SYNOPSIS ON
DEVELOPMENT AND CHARACTERIZATION OF COMPACTION AND
BIOINTERFACIAL BEHAVIOUR OF SOME TABLET AND FILM
FORMULATIONS

Thesis submitted in partial fulfilment of the requirements of the degree of
Doctor of Philosophy in Pharmacy

by

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**Background:**

Advancements in technology and modification in standard compressed tablet and the processes are to achieve better patient acceptance as well as enhanced bioavailability. The major benefits behind the newer tablet formulations are easy to administer, minimum dose, less adverse effects and controlled blood levels.

Direct compression is more efficient and economical process as compared to other. Powder flow and compaction characteristics are vital part in the development and manufacture of solid dosage forms. These are dependent on physicochemical and mechanical characteristics of the solid materials used. Several mathematical equations are adopted to characterize the compaction behaviour of the powder under applied pressure. Heckel, Kawakita and Kuno are the most commonly used models.

Recently, extensive investigations are going on to deliver the drug through film type delivery system to overcome the difficulties associated with conventional compressed tablets. Thin film was prepared by casting a mixture of drug, polymer and a suitable plasticizer followed by drying in an oven and characterized the physicochemical properties.

**Objective:**

- Assessment of compressibility of poorly compressible paracetamol in presence of talcum lubricated – microcrystalline cellulose.
- Characterization of biexponential compaction process by tapping and applied pressure.
- Study on tabletability profiles of paracetamol prepared with different ratios with MCC in the presence of talcum.
- The change in apparent density of the biexponential process has been attempted to correlate (level A Correlation) with the tabletability at the same applied pressure.
- To study the effect of paracetamol/ MCC ratio on in vitro drug release.
- Assessment of compressibility properties of metoprolol tartarate with HPMC K 100, Eudragit RL 100, chitosan, hydroxyethyl cellulose and ethyl cellulose at 1:1 ratio by studying the porosity pressure relationship through tapping of Kawakita and Heckel model.
- To study the release rate of metoprolol tartarate from directly compressed tablet.
Investigation on effect of plasticizer such as propylene glycol, polyethylene glycol 400, Dimethyl sulphoxide, and triethanolamine on crystallinity and dissolution of telmisartan from HPMC based film.

Development and characterization of amlodipine bilayer mucoadhesive tablet formulation containing polyacrylate/β–cyclodextrin for better bioavailability.

Study of swelling and erosion of amlodipine tablets and to attempt correlation with buccal permeation.

**Result and Discussion:**

Difference in apparent density due to both tapping and pressure has a direct relation with the compactibility of the powder material. Primary rearrangement packing rate was faster compared to secondary rearrangement packing rate in all powder formulations with a great difference as understood by tapping experiment. Density difference due to compaction under pressure by particle rearrangement was very high compared to compaction by plastic deformation in all the powder formulations. Apparent density has been increased in all MCC based dry powder formulations and least improvement was observed in the formulations containing least amount of MCC compared to paracetamol alone. Compressibility and mechanical strength increased with the increase of MCC loading in the powder formulation. Moreover, in some cases talcum also supported increased compressibility with its increased content in the formulation. Packing rate was not observed to be directly related to the compression ability of the powder material rather it gave the idea of fast or slow consolidation process. A “level A” correlation has been established between compaction process and tabletability. Drug dissolution was found faster as MCC loading increased in the tablet formulation.

This contemplate investigated the fundamental compressive ability of distinctive polymers in the design of directly compressed metoprolol tartarate tablet. The compressibility aspects of the binders have been analysed by Heckel and Kawakita models. The investigation uncovered that polymer HPMC K100 possessed great sustaining property whereas for preparation of fast dissolving tablet chitosan might a polymer of choice.

Effect of plasticizers such as propylene glycol (pg), polyethylene glycol 400(peg), dimethyl sulfoxide (DMSO) and triethanolamine (Tea) on crystallinity of telmisartan in HPMC matrix films was examined using PLM, SEM, and XRD. The film with Polyethylene
glycol produced a relatively smooth surface in comparison to the other films in submicron level. Both water-soluble HPMC and plasticizer were compatible with the drug and did not phase separate upon solvent evaporation. Plasticized-HPMC has a major role in the significant inhibition of crystal growth of drug in the film. Based on all the results, the increased order of amorphization of drug was observed in the film formulation as: T$_{pg10}$ < T$_{pg30}$ < T$_{dmsoc30}$ < T$_{peg30}$ < T$_{tea30}$. Relatively amorphous state of telmisartan in presence of triethanolamine as plasticizer is technologically more advantageous than the others owing to its anticipated better bioavailability. Although it is a thermodynamically unstable state, a physical stability study at 40°C/75% RH for 6 weeks revealed no significant change of the amorphous phase of the drug in T$_{pg30}$, T$_{dmsoc30}$, T$_{peg30}$ and T$_{tea30}$ films.

Amlodipine bilayer buccal tablets were produced using HPMC matrix system containing polyacrylate polymer/β-cyclodextrin as the drug layer and ethyl cellulose as the non-swellable backing layer. Tablet without β-cyclodextrin and only HPMC showed less pronounced adhesion, but when used in combination with polyacrylate polymer, its overall adhesion was increased. It was proposed that HPMC/CBP in 75: 25 ratios, the potential for hydrogen bonding reached the maximum due to the saturation of functional groups at the bio interface of tablet-mucus. Significant change in adhesion force and swelling properties in the presence of cyclodextrin has not been found. Cyclodextrin did not hamper the bioadhesion bond formation between amlodipine tablets and mucin. AMB-BCD inclusion complex improved permeation spectacularly due to its improved dissolution at the site of bio interface of tablet and buccal mucosa. Buccal permeation has been increased with the increase of HPMC proportion in the rest of the formulations as observed in in-vitro dissolution. Drug dissolution was mainly by diffusion and partially erosion based whereas, buccal permeation mainly by erosion and partially diffusion based. Level A correlations between ex vivo and in vitro data have been established so that determination of the swelling index or drug release alone is sufficient to predict the buccomucosal permeation and this gives idea about the in vivo behaviour of amlodipine tablets. Level C correlations of the force of adhesion ex vivo versus the rate of swelling in vitro, and permeability coefficient through buccal mucosa ex vivo versus erosion index in vitro have also been suggested. These correlations could be utilized for ensuring batch-to-batch consistency in ex vivo performance of the buccal tablets. Formulation AHB$_{1:1}$ will be the most suitable when faster permeation is required, conversely AH$_{3}C_{1}$ will be the most appropriate when sustained permeation is required.
**Conclusion:**

- In all powder formulations the primary rearrangement packing rate was faster compared to secondary packing.

- Under applied pressure, density difference due to compaction by particle rearrangement was observed to be very high compared to compaction by plastic deformation in the formulations.

- Increase in MCC concentration significantly increases in mechanical strength of the formulation.

- Level A correlation has been established between tensile strength and apparent density change at the same pressure.

- The drug dissolution rate from the compacted tablet was enhanced with Increased loading of MCC.

- The result from Heckel and Kawakita analysis revealed that hydroxy propyl methyl cellulose and chitosan are suitable release retardant and fast releasing agents for preparation of metoprolol tartarate directly compressed tablet respectively.

- The maximum amorphization of drug was observed in the film formulation of telmisartan containing triethanolamine which is more advantageous in terms of better bioavailability compared to other plasticizer.

- Profound improvement in dissolution of the drug amlodipine besylate from cyclodextrin complex was found.

- Due to the improved dissolution significant permeation was observed at the site of bio interface of the tablet and buccal mucosa.

- The drug release followed mainly by diffusion and partially by erosion mechanism.