Chapter-7

Summary and Conclusion

7.1 SUMMARY

Recent advancements in technology provide viable dosage alternative for patients who have difficulty in swallowing the tablet. Oral disintegrating and dissolving tablets are one of them and differ from traditional tablets in that they are designed to be dissolving on tongue rather than swallow whole. Various technology used in the manufacturing of mouth dissolving/disintegrating tablets are; freeze drying, direct compression, spray drying, sublimation etc. Many patented technologies like Durasolv®, Flash Dose®, Flashtab®, Oraquick®, Orasolv®, and Zydis® have also gained importance in the international market. Orodispersable tablets dissolve and/or disintegrate rapidly in the saliva without the need for water. Some tablets designed to dissolve in saliva within few seconds, are true mouth dissolving tablets. The basic approaches for developing mouth dissolving tablets include maximizing the porous structure of the tablet matrix. Thus we tried to formulate mouth dissolving tablets giving complete dissolution of the formulation with minimum residue and concentrated on complete dissolution of all ingredients rather than use of insoluble super disintegrates. For preparation MDTs, levocetirizine as bitter drug and Cefixime as poorly aqueous soluble drug was selected.

In characterization of drug, Levocetirizine shows similar UV Absorption peak at 231nm in acidic solution (0.1N HCl solution and in simulated saliva) indicated no change in the absorption peaks with pH. Differential Scanning Calorimeter (DSC) thermogram showed endothermic peak of levocetirizine at 221.7°C, which correspond to its melting point and the purity was confirmed by FTIR study. Second drug, Cefixime was also characterized by UV spectroscopy, DSC, and FTIR and confirms its purity.

The bitter taste of Levocetirizine was masked by inclusion complexes and solid dispersion by mannitol in comparison to ion exchange resin. The results of evaluation indicated that the resin complex does not release the drug in saliva and thus the drug become unavailable to taste bud (masked the bitter taste of drug) due to decreased solubility of levocetirizine at saliva pH although releases the drug in acidic pH 1.2 (0.1N HCl), but produces the gritty appearance. Taste masking of levocetirizine diHCl with BCD was found
due to hindrance of the drug by forming inclusion complex thus unpleasant tastes or odors was hidden from the sensory receptors by encapsulating them within the BCD cavity. With sugar derivatives (Mannitol), solid dispersion of Mannitol at 1:3 ratio was found palatable; 1:4 ratio was tasteless (>90% volunteers reported). In solid dispersion, levocetirizine and mannitol dispersion was at molecular level and creates a hydrated coating around the drug molecule therefore prevent attachment with taste bud receptor on the tongue in the mouth cavity thus have no or little taste or odor and are much more acceptable to the patient.

The solubility of pure drug (Cefixime) was found to be 352±14mcg/ml at gastric pH (in 0.1N HCl) and 321±25mcg/ml. By forming inclusion complex with BCD in different ratios, the solubility was enhanced linearly with increased concentration of BCD and also independent of the physiological pH at higher concentration (4204±42mcg/ml at gastric pH, 4153±78mcg/ml at saliva pH). By using sugar derivatives, mannitol fails to increase the solubility of Cefixime in physical mixture (816±19mcg/ml in gastric pH, 755±76mcg/ml at pH 6.2 in ratio 1:5) but by preparing solid dispersion of the cefixime with mannitol, solubility increases linearly with mannitol concentration (3485±23mcg/ml in gastric pH, 3403±56mcg/ml at pH 6.2 in ratio 1:5). This was due to the mannitol solid dispersion at molecular level and creates hydrated environment around the Cefixime thus increases its solubility.

In Preliminary formulation trials, formulations with superdisintegrant and pregelatinized starch gives rough texture with insoluble residue. techniques such as sublimation and effervescent were finalized for MDTs preparation due to very quick disintegration and lack of insoluble residue. Mannitol was found to be the most suitable excipient due to its complete solubility and easy compressibility. In effervescence approach, Citric Acid was preferred in place of tartaric acid due to its suitability to most of citrus flavors along with its taste.

Tablets prepared by sublimation technique, all the formulation shows very good content uniformity (>96.5±0.53%) but MDTs have problem in Friability (>20% in batch S5) and Hardness (decreases with increase in the porosity). However, in case of tablets by
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The effervescent method, MDTs shows sufficient hardness (>4 kg/cm²) with minimum friability (<0.7%) and also posses good content uniformity (>98.1±0.13%) and passes the weight variation test. For Cefixime MDTs, MDTs shows sufficient hardness (>4.76 kg/cm²) with minimum friability (<0.57%) and also posses good content uniformity (>97.3±2.33%). So Batch C4 was finalized for animal studies due to sufficient hardness, minimum friability with no moisture gain storage. The disintegration mechanism showed that all the formulation disintegrates within one minute and complete dissolution of the formulation without shaking. The microscopic study of the disintegration shows that the formulation disintegrates quickly and the crystals of mannitol dissolved completely within seconds giving no residue.

MDTs prepared by sublimation showed least disintegration time (less than 1 min. without shaking), maximum in vitro dissolution rate (T₅₀% = 1.5 min., T₉₀% = 4 min.) and least in vivo mouth disintegration time (15±4 sec.) with porosity. MDTs prepared by effervescent method (Batch E4 and E5) shows least disintegration time (less than 1.5 min. without shaking), maximum in vitro dissolution rate (T₅₀% < 3 min., T₉₀% < 8 min.) and least in vivo mouth disintegration time (< 35 sec) and batch E4 shows better patient compliance in comparison to batch E5 in respect of sour taste due to high conc. of sodium bicarbonate. MDTs of Cefixime: Batch C4 and C5 shows least disintegration time (less than 2 min. without shaking), maximum in vitro dissolution rate (T₅₀% < 2.5 min., T₉₀% < 7.5 min.). Formulation C4 was selected for animal study

Selected formulation of Cefixime MDT (C4) was evaluated for Ex-vivo permeability studies as per the procedure described in Methodology. Result shows that only <10% Cefixime was permeated through the intestinal membrane from formulation as well as pure drug in 30 minutes and permeability increased after 1 hours. This may be due to the initiation of dissolution and absorption of Cefixime through intestinal membrane. The permeability of Cefixime was linear from pure drug and only 57.99±4.3% drug was permeated even after 10 hours. In formulation C4, more than 53.18±3.6% of the drug was absorbed within 4 hours (T₅₀% = 3.5 hrs and T₉₀% = 9 hrs) and found 99.87±3.8% permeation within 10 hours of study.
Thus, in formulation C4, the permeability of Cefixime was enhanced in comparison to pure drug (\(T_{1/2} < 3.5\)hrs in formulation, \(T_{1/2} < 9\)hrs in pure drug).

In Pharmacodynamic study in animal, the plasma concentration of the orally administered Cefixime pure drug and formulation C4 (2mg equivalent) were determined by zone of inhibition (mm) and shows that the Antimicrobial activity of formulation C4 (ZOI= 14±1.0 in 2.5hrs.) was found more (table 6.3, fig 6.4) in comparison to pure drug (ZOI= 11±1.0 in 2.5hrs.). The peak plasma concentration (15.09±2.1 mcg/ml and 22.64±1.8mcg/ml) were found to be achieved in 2.5 hrs in animal from Cefixime in comparison to formulation (C4). The absorption of Cefixime from formulation (C4) was more compared to the Cefixime pure drug. Further follow up of the plasma concentration shows that in at least 2.5 hours Cefixime attained peak plasma concentration in pure drug as well as in formulation. The elimination half life of Cefixime in the animal was found to be 3.58±0.21 hrs and 4.17±0.32 hours respectively and clearance of Cefixime was found almost same in both cases (0.1938±0.0221 h\(^{-1}\) and 0.1664±0.0143 h\(^{-1}\)). Thus, the antimicrobial activity of Cefixime was enhance in formulation (C4) in comparison to the pure drug (>77.89% with \(C_{\text{max}}\) 22.64±1.8mcg/ml in 2.5hrs.)

In pharmacokinetic study, The peak plasma concentration (Cp) from pure drug was found 14.64±1.9mcg/ml in 2.5 hours (table 6.8) whereas in formulation (C4), Cp was enhanced to 19.21±2.1mcg/ml indicating more absorption of Cefixime from formulation (C4) was as compared to the Cefixime pure drug. the elimination half life of Cefixime in the animal was found to be 3.41±0.45 hours and 3.91±0.62 from pure drug and formulation (C4) respectably and clearance of Cefixime was found almost same in both cases (0.2033±0.0341 h\(^{-1}\) and 0.1772±0.0114 h\(^{-1}\)). The AUC\(_{0-\infty}\) of formulation was found 121.3±8.4 in comparison to Cefixime pure drug (77.9±8.7), thus bioavailability of the drug was found to enhanced by more than 50% in formulation (C4) in comparison to the pure drug (\(C_{\text{max}} = 19.21±2.1\)mcg/ml in 2.5hrs.).
7.2 CONCLUSION

In Preliminary study:

- **Taste masking** of bitter drug (levocetirizine diHCl) was successfully done using mannitol solid dispersion (ratio 1:4) and BCD in comparison to Ion exchange resign with completely soluble complex.
- **Solubility** of poorly aqueous soluble drug (Cefixime) was also enhanced using mannitol solid dispersion in comparison to BCD inclusion complex.

In conclusion, Drug solid dispersion with mannitol can be utilized for both (taste masking as well as to enhance the solubility) and does not shows any interaction with drugs (as indicated by DSC, XRD etc.)

Formulation:

- **MDTs with superdisintegrants** (using SSG, MCC) give rough texture in mouth.
- **For MDT Formulation**, mannitol was found most suitable in comparison to Lactose and Glucose due to quick dissolution and palatable taste.
- **Citric acid** was found more palatable in comparison to tartaric acid as citric acid have additional benefits (best suited with citrus flavors, suppress the unpleasant taste)
- **MDTs prepared by sublimation** (batch S5) showed least disintegration time (less than 1min. without shaking), maximum *in vitro* dissolution rate (*T*\(_{50}\)% = 1.5 min., *T*\(_{90}\)% = 4min.) and least *in vivo* mouth disintegration time (15±4 sec). with porosity but have the problems of hardness (<2 kg/cm\(^2\)) and friability (>10%) thus have not industrial adaptability.
- **MDTs prepared by effervescent method** have sufficient hardness (>4 kg/cm\(^2\)) and friability (<0.7%) and prepared by usual wet granulation (method 2) thus have very good industrial adaptability. Batch E4 and E5 shows least disintegration time (less than 1.5 min. without shaking), maximum *in vitro* dissolution rate (*T*\(_{50}\)% < 3min., *T*\(_{90}\)% < 8min.) and least *in vivo* mouth disintegration time (< 35sec) and batch E4 shows
better patient compliance in comparison to batch E5 in respect of sour taste due to high concentration of sodium bicarbonate.

- **MDTs of Cefixime:** Batch C4 and C5 shows least disintegration time (less than 2 min. without shaking), maximum *in vitro* dissolution rate ($T_{50\%} < 2.5$ min., $T_{90\%} < 7.5$ min.). Formulation C4 was selected for animal study

In conclusion, MDTs with patient compliance (without rough texture and insoluble residue), industrial adaptability can be prepared by modified wet granulation effervescent method.

**Ex-Vivo / In-Vivo studies:**

- **Permeability studies:** Formulation C4 has enhanced the drug permeability ($T_{50\%} < 4$ hrs., $T_{90\%} < 9$ hrs.) whereas the pure drug permeates only $57.99\pm4.3$ in 10hrs. ($T_{50\%} = 9$ hrs.)

- **Pharmacokinetics:** From pharmacokinetic parameter, bioavailability of the drug was enhance in formulation C4 (>50% enhancement, $C_{\text{max}} 19.21\pm2.1$ mcg/ml in 2.5hrs.)

- **Pharmacodynamics:** Antimicrobial activity of formulation C4 (ZOI= 14±1.0 in 2.5hrs.) was found more in comparison to pure drug (ZOI= 11±1.0 in 2.5hrs.)

In conclusion, in formulation C4, the bioavailability of Cefixime was enhanced in addition to the antimicrobial activity