Chapter -1

INTRODUCTION
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1.1. Development of compressed tablet and film formulations

Different delivery technologies and administrative routes have been developed to ensure optimal administration of therapeutic agents. Advancements in technology and modification in standard compressed tablet are implemented to achieve better patient acceptance as well as enhanced bioavailability. The major benefits behind the newer tablet formulations are ease of administration, minimal dose, less adverse effects and controlled blood levels.

Several novel approaches are being taken in to consideration for improvement of current drug delivery technology. Meka et al., (2016) designed and evaluated diltiazem hydrochloride floating tablets for establishing improved bioavailability. Innovative techniques like hot melt and thermoplastic granulation processes were reported for the preparation of buoyant sustained release venlafaxine tablets (Harshal et al., 2014; Goswami et al., 2011) Goswami and co-workers study suggested that the famotidine mucoadhesive sustained release tablets using HPMC-K4M and tragacanth were more promising in sustaining drug delivery in controlled manner compared to other formulations. A newly developed mucoadhesive antifungal tablet of clotrimazole was fabricated to improve the oral bioavailability by increasing the solubility of the drug. A recently reported mucoadhesive clotrimazole tablet developed for improvement of oral bioavailability by increasing the solubility of the drug (Dhakeet et al., 2011). Buccal repaglinide tablets developed by wet granulation process showed good mucoadhesive strength and sustained release rate (Patel et al., 2014). Improvement of bioavailability and other physicochemical characteristics were observed in mucoadhesive tablet of niacin (Gajananv et al., 2010). Some permeation enhancers were also used in direct compressed tablet formulation for improving delivery of tizanidine hydrochloride (Gazzi et al., 2009). Increased delivery of venlafaxine through buccal administration has been achieved by formulating directly compressed tablet containing microparticles (Abruzzi A. et al., 2015). The directly compressed mouth dissolving tablet of water insoluble drug oxycarbazepine showed improved therapeutic level in comparison with counter part (Anupam et al., 2009).
Cinnarizine mouth dissolving tablets demonstrated enhanced bioavailability when formulated with the effervescent and super disintegrants (Patel et al, 2012).

**Processing of compressed tablet**

A tablet is a solid dosage form prepared by compression of a formulated powder bed in an enclosed die cavity. The three major methods of developing powde blendrs for tablet making are: (i) Wet Granulation, (ii) Dry Granulation, and (iii) Direct Compression.

![Diagram]

**Fig. 1.1: Schematic representation of tablet compression processes**
The most adopted process in pharmaceutical industry is wet granulation. Wet granulation process involves a number of unit operation steps which makes it time consuming. In dry granulation process the powder mixture is compressed without the use of heat and solvent. This process comprises two basic procedures, formation of a compact of the material by compression (slugging) followed by size reduction and particles lubrication followed by compression. Direct compression is more efficient and economical process as compared to other two processes. Tablets prepared by direct compression possess enhanced stability compare to tablet from wet granulation process which is an added benefit. The directly compressed tablet involves only limited steps i.e dry blending, lubrication and compaction of a mixture of active pharmaceutical ingredient (API) and necessary excipients omitting the wetting and drying steps (Fig. 1.1) (Bolhius 1973).

**Characterization of Tablet compression**

Powder flow and compaction characteristics are vital part of the development and manufacturing of solid dosage forms. These are involved in virtually every stage of manufacture such as conveying, blending, transfer, storage, feeding, and compression. These are dependent on physicochemical and mechanical characteristics of the solid materials used. The deformation of pharmaceutical materials has been recognized to be time dependent and researchers have found that the time dependency is related to a consolidation mechanism (Maarschalk et al., 1996). Several mathematical equations were adopted to characterize the compaction behaviour of the powder under applied pressure. The most commonly used models are discussed below.

**Heckel model** - The equation dictates the densification phenomenon of the powder which related to the process of volume reduction during die filling and particle rearrangement before deformation and bonding Eq.1.1.

\[ \ln \left( \frac{1}{1-D} \right) = KP + A \]  

(1.1)

Where, \( D \) is the ratio of the density of the powder mass at pressure \( P \) to the density of the powder mixture (i.e. relative density). \( K \) is the slope of the straight portion of the graph, reflects the plasticity of the materials and \( A \) is the intercept which is a constant.
A Heckel profile is normally comprised of three different regions; (Figure 1.2) an initial non-linear part related to particle rearrangement (Region I), linear part signifies whether the data is obeying the expression either plastic or elastic (Region II), and finally a non-linear region (Region III) signifying the plastic deformation of the compact (Sun et al., 2001). These three different regions are normally explained with the compression mechanisms (Heckel et al., 1961; Shapiro et al., 1995; and Duberg et al., 1982).

![Diagram of Heckel plot regions](image)

**Fig. 1.2: Graphical presentation**

- **Heckel plot (I) particle rearrangement**
- **(II) elastic deformation**
- **(III) Plastic deformation**

**Kawakita model** - It states the relationship between the volume reduction of a powder column and the applied pressure. The equation is:

\[
\frac{P}{C} = \frac{P}{\alpha} + \frac{1}{ab}
\]

\[
C = \frac{\rho_0}{\rho_p}
\]

Where, \( C \) is the degree of the volume reduction, \( P \) is the pressure, \( \rho_0 \) is bulk density, \( \rho_p \). Apparent density at pressure \( P \), \( \alpha \) is the initial porosity obtained from the reciprocal of the slope measured from the linear part of the plot \((P/C)\) against pressure which is a straight line. \( ab \) intercept extrapolated the linear portion of the plot. \( b \) has the dimension of the reciprocal of stress Figure 1.3.
Kuno model- This model describes a monoexponential relationship between the change in apparent density of a powder bed and number of tapping as equation 1.3. Biexponential equation can describe the packing process of powder material under both tapping and pressure. Kuno model is used for the determination of particle rearrangement and compression behaviour from tap density and compaction data. Particle rearrangement could be divided into two stages as primary and secondary rearrangement.

\[ \rho_t - \rho_n = (\rho_o - \rho_n) \exp(-KN) \]  

(1.3)

Where \( \rho_t \) is the apparent density at equilibrium, \( \rho_n \) is the apparent density at Nth tapped state, \( \rho_o \) is the apparent density at initial cascade state and \( K \) is the rate of packing process under tapping.

Powdered materials behave differently to densification during compaction process because they have voids. Some commercially available directly compressible binders, microcrystalline cellulose (MCC), starch, lactose, dicalcium phosphate (DCP) were studied for their physicochemical properties and binding capacity using Heckel and Kawakita equation. The investigation revealed that MCC had moderate flowability, excellent compressibility. Starch, lactose, and sugar generally exhibited moderate flowability, compressibility, and hardness; DCP had excellent flowability, but poor compressibility and hardness. Yeli Z et al., 2003 and Armstrong et al., 1989 suggested that differences in tablet tensile strength due to tableting speed could be accounted for porosity changes.

Significant difference was observed in solid fraction, tablet strength and disintegration time of a tablet compressed using eccentric press and a rotary press.
(Hancock et al., 2003). Maarschalk 1996 investigated tensile strength as a function of tablet porosity for sorbitol which was independent of compression speed. During compression powder experiences different complex processes i.e. expulsion of entrapped air, closeness of the particles, enhancement of the interparticular bonds, plastic deformation and finally formation of a coherent mass of different characteristics. These variable characteristics are studied to forecast the compressibility of the powders.

Tabletability is the capacity of a powder to be transformed into a tablet of specified strength under the effect of compaction pressure. It is represented by a plot of tensile strength versus compaction pressure. Characterization of the tabletability provides excellent insight into the compaction process and mechanical properties of a material.

Compressibility is the ability of a material to undergo a reduction in volume as a result of an applied pressure. It is represented by a plot of porosity versus compaction pressure.

Compactibility is the ability of a powdered material to be transformed into tablets with strength during densification. It is represented by a plot of tensile strength versus solid fraction (Leuenberger H et al., 1986). Tensile strength is calculated from breaking force. The density of particles and Particle size are important properties which are also the key factors affecting the average weight, friability, dissolution, permeation and function of many pharmaceutical materials in addition to tablet strength. Mc Kenna et al., 1982 studied the correlation between the internal forces of friction and cohesion of the powders and the tensile strength. Carr's compressibility index is a one point determination and serves as an empirical guide to flowability and consolidation behavior of a powder.

1.2. Development of film formulation

Swallowing difficulty during administration of drug associated with conventional compressed tablets is a prime concern to the formulator. To minimize the difficulty of administration, a substitute approach is necessary. Significant Investigation and studies have been carried out for advancement of film type drug delivery systems to improve patient compliance. Plasticizer and polymers are the key components in film formulation which include natural or synthetically produced. Hydroxy propylmethylcelluloses (HPMC), chitosan, sodium alginate, Eudragit are some of the examples. To attain the desired film
properties these polymers may be used either alone or in combination in different ratios. Different drugs are being delivered efficiently either systemically and/or locally by this concept. Before formulation development, information with respect to the properties of the API is gathered. These properties are helpful to formulate a proficient thin films for effective delivery of medication.

Mouth dissolving film is an example of the film type dosage forms that releases the drug by rapid disintegration and solubilisation within the oral cavity. This leads to improvement of the Intra-oral absorption, by passing first-pass effects, rapid onset of action and reduction of API quantity. Optimum delivery of metoprolol succinate was achieved through oral film containing HPMC E5 and HEC after a scheduled time of drug release study (Nagendra et al., 2015). In animal study the analgesic property of etoricoxib film was better than immediate release tablets (Senthilkumar et al., 2014). Buccal delivery of a highly soluble drug rizatriptan benzoate was successful using tamarind seed polysaccharide as a mucoadhesive polymer (Amelia et al., 2013). Bioavailability of enalapril maleate was enhanced by the concept of mucoadhesive buccal film formulation (Semalty et al., 2010). Mucoadhesive buccal film of acyclovir was prepared by complexing a hydrophilic polymer with hydroxy propyl beta-cyclodextrin in the molar ratio of 1:1, which improved drug release rate significantly (Ankita et al., 2011).

**Processing of Film formulations**

Various methods are available for fabrication of film preparation and out of these solvent casting is a preferable one. A homogeneous mixture of drug and polymer is prepared in an aqueous and/or organic solvent system. The viscous liquid mixture is poured slowly on a flat surfaced container and spreaded. The product is dried at low temperature to evaporate the solvent. The dried film is cut into suitable shape and size depending upon the required dose of the formed strip. Hot-melt extrusion (HME) technique for film preparation does not require organic solvent. It is the process of applying heat and pressure to melt a drug- polymer blend and force it though an orifice in a continuous process. HME is a well-known process for heat stable drug- polymer system and is developed to produce polymeric matrix products of uniform shape and density.
Characterization of film

An ideal thin film, should have adequate flexibility, softness, elasticity, and good physicochemical stability. Characterization of film includes determination of mechanical strength, hydration (swelling), in vitro drug release, permeation and surface morphology. Thickness measurement is necessary as it directly correlates with the amount of drug in the films and easy administration. The ideal thickness is measured by vernier caliper, electronic digital micrometer, screw gauge, or scanning electron microscopy (SEM) images. Polymeric films should possess enough tension strength to withstand handling in different environment but should not be too flexible because greater elongation during cutting and packaging might cause variation in film amount resulting in non-uniformity of API per film.

Folding endurance is a breaking strength measurement to know the flexibility of thin film which is important when considering that the films can be administered without breakage. The folding endurance is determined by folding the film repeatedly at 180° angle of the plane at the same place until it breaks. The film exhibiting folding endurance value of 300 or more is considered to have excellent flexibility.

Moisture content is vital parameters which affects different physicochemical properties of the film. In general, the moisture content of the film is determined by using several methods like Karl Fischer titration or by weighing method. Swelling properties of films are generally observed as the polymers employed for making films are hydrophilic. Swelling of the polymers is related to bioadhesion, release of the drug and polymer hydration. Surface morphology of the films is observed using light microscopy, scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Study on release rate of the drug from the film is an essential parameter as it is the rate determining step in the process of absorption of the drug. Drug release and permeation study related to bioavailability are measured by dissolution and permeation study.

1.3. Drug delivery and Bio-interfacial phenomena

Drug delivery refers to transportation of active pharmaceuticals to the body safely to achieve the required therapeutic effect. This transportation is very complex biological process and very difficult to comprehend. The membrane characteristics are not constant
because the constituents are not always homogenously arranged. Due to this complexity the exact mechanism behind biophysical interaction with drugs, biological membrane and drug delivery systems is very difficult to investigate. Several factors such as hydrophobicity, hydrophilicity, surface charge, size of the delivery system, swelling, erosion and disease conditions influence the biointerfacial drug delivery system and the bioadhesive behaviour. For efficient drug delivery through biological system sufficient information regarding bio distribution, bioaccumulation and interaction of biological membrane with drug delivery systems are essential. (Chiranjeevi, et al., 2009). Methocel E5 Premium LV based triclosan film (2.2%w/v) exhibited excellent film properties (Dinge et al., 2008). Carvedilol buccal patch has shown enhanced bioavailability and further physicochemical charactization confirmed no significant interaction between polymer and drug (Thimmasetty et al., 2008).

Recently a number of drug delivery systems are under investigation. Among these polymeric thin films are designed to stand out as a dosage form to overcome the limitations associated with existing dosage forms such as inconvenience of administration, lower bioavailability and patient non-compliance.

The current research work was carried out comprising of the following subdivisions:

(a) Several researchers have utilized Kuno equation (monoexponential process) and reported “packability” value without illustrating graphical profile to characterize the tablet compaction process. Absence of graphical profile lacks actual mechanisms of “packability” scenario. In this research, biexponential process of compression which involves the change in apparent density under tapping and pressure has been applied for the powder formulation. The change in apparent density of the biexponential process has been attempted to correlate (level A correlation) with the conventional tabletability after mechanical testing at the same applied pressure.

(b) Porosity-pressure relationship of several commonly used tablet excipients combining with a model drug has been carried out in order to obtain a better understanding of binding functionality and compressibility. Further, physicochemical characterization were attempted.
(c) Extensive literature survey revealed that the effect of plasticizer on drug crystalinity in film type drug delivery systems has not been well-defined. This subdivision of research work emphasized the influence of plasticizers on crystalline behaviour of a class II type of a model drug in the polymeric matrix. All plasticizers chosen were of hydrophilic type containing hydroxyl or aminofunctions.

(d) Amlodipine, a Ca^{2+} channel antagonist undergoes extensive first pass metabolism and exhibits low bioavailability. Bioadhesive bilayer tablet formulations containing HPMC alone and in combination with polyacrylate polymer (drug–β-cyclodextrin complex) were prepared for the improvement of permeation of amlodipine in a unidirectional way toward the buccal mucosa which is supposed to improve bioavailability. This type of work has not been reported earlier and described in this section.