Summary & Conclusions
5. SUMMARY AND CONCLUSIONS

In the present study, micromeritic and mechanical properties of Metformin HCl and Chlorzoxazone were improved using cocrystallization, pelletization, crystallo-co-agglomeration and cogrinding approaches.

Suitable analytical methods (UV spectroscopy) were established and validated in phosphate buffer pH 6.8 solution.

A detailed description of preparation of cocrystals, pellets, CCA and coground mixture was given. The evaluation parameters like flow and packability, capillary melting point, microscopic determination and morphology, micromeritic, various mechanical properties, DSC, FT-IR and X-ray diffraction were used for characterization. The pharmaceutical importance was derived using solubility and dissolution studies. Directly compressible formulations were prepared from cocrystals, CCA and coground mixtures.

The general morphology of Metformin HCL was observed and documented with figures. Compressibility and handling properties for prepared samples were evaluated. The data of melting points (DSC) and FT-IR were included. These results were confirmed through XRD. Aqueous solubility and dissolution rates of different samples and formulations of optimized samples were explained in the form of tables and graphs. Stability study for optimized samples and its formulations were carried out. A similar study was carried out for studying the Chlorzoxazone also.

Metformin HCl

1. Co-crystals of Metformin HCl were optimized with lactose anhydrous in 1: 0.5 weight ratio to improve physicochemical and physicomechanical properties using deep freezing technique. The stoichiometric ratio of optimized cocrystals was found to be 1: 0.78 between Metformin HCl and lactose anhydrous. Other ratios of combination of Metformin HCl and lactose anhydrous did not yield crystals with good flow properties. The other excipients could not bind the drug in a manner to prepare
CCA or pellets. Because of higher aqueous solubility, co-grinding was not applied to Metformin HCl.

2. The crystal morphology exhibited differences between pure drug and cocrystal material when observed under optical microscope.

3. The flow properties and compressibility of prepared cocrystals were remarkably improved compared to pure Metformin HCl, which was due to equidimensional shape of co-crystals. SEM analysis also confirmed equidimensional shape of co-crystals of Metformin HCl.

4. Cocrystals showed higher aqueous solubility in all the buffer solutions compared to pure drug.

5. Cocrystals showed lower melting point in DSC compared to pure drug, which indicated a formation of new phase, which was further confirmed from FT-IR analysis. The results showed formation of weak hydrogen bond between \(-\text{NH}_2\) of Metformin HCl and \(-\text{OH}\) of lactose anhydrous, which was confirmed after three months stability study.

6. Lower peak intensities and different angle of diffractions further in pXRD analysis confirmed the formation of cocrystals.

7. Tablets prepared from co-crystals of Metformin HCl showed good compressibility, hardness, tensile strength, disintegration and less friability compared to tablets prepared from pure drug.

8. Though the dissolution was not a prerequisite for Metformin HCl as being a salt form it is highly water soluble, cocrystals of Metformin HCl with lactose anhydrous showed very high rate of dissolution compared to pure drug.
9. The three months stability study of cocrystals, pure drug and their dosage forms showed its stable nature at 40 °C / 75% RH.

Chlorzoxazone

1. Pellets, CCA and coground mixture of drug: PEG 4000 (1:3) combination was optimized using emulsion solvent diffusion, crystallo-co-agglomeration and ball milling techniques, respectively. Cocrystallization with different excipients yield needle shaped crystals, which imparted poor flow to the crystals.

2. Only ethyl cellulose: HPMC E50LV (1: 2.58) combination could be able to generate pellets where HPMC played a key role in covering the pellet with a good sphericity.

3. A $3^2$ full factorial design and response surface methodology were applied in order to prepare pellets of Chlorzoxazone.

4. The morphology of optimized pellets showed good sphericity when observed under optical microscope.

5. Flow property and compressibility of the optimized pellets showed remarkable improvement because of its spherical nature compared to pure drug.

6. Melting endotherm of pellets and pure drug were similar. It was an indication of good compatibility of used excipients with drug. It was further confirmed with FT-IR analysis.

7. Lower peak intensity of pellets compared to pure drug in pXRD was an indication of reduction in crystallinity of drug in pellets.
8. Crystallo-co-agglomerates (CCA) in combination of PEG 4000, ethyl cellulose and PVP K30 (each in 2% w/v) showed excellent handling properties.

9. CCA were found spherical morphologically when observed under optical microscope.

10. Flow property and compressibility of CCA was improved considerably compared to pure drug. It was due to spherical and equidimensional shape of CCA.

11. Similarity of melting peak between optimized CCA and pure drug in DSC thermogram indicated good compatibility between drug and excipients used. It was also confirmed using FT-IR analysis.

12. Reduction in crystallinity of drug in CCA compared to pure drug was confirmed due to low intensity of peaks in pXRD spectra.

13. Amorphization in Chlorzoxazone was successfully obtained in case of PEG 4000 only.

14. Flow property and compressibility of coground samples were remarkably improved due to size reduction and equidimensional shape of the particles compared to pure drug.

15. Melting peak in DSC endotherm of coground mixture was near to melting peak of PEG 4000, which confirmed the dissolution of drug in PEG 4000 when it got melted. The compatibility was confirmed using FT-IR analysis.

16. Peak intensities of coground mixture in case of pXRD study were greatly reduced compared to pure drug, which was an indication of amorphization of drug after cogrinding.
17. Coground mixture showed higher aqueous solubility in all the buffer solutions compared to pure drug due to amorphization as well as the presence of hydrophilic polymer, PEG 4000.

18. Tablets prepared from CCA and coground mixture of Chlorzoxazone showed good strength compared to pure drug.

19. Pellets and CCA showed improvement in dissolution profile of powder as well as formulation compared to pure drug. Coground sample showed almost 2.5 times improvement in dissolution profile compared to pure drug. This increased rate of dissolution was due to amorphization of drug.

20. The stability study of CCA, coground mixture and their dosage forms showed its stable nature. It also indicated a good stabilization of drug by PEG 4000 after converting the crystalline drug to amorphous form.

Overall, the study manifested that, the above mentioned approaches not only improve the physicochemical and physicomechanical properties of drugs but also improve manufacturability of drug and convert it to a highly compressible intermediate form which can be utilized for direct compression technology, instead of using a highly tedious, laborious, uneconomical and complicated wet granulation technology. It may be an advantage for developing it on a commercial scale for manufacturing of tablets, with improved pharmacokinetic performance.