CHAPTER 1

INTRODUCTION

1.1 ALLERGIC RHINITIS

Allergic rhinitis is an allergic inflammation of the nasal airways. It occurs when an allergen, such as pollen, dust, or animal dander (particles of shed skin and hair) is inhaled by an individual with a sensitized immune system. Allergic rhinitis can be seasonal or perennial. Symptoms of seasonal allergic rhinitis occur in spring, summer and/or early fall. They are usually caused by allergic sensitivity to pollens from trees, grasses or weeds, or to airborne mold spores. People with perennial allergic rhinitis experience symptoms year-round. It is generally caused by sensitivity to house dust mites, animal dander, cockroaches and/or mold spores. Underlying or hidden food allergies rarely cause perennial nasal symptoms.

IgE bound to mast cells are stimulated by allergens, causing the release of inflammatory mediators such as histamine (and other chemicals). This usually causes sneezing, itchy and watery eyes, swelling and inflammation of the nasal passages, and an increase in mucus production. Symptoms vary in severity between individuals. Very sensitive individuals can experience hives or other rashes.

These nasal allergies are estimated to affect approximately 50 million people in the United States, and its prevalence is increasing affecting as many as 30 percent of adults and up to 40 percent of children. More than 13.4 million visits to physician offices, hospital outpatient departments and emergency departments were due to allergic rhinitis (http://acaai.). In 2012, 7.5% or 17.6 million adults were diagnosed with hay fever in the past 12 months (Summary Health Statistics, 2012). In 2012, 9.0% or 6.6 million children reported hay fever in the past 12 months (Summary

Health Statistics, 2012). Worldwide, allergic rhinitis affects between 10% and 30 % of the population (WHO, 2012).

Signs and symptoms

The characteristic symptoms of allergic rhinitis are:

- Rhinorrhea (excess nasal secretion),
- Itching,
- Sneezing fits,
- Nasal congestion and obstruction

Characteristic physical findings include conjunctival swelling and erythema, eyelid swelling, lower eyelid venous stasis (rings under the eyes known as "allergic shiners"), swollen nasal turbinate's, and middle ear effusion.

There can also be behavioural signs; in order to relieve the irritation or flow of mucus, patients may wipe or rub their nose with the palm of their hand in an upward motion: an action known as the "nasal salute" or the "allergic salute". This may result in a crease running across the nose (or above each nostril if only one side of the nose is wiped at a time), commonly referred to as the "transverse nasal crease", and can lead to permanent physical deformity if repeated enough.

Classification

Allergic rhinitis may be seasonal or perennial. Seasonal allergic rhinitis occurs in particular during pollen seasons. It does not usually develop until after 6 years of age. Perennial allergic rhinitis occurs throughout the year. This type of allergic rhinitis is commonly seen in younger children.

Allergic rhinitis may also be classified as Mild-Intermittent, Moderate-Severe intermittent, Mild Persistent, and Moderate-Severe Persistent. Intermittent is when the

symptoms occur <4 days per week or <4 consecutive weeks. Persistent is when symptoms occur >4 days/week and >4 consecutive weeks.

Treatment

Antihistamine drugs can be taken orally and nasally to control symptoms such as sneezing, rhinorrhea, itching, and conjunctivitis. It is best to take oral antihistamine medication before exposure, especially for seasonal allergic rhinitis. In the case of nasal antihistamines like azelastine antihistamine nasal spray, relief from symptoms is experienced within 15 minutes allowing for a more immediate 'as-needed' approach to dosage.

Ophthalmic antihistamines (such as azelastine in eye drop form and ketotifen) are used for conjunctivitis, while intranasal forms are used mainly for sneezing, rhinorrhea and nasal pruritus.

Antihistamine drugs can have undesirable side-effects, the most notable one being drowsiness in the case of oral antihistamine tablets. First-generation antihistamine drugs such as diphenhydramine cause drowsiness, but second- and third-generation antihistamines such as cetirizine and loratadine are less likely to cause drowsiness (http://acaai.).

1.2 ORAL DISPERSIBLE TABLET (ODT)

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms (Jashanth Singh and Rajmeet Singh, 2009). Often times, people experience

inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Oro- dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. Orodispersible tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolves or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form. The advantage of mouth dissolving dosage forms are increasingly being recognized in both, industry and academics. ODTs are distinguished from conventional sublingual tablets, buccal tablets, and lozenges, which require more than a minute to dissolve in oral cavity. Although chewable tablets have been on the market for some time, they are not the same as the new ODTs. Patients for whom chewing is difficult or painful can use these new tablets easily. ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth.

DEFINITION

An orally disintegrating tablet (ODT) is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT. Their growing importance was underlined recently when European pharmacopoeia adopted the term “Orodispersible tablet” as a

tablet that to be placed in the mouth where it disperses rapidly before swallowing. According to European pharmacopoeia, the ODT should disperse/disintegrate in less than three minutes.

The **US Food and Drug Administration** Centre for Drug Evaluation and Research (CDER) defines, in the "Orange Book", an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Orodispersible tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, fast dissolving tablets, rapimelts, and porous tablets, quick dissolving etc (Chemate SZ and Chowdary KPR, 2011).

ADVANTAGES OF ODTS (Adel M *et al*., 2005**)**

- ODT can be administered to the patients who cannot swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, patients with oesophageal problems & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients and thus improves patient compliance.
- ODT is most convenient for disabled, bedridden patients, travellers and busy people, who do not always have access to water.
- Good mouth feel property of ODT helps to change the perception of medication as bitter pill particularly in pediatric patients.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- ODT opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management.
- No specific packaging required and can be packed in push through blisters. Good chemical stability as conventional oral solid dosage form.

- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.
- Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.
- No chewing needed.
- Cost effective.

IDEAL PROPERTIES OF ODTS (Jaysukh J Hirani et al., 2009**)**

- The performance of ODTs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water. Various technologies have been developed that enable ODT to perform this unique function. An ideal ODT should meet the following criteria:
- Does not require water for oral administration yet disintegrates and dissolves in oral cavity within a few seconds.
- Has sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling.
- Allow high drug loading.
- Has a pleasant mouth feel.

- Is insensitive to environmental conditions such as humidity and temperature.
- Is adaptable and amenable to existing processing and packaging machineries.
- Leave minimal or no residue in the mouth after oral administration.

THE NEED FOR DEVELOPMENT OF ODTS

The need for non-invasive delivery systems persists due to patient poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

PATIENT FACTORS (Slowson M and Slowson S, 1985; Doheny K, 1993; Chang RK *et al*., 2000; Bogner RH and Wilkosz MF, 2008)

Orally disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms. Patients who are unwilling to take solid preparation due to fear of choking
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H_2- blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their

daily dose of an atypical antipsychotic.

- A patient with persistent nausea, who may be in journey, or has little or no access to water.

EFFECTIVENES FACTOR

Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pre-gastric absorption from some formulations in those cases where drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs (Yarwood R. Zydis, 1990). Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pre-gastric segments of GIT (Pfister WR and Ghosh TK, 2005).

CHALLENGES IN FORMULATING ODTS

Palatability (Brown D, 2001; Reddy LH and Ghosh BR, 2002)

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

Mechanical strength (Chang RK et al., 2000; Aurora J & Pathak V, 2005; Hamilton EL and Luts EM, 2005)

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low

compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® b y Yamanouchi-Shaklee, and
Durasolv® by CIMA labs.

Hygroscopicity (Habib W *et al*., 2000**)**

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

Amount of drug (Brown D, 2001; Ghosh TK et al., 2005)

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Aqueous solubility (Seager H, 1998; Lies MC *et al*., 1993)

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablet (Sugihara M, 1986)

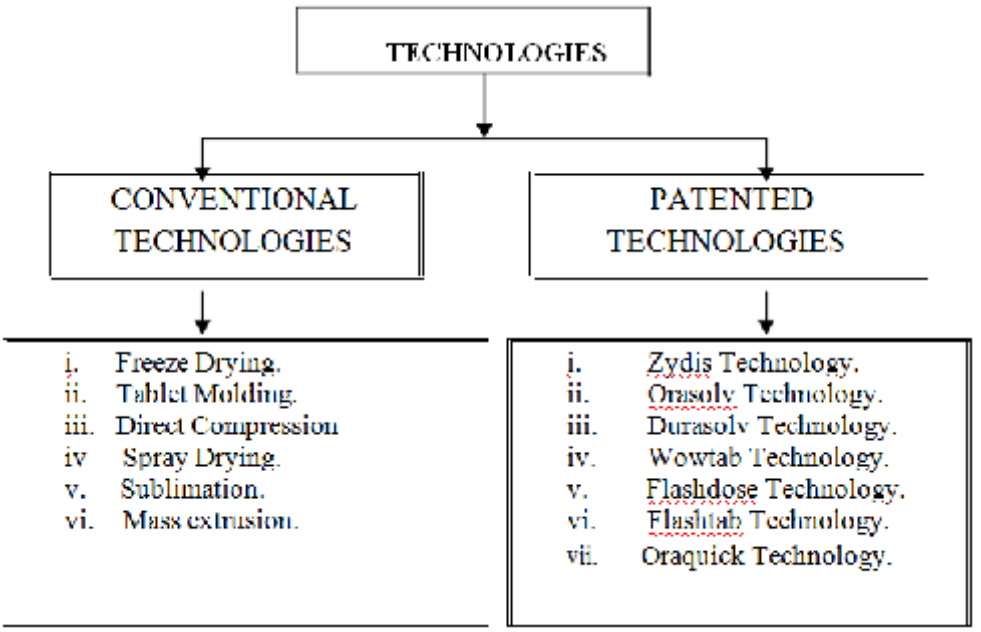
The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

SELECTION OF ODT DRUG CANDIDATES

Several factors must be considered when selecting drug candidates for delivery as ODT dosage forms. In general, an ODT is formulated as a bioequivalent line extension of an existing oral dosage form. Under this circumstance, it is assumed that the absorption of a drug molecule from the ODT occurs in the post gastric GIT segments, similar to the conventional oral dosage form. But this scenario may not always be the case. An ODT may have varying degrees of pre gastric absorption and thus, the pharmacokinetic profiles will vary (Lies MC *et al*., 1993). Therefore, the ODT will not be bioequivalent to the conventional oral dosage form. For example, ODT formulations of selegiline, apomorphine, and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form (Pfister WR and Ghosh TK, 2005; Ostrander K, 2003). It is possible that these differences may, in part, be attributed to the drug molecule, formulation, or a combination of both. If significantly higher plasma levels have been observed, pre gastric absorption leading to the avoidance of first-pass metabolism may play an important role. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT (DeRoche CC, 2005).

TECHNOLOGIES USED TO MANUFACTURE ORODISPERSIBLE TABLETS

The technologies used to manufacture orodispersible tablets can be classified as:



a) Drying (Biradar SS *et al*., 2006**)**

A process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilisation results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

In this method, moulded tablets are prepared by using water soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is moulded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Moulded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.

b) Molding (Dobetti L, 2001)

Molding process includes moistening, dissolving, or dispersing the drug with a solvent then molding the moist mixture into tablets (compression molding with lower pressure than conventional tablet compression), evaporating the solvent from drug solution or suspension at ambient pressure (no vacuum Lyophilisation), respectively.

The molded tablets formed by compression molding are dried. As the compression force applied is lower than conventional tablets, the molded tablets results in highly porous structure, which increases the disintegration and dissolution rate of the product.

c) Direct Compression (Seager H.J.,1998)

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilisation depends on single or combined action of disintegrants, water soluble excipients and effervescent agent.

d) Spray-Drying (Dong Y *et al*., 2007)

Spray drying can produce highly porous and fine powders that dissolve rapidly. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatines as supporting agents, Mannitol as bulking agent, sodium starch glycolate or croscarmellose sodium as disintegrating and an acidic material(e.g. citric acid) and / or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrate within 20 seconds when immersed in an aqueous medium.

e) Sublimation (Kizumi K *et al*., 1997**)**

The presence of highly porous structure in the tablet matrix is the key factor for rapid disintegration of ODT. Even though the conventional tablets contain highly water soluble ingredients, they often fail to disintegrate rapidly because of low porosity, to improve the porosity; volatile substances such as camphor can be used in tabletting process, which sublimates from the formed tablet.

f) Mass Extrusion (Dong Y *et al*., 2007**)**

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet.

1.4 PATENTED TECHNOLOGIES FOR ORODISPERSIBLE TABLETS

a) Zydis Technology (Shangraw R *et al*., 1980**)**

Zydis, the best known of the fast-dissolving/disintegrating tablet preparations was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A Zydis tablet is produced by lyophilizing or freeze-drying the drug in a matrix usually consisting of gelatine. The product is very lightweight and fragile, and must be dispensed in a special blister pack. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds. The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth.

b) Orasolv Technology (Shangraw R *et al*., 1980**)**

Orasolv Technology has been developed by CIMA labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent.

Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

c) Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tabletting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

d) Wowtab Technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water ". In this process, combination of low mouldability saccharides and high mouldability saccharides are used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

e) Flash Dose Technology

Flash dose technology has been patented by Fuisz. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. A flash dose tablet consists of self-binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing.

f) Flash Tab Technology

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation, and extrusion spheronization. All the processing utilized conventional tabletting technology.

e. Oraquick (Darna B *et al*., 2011**)**

This technology is patented by K.V Pharmaceuticals. It utilizes taste masking microsphere technology called as micro mask, which provides superior mouth feel, significant mechanical strength, and quick disintegration/dissolution of product (Bandari S et al., 2008). This process involves preparation of micro particles in the form of matrix that protects drug, which can be compressed with sufficient mechanical strength. Low heat of production in this process makes it appropriate for heat-sensitive drugs.

f. Nano Crystal technology

Elan's proprietary NanoCrystal technology (Nanomelt TM) can improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal particles are small particles of drug substance, typically less than 1000 nm in diameter, which are produced by milling the drug substance using a proprietary wet milling technique.

g. Pharmaburst technology

SPI Pharma, New castle, patents this technology. The Pharmaburst ODT uses a proprietary disintegrate (Pharmaburst) that is based on Mannitol blended with

conventional tabletting aids. It utilizes the co processed excipients to develop ODT, which dissolves within 30-40 s. This technology involves dry blending of drug, flavor, and lubricant followed by compression into tablets.

h. Frosta technology (Biradar SS *et al*., 2006)

Akina patents this technology. The frosta technology is based on the compression of highly plastic granules at low pressure to prepare fast melting tablets. The highly plastic granules are composed of three components: a plastic material, (Maltrin QD M580 and MaltrinM180 are maltodextrin and corn syrup solids) a water penetration enhancer (Mannogem EZ Spray) and a wet binder (sucrose, polyvinylpyrrolidone and hydroxypropyl methylcellulose). Each of the three components plays an essential role in obtaining tablets with higher strengthened faster disintegration time.

j. Advantol™ 200 (Biradar SS *et al*., 2006)

Advantol™ 200 is a directly compressible excipients system offering "Soft-Melt" functionality and specially formulated for nutraceutical applications. SPI Pharma's Advantol platform uses proprietary co-processing technology. Advantol requires no special manufacturing equipment or tooling. Advantol formulations utilize a standard rotary tablet press with standard tooling under normal tabletting temperature and humidity conditions to make robust "soft-melt" tablets.

k. Advatab (Biradar SS *et al*., 2006)

Advatab tablets disintegrate rapidly in less than 30 seconds. These tablets are prepared using polymer-coated drug particles that are uniformly dispersed in an ultra-fine, low-water content, rapidly disintegrating matrix with superior organoleptic properties. Advatab tablets are compressed using a proprietary,

patented, external lubrication system in which the lubricant is applied only to the tablet surface, resulting in robust tablets that are hard and less friable and can be packaged in bottles or blister.

l. Quicksolv technology

This technology is patented by Janssen Pharmaceuticals. It uses two solvents in formulating a matrix which disintegrates instantaneously. Methodology includes dissolving medium components in water and the solution or suspension is frozen. Then dry the matrix by removing water using an excess of alcohol (solvent extraction). Thus the product formed has uniform porosity and adequate strength for handling.

m. Ziplet technology (Debetti L, 1999**)**

In ziplet technology water insoluble drugs or drugs as coated micro particles are used. The addition of a suitable amount of water-insoluble inorganic excipients combined with Disintegrants imparted an excellent physical conflict to the oral dissolving tablet (ODT) and the simultaneously maintained optimal disintegration.

The use of water-insoluble inorganic excipients offer better enhancement of disintegration in comparison to the most commonly used water soluble sugars or salts. Tablets primarily of water soluble components often tend to dissolve rather than disintegrate and concentrated viscous solution is formed which reduces the rate of water diffusion into the tablet core.

EXCIPIENTS USED IN PREPARATION OF ODT

The general excipients used in manufacturing of ODTs are various grades of

- **Diluents** like Lactose, sugar based excipients, Micro crystalline cellulose, Xylitol and the combination of these excipients
- **Superdisintegrents** like crospovidone, sodium starch glycolate, L- Hydroxypropyl cellulose, Kyron T-314 etc.
- **Artificial sweeteners** like sucralose, aspartame, saccharine sodium etc.
- General **binders** and **lubricants.**

Among all the excipients used in the preparation of ODTs, the key role playing excipients are Diluents (as they improve the mouth feel, improves dissolution and sometimes mask taste of drug) and super disintegrants (as the tablet need to disintegrate in the mouth cavity within seconds). Among all the diluents, sugar based excipients are mostly preferable as the tablet is going to disintegrate in the mouth cavity, hence requires good mouth feel for compliance.

SUGAR BASED EXCIPIENTS (Fuisz RC; Cherkuri SR,1996; Myers GL *et al*., 1996; Myers GL *et al*., 1999; Misra TK *et al*., 1999**)**

The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel.

Mizumoto *et al*., 1996 have classified sugar-based excipients into two types on the basis of molding and dissolution rate.

Type 1 saccharides (lactose and mannitol) exhibit low mould ability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high mould ability and low

dissolution rate.

Mouldability is defined as the capacity of the compound to be compressed/ molded. The mouldability of type 1 saccharide can be improved by granulating it with type 2 saccharides. WOWTAB technology used in Benadryl fast melt tablets uses this technique (Joshi AA and Xavier D, 2004).

Disintegrants are the excipients used in a tablet formulation to promote disintegration of the tablet and thereby make the drug available for dissolution. The disintegrants usually act by various mechanisms to disintegrate the tablet in a medium.

MECHANISM OF SUPERDISINTEGRANTS

There are four major mechanisms for tablets disintegration as follows

1. Swelling (Sahu *et al*.,2012)

The most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

Ex: croscarmellose sodium, sodium starch glycolate, crospovidone, alginic acid etc,.

2. Porosity and capillary action (Wicking) (Sahu *et al*.,2012)

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon

hydrophilicity of the drug/ excipients and on tabletting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.Ex: calcium silicate, croscarmellose sodium, crospovidone.

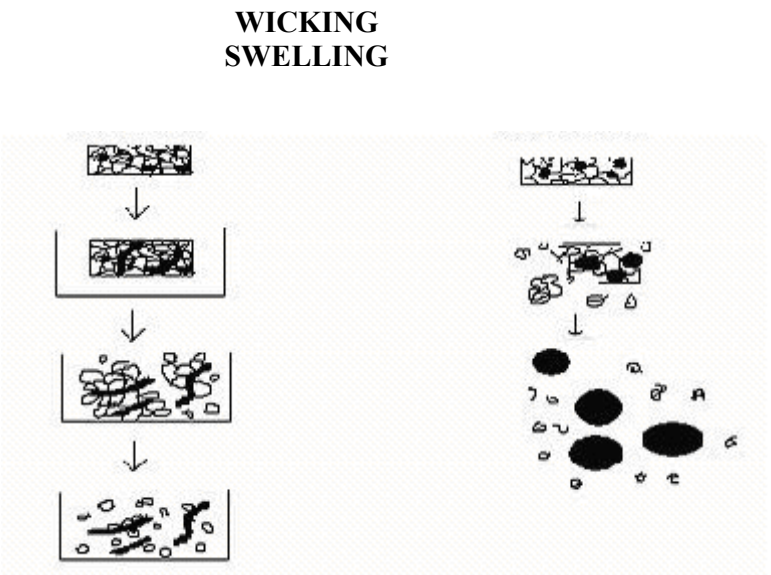


Fig 1: Wicking and Swelling Action of Superdisintegrents.

3. Due to disintegrating particle/particle repulsive forces (secondary to wicking) (Sahu *et al*.,2012)

Another mechanism of disintegration attempts to explain the swelling of tablet made with non-swellable disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

4. Due to deformation (Sahu *et al*.,2012)

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied. Ex: Starch.

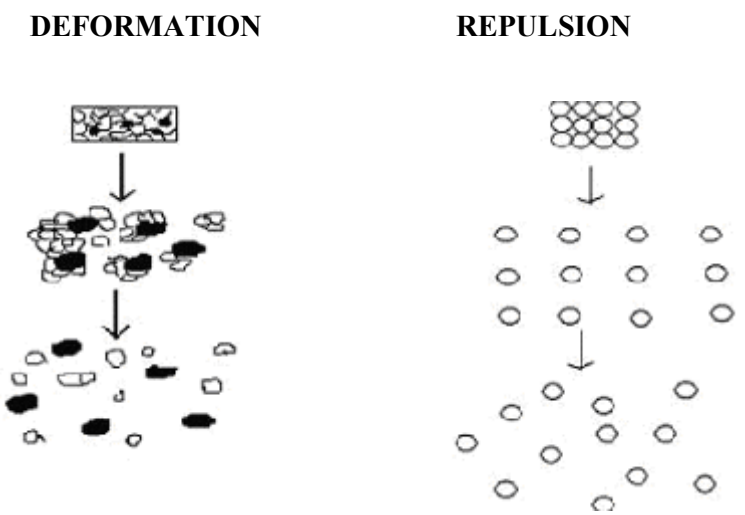


Fig 2: Deformation and Repulsion action of Superdisintegrents

5. Heat of wetting (air expansion)

When disintegrates through exothermic properties gets wetted, Localized stress is produced due to capillary air expansion, this helps in breakdown of tablet.

6. Due to release of gases (Sahu *et al*.,2012)

Carbon dioxide released within tablets continuously wetting Due to contact between bicarbonate and carbonate with citric Acid or tartaric acid. The tablet disintegrates due to generation of pressure inside the tablet. As these disintegrates are highly Sensitive to small changes in humidity level and temperature, Strict control of

environment is required during manufacturing of the tablets. The effervescent blend is either added Immediately prior to compression or can be added into Separate fraction of formulation.

7. By enzymatic reaction (Sahu *et al*.,2012)

These enzymes destroy the binding action of binder and helps In disintegration. Actually due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous Increase in the volume of granules to promote disintegration.

METHOD OF ADDITION OF DISINTEGRANTS

Superdisintegrents are generally used at low level in the solid dosage form, typically 1- 10% by weight of the dosage unit. Examples of Superdisintegrents are croscarmellose sodium, crospovidone, sodium starch glycolate which represent example of a cross linked cellulose, cross linked polymer and a cross linked starch respectively.

The requirement placed on the tablet disintegration should be clearly defined.

Selection of superdisintegrants (Pahwa R. and Gupta N,2011)

The ideal disintegrant has

- Poor solubility.
- Poor gel formation.
- Good hydration capacity.
- Good molding and flow properties.
- No tendency to form complexes with the complexes with the drugs.

Disintegrants are essentially added to the tablet granulation for causing the compressed tablet to break or disintegrant when placed in the aqueous environment. There are three methods of incorporating disintegrating agents into the tablet:

- Internal addition (Intra-granular).
- External addition (Extra-granular).
- Partly Internal and External.

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are used, part of disintegrant can be added internally and part externally. This provides immediate disruption of the tablet into previously compressed granules to the original powder particles. The two step method usually produces better and more complete disintegration than the usual method of adding disintegrant to the granulation surface only.

1.3 CHEWABLE TABLETS

Chewable tablets are the tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing.

Successful tablet formulation development involves the careful selection of ingredients in order to manufacture a robust solid dosage form. Choosing the appropriate excipient to perform a specific function in a tablet formulation, such as disintegration or lubrication can be critical to achieving acceptable manufacturing performance. Sweeteners, both naturally occurring and synthetic, are one type of functional excipient commonly used in chewable tablet formulations to mask unpleasant tastes and facilitate pediatric dosing (Mullarney MP *et al*., 2003).

Ideally chewable formulations should have smooth texture upon disintegration,

pleasant taste and no bitter or unpleasant after taste. Upon chewing, they are broken down in the mouth and release their ingredients in the process and therefore, do not have much lag time as required for the disintegration of tablets before absorption from stomach (Biradar SS *et al*., 2006).

Loratadine is a piperdine derivative and is a long acting selective peripheral H1 antagonist which lacks CNS depressant effects used in the treatment of allergic skin disorder, specially atopic dermatitis and urticaria, allergic rhinitis, acute coryza, ocular allergies at the dose of 10 mg once a day in adult and 5 mg in 2-12 years children (Kay GG and Harris AG, 1999).

Children find it difficult to swallow the normal tablets of Loratadine. So in order to avoid this problem, chewable tablets are most preferable. Hence it was decided to formulate Loratadine chewable tablet to improve the compliance in children. Additionally, chewable tablets facilitate more rapid release and hence more rapid absorption of active ingredients and provide quick onset of action (Jagdale S et al., 2010).

Chewable tablets are often employed when active ingredient is intended to act in a localised manner rather than systemically (European Patent Application, 1990).

Chewable tablet is one that is palatable and may be chewed and ingested with little or no water (Gary ML and Patrick M, 2008).

Manufacturing of chewable tablet is generally done using either a wet granulation process or direct compression. Increasingly, micronized and submicron forms of therapeutically and/or physiologically active substances are being incorporated into tablet formulations to take advantage of the enhanced absorption characteristics of these forms (Chavkin *et al*., 1998 and Kashid *et al*., 2009).

They are also used in the administration of antacids and carminatives (to remove excessive amount of gas in the stomach and intestines) (Kanig JL and Rudnic EM). Mannitol is widely used as an excipient in chewable tablets for its non hygroscopic nature for moisture sensitive drugs (Bankar UV and Sharma MM, 1992).

Chewable tablet formulations, particularly those containing pharmaceutically active agents, present issues of organoleptic characteristics of odor, taste, appearance and mouth feel. The formula ingredients and manufacturing process both play a role in obtaining the desired organoleptic properties (Mithal BM, 1997 and Singhavi I& Bhatia N, 2006).

Advantages of chewable tablets (Drug Dosage Form II a & b**)**

1. Provide quick and complete disintegration of the tablet and thus obtain a rapid drug effect after swallowing and dissolution.
2. Easy administration, especially for children and elderly people.
3. Could be administered when water is not available.

The main objective of present study is to formulate and evaluate Loratadine chewable tablet dosage form with different excipients and their impact on the formulations and there by develop the robust formula with better patient compliance and drug release. The manufacturing process used was wet granulation process.

4. Provide quick and complete disintegration of the tablet and thus obtain a rapid drug effect after swallowing and dissolution.
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The main objective of present study is to formulate and evaluate Loratadine chewable tablet dosage form with different excipients and their impact on the formulations and there by develop the robust formula with better patient compliance and drug release. The manufacturing process used was wet granulation process.

1.4 BILAYER TABLETS

Solid oral dosage forms are the preferred route for many drugs and are still the most widely used formulations for new and existing complex-configuration dosage forms such as controlled release (Conte et al., 1993; Nangia et al., 1995; Chidambaram et al., 1998; Abdul and Poddar, 2004), osmotic pumps (Wong et al., 2002), and compression-coated tablets (i.e., tablet within a tablet) (Shivanand and Sprockel, 1998; Zerbe and Krumme, 2002; Ozeki et al., 2004). The controlled-drug delivery systems typically require more demanding mechanical testing, characterization, and monitoring techniques with faster response times than those possible with traditional measurement approaches (Mashadi and Newton, 1987; York et al., 1990; Hancock et al., 2000). In recent years, pharmaceutical drug product manufacturers have oriented their product development activities to fixed dose combinations (FDCs) for treatments like type 2 diabetes, hypertension, pain and HIV/AIDS to mention a few. Several different approaches are employed to deliver the FDC products to the patients such as multilayer tablets (Benkerrour et al., 2004), compression coating, active coating (Desai et al., 2013; Charlton and Nicholson, 2010),bilayer floating tablet (Ranade et al., 2012; Lalita et al., 2013) and buccal/mucoadhesive delivery systems (Park and Munday, 2002; Yedurkar et al., 2012). Among these approaches, the multilayer tablets drug delivery is gaining popularity and particularly the bilayer technology has attracted manufacturers' attention for the development of products for life cycle management (LCM). If

bilayer tablets are inadequately manufactured, the tablets could split apart leading to a very critical defect since it could potentially result in a patient not receiving one of the intended drug component. The residual stress distribution in the tablet is suspected to be a major cause of the resultant tablet inhomogeneity causing the tablet to fracture and split apart (Inman et al., 2007). The fracture of multilayered tablets is often the result of an interfacial crack driven by residual stresses in the tablet and propagating a finite distance within the tablet. This leads to capping and lamination, which may not always be immediately apparent after compaction (Hiestand et al., 1977; Abdul and Poddar, 2004; Inman et al., 2007). It is known that occurrence of the fracture/crack at the interface causes a reduction in the overall elastic stiffness (Young's modulus) and layered tablets become fragile and develop a tendency to fail. Therefore, while the therapeutic (chemical/ pharmaceutical) functions of multilayered tablets are crucial, they need to have sufficient mechanical strength and ruggedness to survive normal processing, handling, packaging, and shipping stresses. Understanding what influences the stress state and mechanical properties of a multilayered tablet and developing specialized techniques for measuring those properties will assist in the understanding of how, and why, defects such as capping, delamination, and cracking occur. According to Wu and Seville (2009), understanding and predicting the mechanical strength of bilayer tablets is of commercial significance since bilayer tablet failures (delamination) due to weak mechanical strength can lead to enormous financial loses. This review mainly focuses on the advantages and the main challenges associated with bilayer compaction technology including impact of material mechanical properties, characterization techniques for interface between layers, compression parameters, as well as features offered by commercial bilayer compression machines.

Key advantages of bilayer tablets

Several advantages of the bilayer technology were reported in the literature. The main ones are listed below.

• Two chemically incompatible active pharmaceutical ingredients (APIs) can be formulated in a bilayer configuration. In some cases, depending on the magnitude of the incompatibility between the two APIs, an intermediate layer needs to be added to provide physical separation between the two layers (Li et al., 1995; Benkerrour et al., 2004; Efentakis and Peponaki, 2008; Vaithiyalingam and Sayeed, 2010).

• Two APIs or the same API with different release profiles can be delivered as a single bilayer tablet (e.g. drugs with an extended release and an immediate release profiles) (Zerbe and Krumme, 2002; Nirmal et al., 2008; Shiyani et al., 2008).

• Combining two or more APIs in a single bilayer tablet reduces the dosing unit burden thereby improving patient compliance (La Force et al., 2008; Charman and Charman, 2002; Bangalore et al., 2007).

• As most bilayer tablets are developed as part of a Life Cycle Management program, the bilayer technology provides possibility of prolonging patent life of a drug product (Veroma and Garg, 2001; Abebe et al., 2010).

• Increased efficacy of the active components due to their synergistic effect (Serebruany et al., 2004; Benkerrour et al., 2004).

Challenges related to bilayer

In spite of the aforementioned technology advantages provided by the bilayer technology, several issues associated with the mechanisms and compression of bilayer tablets have been reported in the literature in recent years. The formulators and process scientists need to overcome the challenges to deliver a robust bilayer

tablet and manufacturing process. Some of the key challenges are:

• Inaccurate individual layer weight control (Charman and Charman, 2002).

• Cross contamination between the layers (Hiestand et al., 1977; Karehill et al., 1990; Poon and Bhushan, 1995; Inman et al., 2007; Akseli et al., 2013).

• Elastic modulus mismatch between the adjacent layers. High elastic modulus ratio between adjacent layers could cause insufficient layer bonding and relatively low interfacial strength (Akseli et al., 2010).

• Reduced production yield and the propensity to delaminate (distinct layers separation) at the non-planer interface between the adjacent compacted layers (Abdul and Poddar, 2004).

• Disproportionate layers weight ratio coupled with low drug load (Martin et al., 2012).

• Insufficient bilayer tablet hardness (Abdul and Poddar, 2004).

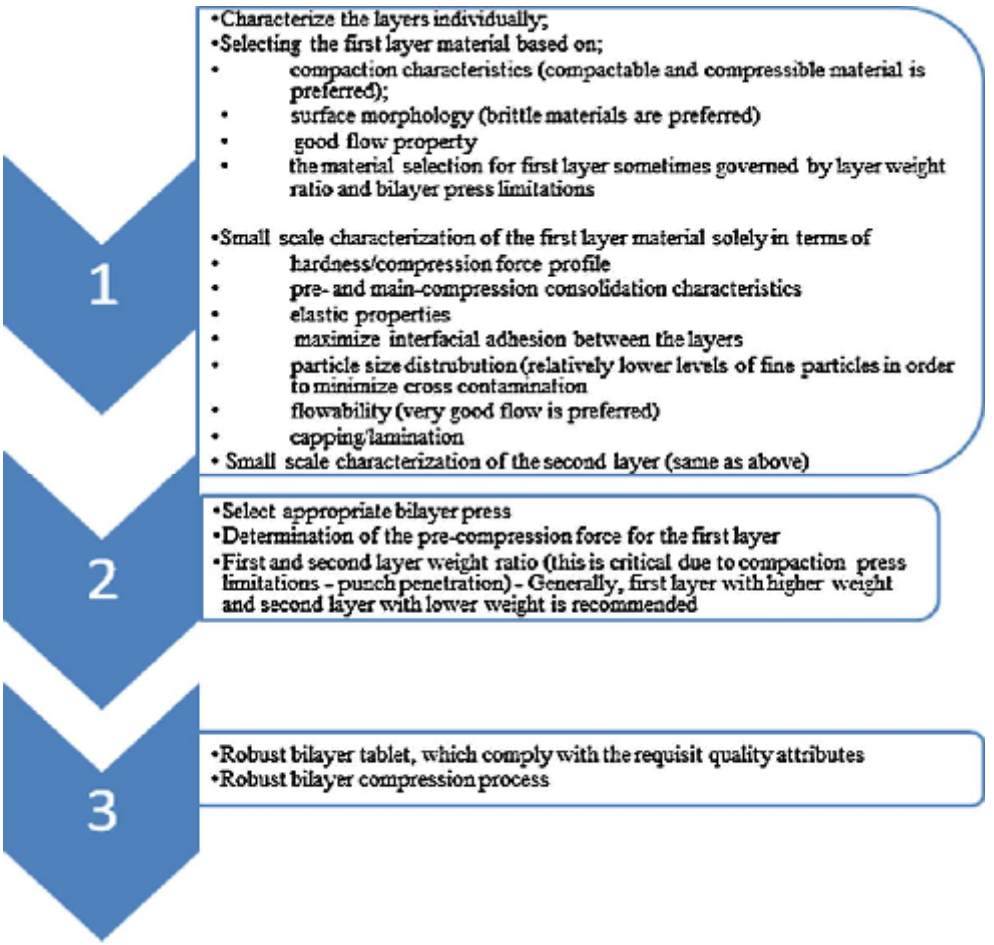
• Long term physical and chemical integrity throughout shelf life.

• Large tablet size, which can impact the swallowability of the unit dose.

• Impact of high temperature and humidity on layer adhesion upon storage (Kottala et al., 2012a).

Overcoming all these challenges requires a focused effort toward addressing the following areas related to material properties and bilayer processing parameters: (i) determination of mechanical properties of each layer, (ii) maximization of interfacial adhesion between the layers, (iii) optimization of the first layer compression force, (iv) quantification/ understanding of factors contributing to delamination, (v) assessment of the impact of layer sequence and layer weight ratio, (vi) development of techniques for small scale material characterization tools that can be applied during bilayer tablet design, and (vii)

selection of appropriate bilayer tablet press alternatives with consistent weight control delivering system.



1. Material properties

Understanding the fundamental material properties (API and excipients) like brittleness (lactose, di-calcium phosphate), plasticity (microcrystalline cellulose) and visco-elasticity (pre-gelatinized starch) is key in the successful development of bilayer tablets. Depending on the drug load in the formulation, either the API property and/or the excipients property will predominantly impact the compaction propertyoftheformulation. Recently, Akseli et al. (2013) suggested that when the first layer was compressed to a low porosity, the bonding with the second layer became difficult and it was impossible to produce intact

bilayer tablets composed of microcrystalline cellulose and pregelatinized starch. This implies that the strength (σ) of the layer was greater than the strength of the interface ($\sigma_{layer} > \sigma_{interface}$). For bilayer tablets (MCC in the first and second layers and tablet diameter of 10 mm) compacted with initial forces of 2 kN and 4 kN, the authors observed that once the second layer compression force reached 18 kN, tablets failed in the first layer rather than in the interface($\sigma_{layer} < \sigma_{interface}$ $_{layer}$), indicating a change in the mode of failure from the inter-layer ($\sigma_{interface}$) to the intra-layer (σ_{layer}) mode.This is in agreement with the findings reported by Lacombe (2006). On the other hand, bilayer tablets composed of MCC in the first layer/starch in the second layer, it was impossible to form intact tablets with a final compression force of 6 kN irrespective of the first layer compression forces. These tablets were split apart along the interface either during the decompression-ejection phase or during post-compaction handling due to weak bonding between the adjacent layers. The outcome of the study helped to establish four different fracture patterns namely: clear-layer break, cap-shape break, half-half break and interface break. This demonstrates how material properties strongly impact the strength of the interface and the individual layers, and also the mode of breakage.

2. Compression

As forces reported in the literature (Li et al., 1995; Inman et al., 2007), compression forces applied on the first layer and the second layer significantly impact the interfacial strength and the adhesion between the adjacent layers thereby contributing to the mechanical integrity of the resultant bilayer tablet. To address this major concern, the compression force requires very close attention. The delamination of bilayer tablets is due to the development of various

mechanical stresses during compression and particularly during the unloading phase and tablet ejection (Anuar and Briscoe, 2010). Podczeck and Al-Muti (2010) reported that if the material forming the first layer of a bilayer tablet was more elastic, the tension introduced into the system weakened the strength of the bilayer tablets. It has been revealed that the way in which failure of a rectangular beam (bilayer tablet) crossed the interface between different layers was an important factor in determining the tensile strength of bilayer tablets (Podczeck et al., 2006). The evaluation of Li et al. (1995) demonstrated that the compression of the first layer was the most critical factor, which affected layer adhesion. The extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity. It was demonstrated that an increase in the punch velocity between 50 and 500 mm/s decreased the porosity reduction on individual layers (Yang et al., 1997).

3. Lubricant

Miller and York (1988) remarked that increased lubricity of a powder blend will reduce the friction between the powder particles that contact with each other or with dies and punches during compression because the lubricant will be distributed uniformly throughout the blend and coat the surface of the particles. In a bilayer configuration, a greater interfacial interaction between the layers can be achieved with low lubricant level for the first layer (Dietrich et al., 2000). The impact of lubricant level when tested (0.25%, 0.5% and 0.75%, w/w magnesium stearate) on tablet strength is more pronounced for plastic materials compared to brittle material (Tye et al., 2005). A study conducted by Kottala et al. (2012a) quantified that the interfacial strength decreased with the increase of magnesium stearate concentration. The tablet surface smoothness increases as the level of lubricant

(magnesium stearate) is increased thereby impacting the interfacial interaction between the first and second layers (Sugisawaa et al., 2009). However, the level of lubricant needed for avoiding picking and sticking of the first layer mainly due to the relatively low compression force must be assessed as part of the formulation and process development.

4. Layer ratio and layer sequence

There are a very limited number of publications on the impact of layer ratio and layer sequence in a bilayer configuration on the mechanical strength and other quality attributes of bilayer tablets(Akseli et al., 2013; Kottala et al., 2013). In general, it is a common practice to have a 1:1 or 1:2 weight ratio between the two layers. In most cases, a layer ratio of 1:3, 1:4 can be encountered and even sometimes a disproportionate ratio of up to 1:6 can be evaluated during development. It is more challenging to maintain a consistent

second layer weight when the first layer weight is large as compared to the second layer weight (for example, ratio of 1:5 or 1:6). In such circumstances, it is preferred to compress the smaller layer weight in the first layer. However, due to mechanical limitations, the features of the current commercially available bilayer presses do not offer the possibility of compressing the smaller weight in the first layer. Therefore, the formulators have no option than placing the material with a larger weight in the first layer with all its associated challenges (Abebe et al., 2013). In such circumstances, Martin et al. (2012) reported that the upper punch penetration depth during the first layer compression force and during the second layer compression force impacted the potency of the second layer API. It was argued that a deeper upper punch penetration into the die might minimize any sort of splashing out of the second layer material from the die during

compression thereby providing potency values close to 100% of label claim. The impact of layer weight ratio on the mechanical strength of the bilayer tablets, which were prepared with MCC and lactose at ratios of 1:3, 1:1 and 3:1 was investigated. There was no significant impact on the breaking force of the bilayer tablets for the materials and ratio ranges studied (Kottala *et al*., 2013).

5. Environmental conditions

The effect of moisture on the strength of bilayer tablets was studied by few authors. Compacts made from hygroscopic materials will respond to the relative humidity of the surrounding air by absorbing/desorbing of moisture into/out of their pore structure (Podczeck, 2012). In addition, if the compacts have been made from, for example, starches, microcrystalline cellulose, crospovidone, hydroxypropyl methylcellulose, polyvinylpyrrolidone, sodium

starch glycolate, and colloidal silicon dioxide, moisture can also penetrate the bulk of the particles of these materials. The uptake of moisture into the porous compacts and/or particles leads to layer expansion and to changes in the Young's modulus of elasticity. Any change in layer dimensions will weaken the interface between the layers and might hence contribute to time-dependent delamination (Jones, 1999).

6. Layer weight control

The materials particle size distribution, flow property and the ability of the bilayer press to accurately control the layer weight are very critical in assuring acceptable content uniformity of the APIs composing the bilayer tablets. Each instrumented bilayer press from different vendors has its own weight control mechanism. The available development and commercial presses offer the possibility of monitoring the first layer weight and the second bilayer weight. To

make situations more complex, no commercially available bilayer press is equipped with a device to sample separately the second layer weight. In general, a minimal precompression force is applied on the first layer, which makes sampling more challenging as the tablets do not come of the press solid enough to weigh. Bilayer presses (Kilian, Fette and Korsch) are equipped with a sampling device for first layer compact, which allow applying an additional compression force on the first layer material and thereby hardening the compact and rendering it more suitable for weight check.

7. Bilayer tablet characterization

The bilayer tablet formulations used for each individual layer should be compressible (i.e., the ability of a material to undergo a reduction in volume as a result of an applied pressure) and compactable (i.e., the ability of a powdered material to be transformed into tablets with strength during densification) on their own, that is, they should show satisfactory reduction in volume and form mechanically strong and coherent solid bodies. From this point of view, the interface between the layers should weld together during compaction and strong adhesion forces should hold the layers together after tablet ejection. However, this is not always the case, and as compressibility and compactability of the individual layers should not be the cause for delamination, other physical mechanisms need to be identified that can explain the problems with delamination. In the studies published by Karehill et al. (1990), Inman et al. (2007) and Akseli et al. (2013), it was reported that the compression force used to form the first tablet layer should be kept at a minimum to provide sufficient surface roughness for nesting and particle interlocking between layers to occur. Due to the increase in surface roughness, there is a larger contact area between

the layers, which enhances interlayer adhesion. Some benefits of bilayer tablet characterization in early formulation development are (i) quantitatively determine the interfacial strength in bilayer tablets, (ii) detect unusual or extreme properties of compacted layers, (iii) ensure lot-to-lot consistency of the resultant tablets, (iv) rationale strategy to guide formulation development and for the selection of compatible product formulations and manufacturing processes, (v) explain material failure mechanisms during tablet manufacturing, (vi) understand the effect of the factors specific to tableting equipment (e.g., speed of operation, applied forces, etc.), (vii) reduction in energy consumption by minimization of faulty tablet production, and (viii) environmental issues and concerns related to the management of waste materials.