrs. time interval.

• Formulation with Carbopol 934 (B.No. E4) as release retarding agent shows incomplete release at 8 hrs.

• Formulation with Carbopol 940 (B.No. E5) as release retarding agent found satisfactory with respect to dissolution behavior and floating lag time.

• The tablets of different formulations were subjected to various evaluation tests such as weight variation, thickness, hardness, friability, floating lag time, dissolution and drug content.

• The average percentage deviation of all tablet formulations was found to be within the limit. Hence all the formulations passed the uniformity of weight.
Another measure of a tablet’s strength is friability. Friability of the tablets was evaluated by using Roche friabilia, the percentage of friability for all the formulations was below 1%, indicating that the friability was within the prescribed limits.

Drug contents of all formulation are also within the limit and found satisfactory.

Optimized batch was subjected to accelerated stability as per ICH guideline for three months 40°C and 75 % RH.

Optimized batch is selected for in-vivo buoyancy study (i.e X-RAY indicating photo).

For in-vivo buoyancy study Barium sulphate is used as opacifier for X-RAY.

### 7.1.3 Conclusion

By considering above mentioned trial details for Metformin – Glimepiride bilayer floating tablets following conclusion have been derived:

For floating lag time and dissolution there is no floating observed in B.No. A1, A2, A3, A4. Erosion and bursting observed in B.No. D2 and D3. For B.No. B2, B3, B4 floating lag time is more then 20 minutes. B.No. E1, E2, E3 does not show complete release in dissolution. B.No. C1 and C2 had been taken for optimization of Sodium bicarbonate. B.No. E4 had been taken with Carbopol 934 and B.No. E5 had been taken with Carbopol 940.

For floating SR layer 60 mg Sodium bicarbonate is finalized based on optimization trial and floating time compare to other salt. Carbopol 940 is finalized based on complete release of Metformin HCl. HPMC K100M is used as rate controlling agent. Accelerated stability data (3 month 40°C / 75 % RH) found satisfactory for optimized batch (B.No. E5)

**In-Vivo Buoyancy Study** (i.e X ray photo) after 2 hrs. and 7hrs. after admission of optimized batch shows promising results.

From all the above data it had been concluded that B.No. E5 is suitable and better intragastric floating drug delivery system of Metformin HCl as sustained release component and glimepiride as immediate release component.
7.2 Summery and Conclusion for Preparation of Omeprazole Gastro-Resistance Capsules

7.2.1 Summery for Preparation of Omeprazole Gastro-Resistance Capsules
Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H+/K+ ATPase, or more commonly just gastric proton pump) of the gastric parietal cell.

Drugs such as pantoprazole, Omeprazole, esomeprazole which have an irritant effect on the stomach and must be absorbed in the gastrointestinal tract and because it is unstable under acidic conditions, enteric delivery systems are required. Similarly, certain groups of Azoles (Lansoprazole, Esomeprazole, omeprazole, and all grouped azoles) are acid-unstable. For such types of drugs, enteric coating added to the formulation tends to avoid the stomach's acidic exposure, delivering them instead to a basic pH environment (intestines pH 5.5 and above) where they do not degrade, and give their desired action. The purpose of this study was to prepare and formulae the Enteric coating of azoles.

Omeprazole is proton pump inhibitor and used as an antiulcer agent. As drug-delivery systems become more sophisticated, the role of pellets in the design and development of dosage forms is increasing. Formulation of drugs in multiple-unit dosage forms, such as coated pellets filled in capsules offers flexibility as to target-release properties. Drugs such as Omeprazole which have an irritant effect on the stomach and must be absorbed in the gastrointestinal tract and because it is unstable under acidic conditions, enteric delivery systems are required. The study was undertaken with an aim to formulate Omeprazole enteric coated pellets.

7.2.2 Development and characterization of Omeprazole Gastro-Resistance Capsules
The aim of the product development was to formulate Omeprazole 20 mg Capsules, which are robust, stable and comparable with reference product.

Formulation development was initiated with reference product characterization.

After reference product characterization Preformulation carried out with proposed excipient.

Following mentioned study were performed for preparation of Omeprazole Gastro Resitance Capsules:-
Studies performed on the active coating suspension
The mixture of Hydroxy Propyl cellulose (L-HPC) and Hypromellose (HPMC) was used as a polymer solution. Lactose anhydrous was added as the filling material. Disodium hydrogen Phosphate dodecahydrate was used as Stabilizing agent. Omeprazole was added but it very hardly became wet in the polymer solution in water. Then it was decided to add a wetting material.
Anionic surfactant Sodium Lauryl sulphate was added into the formula as a wetting agent and it was experienced that Omeprazole formed a suspension in a very short time.
The active coating suspension prepared according to the above formulation is sprayed on the sugar spheres and the first coating layer is performed.

Studies performed on the Seal coating
Observing humidity and Temperature affect the Omeprazole, it was decided to perform another coating (Protector coating) between the two coating processes (active and enteric coating). By using HPMC solution in water, the protector coating was realized just before the enteric coating process and thus, if the product is stored under ambient conditions, the acidic residue of the enteric coating can degrade the Omeprazole active ingredient before it is administered to a patient. the interaction of Omeprazole with the Poly methacrylic polymer is thus prevented by introduction of Barrier coating between drug coating layer and Enteric Coating layer.

Studies performed on the enteric coating solution
To avoid from the contact of Omeprazole with the gastric juice, it was decided to perform an enteric coating.
To improve the stability of the core that is containing Omeprazole the excipients should give alkaline reaction HPMC Phthalate is used as an enteric coating polymer.
To avoid from cracking of the coated substance, PEG 6000 was added into the coating solution as plasticizer and talc as anti sticking agent.
Seal coating performed from 0.5 % w/w to 7.5 % w/w and enteric coating were performed from 8 % w/w to 17.5 % w/w.
Optimized formulation batch (D) were charged for photo stability as per ICH guideline.

7.2.3 Conclusion
Assay of Batch No. A, B, C, D, E, F and G found satisfactory shows that the process is sufficiently optimized and no loss found during pelletisation. The above mentioned
data reveals that 0.5 % w/w weight gain seal coated pellets shows discoloration of pellets. This shows that increase in seal coating required to protect the drug form enteric coated layer. 17.5 % w/w weight gain Enteric coated pellets shows slower initial release as compare to reference samples. Weight gain of seal coating on drug coated pellets from 2.5 % w/w to 7.4 % w/w and weight gain of enteric coating on seal coated pellets from 8.5 % w/w to 17.5 % w/w reveals good dissolution characteristics and pass as per British Pharmacopoeia 2012.

From the above executed trials it had been concluded the for seal coating stage in B.No. A it is 0.5 % w/w weight gain it shows discoloration of pellets. B.No. B,C,D,E,F,G passes dissolution as per British Pharmacopoeia 2012 but B.No. D with 3.5 w/w seal coating and 12.8 % w/w enteric coating shows closer dissolution profile compare to reference sample.

From photostability data it can be concluded that formulation is light sensitive as there is change in description of unpacked capsules and change in impurity level (increase in trend )so decided to pack as soon as possible and intermediate product should be stored in light resistant container.
7.3 Summery and Conclusion for Preparation of Doxycycline Gastro-Resistance Tablets

7.3.1 Summery for Preparation of Doxycycline Gastro-Resistance Tablets
Gastro-Resistance tablets are solid and single unit dosage forms meant for oral administration are formulated in such a way that to bypass the acidic environment to the stomach and release the active content in the basic environment of the intestine. Doxycycline is an universal antibiotic use to treat gram negative infections where the susceptible organism was strongly proven to be present and also used to treat different microbial infections. It is an tetracycline antibiotic. Its half life is around 18 to 22 hours and 80% of the dose is absorbed through small intestine.

The IR formulation of doxycycline cause adverse effects like diminish patient compliance and so does not give required therapeutic effect. The standard formulation of doxycycline cause vomiting and nausea up to three times higher then the other antibiotics. Because of vomiting and nausea the patient discontinue the medicament which had been prescribed by the physician. There are also impaired absorption of doxycycline from the immediate release formulation of doxycycline.

There is also Hepatotoxicity associated with the standard formulation of doxycycline. Nausea, vomiting, giissitis, dysphagia, enterocolitis, Anorexia, monilial overgrowth in the anogenital region. All the disorder had been caused by both oral and intravenous administration of tetracyclines. When there is oral administration of tetracyclines in the form of tablets or capsule there are also instances of esophageal ulceration.

The pH of small intestine in different regions was found to be 5 to 7 PH in duodenum, 6 to 7 PH in jejenum and 7 PH in ileum. Eudragit and HPMC phthalate polymers are selected where the dissolution properties are above PH 6.0 and PH 6.4 respectively. Different Polymers and different weight build up of coating suspension are designed to develop the targeting action of doxycycline in small intestine.

7.3.2 Development and characterization of Preparation of Doxycycline Gastro-Resistance Tablets
Several technologies have been used in the development of enteric coated tablets and in the preset investigation Gastro resistant delayed release of Doxycycline were formulated by Dry mix technique then compression followed by enteric coating.

Flow property, tabletting appearance, Hardness, thickness, friability, Disintegration time and various other physical attributes of formulation found satisfactory.
In the present formulation development four different delayed release polymer were utilized that are cellulose acetate phthalate, hypromellose phthalate, Eudragit L 30 D 55 and Acryl EZE. For the process suitability the other inactive ingredient are also added in the coating suspension they are talc and triethyl citrate. Talc is used as intitacking agent and triethyl citrate is utilized as plasticizer. Because of the nature of enteric coating polymer they protect the dosage form against the acidic environment of stomach and readily release the active content in the basic pH of intestine. The compressed were coated with 5 % w/w with all the mentioned enteric coating polymer. When these formulation exposed to 0.1 N HCl in the disintegration test apparatus the tablets fails in the disintegration. The enteric coating film looses the integrity. So there require the increase in the enteric coating to the formulation. Thus the compress tablets were coated with 9 % w/w with all the above mentioned enteric coating polymer. The 9 % w/w enteric coating polymer when exposed to the acidic environment in the apparatus the tablets remains intact for 2 hours.

9 % w/w enteric coated tablets were evaluated for the drug release profile via dissolution. Formulation D5, D6, D7, D8 were exposed to 0.1 N hydrochloric acid for two hours and subsequently the same unit was exposed to phosphate buffer pH 6.8 for 45 minutes. From available data it can be concluded that there is acid uptake is less than 10 % which ranges from 0.27 % to 2.87 % when the 9 % w/w weight gain enteric coated tablet is exposed to the acidic media. But when the media is changed from acidic side to the basic side it leads to rapid dissolution of doxycycline from all the studied formulation. The formulation evaluated had also shown good physical attributes.

7.3.3 Conclusion

Gastro resistance Doxycycline tablets were formulated by utilization of four different enteric coating polymer they are Hypromellose phthalate, Acryl EZE cellulose acetate phthalate, Eudragit L30 D 55 to achieve 5 % w/w weight gain. When the formulations evaluated to dissolution at 0.1 N HCl for two hours the dosage form fails to dissolution test. But when the formulation coated with 9 % weight gain it passes the dissolution test. When these 9 % weight gained enteric coated formulation exposed to acidic media followed by alkaline media it dissolve faster in alkaline media. Formulation D5 and D8 shows faster release in alkaline media compare to D6 and D7. D5 and D8 contains delayed release polymer as Eudragit L30 D 55 and Acryl EZE respectively. D6 and D7 contains enteric coating polymer as Hypromellose phthalate
and Cellulose acetate phthalate. Formulation D5 and D8 remains intact in the acidic media for two hours.