Tablet direct compression methods

Tablets are solid dosage forms usually prepared with the aid of suitable pharmaceutical excipients. The excipients can include binders, glidants (flow aids) and lubricants to ensure efficient tableting; disintegrants to promote tablet break-up in the digestive tract; sweeteners or flavours to enhance taste; and pigments to make the tablets visually attractive. They may vary in size, shape, weight, hardness, thickness, disintegration, and dissolution characteristics and in other aspects, depending on their intended use and method of manufacture. Most tablets are used in the oral administration of drugs. Many of this are prepared with colorants and coatings of various types. Other tablets, such as those administered sublingually, buccally, or vaginally, are prepared to have features most applicable to their particular route of administration. Tablets are prepared primarily by compression, with a limited number prepared by molding. Compressed tablets are manufactured with tablet machines capable of exerting great pressure in compacting. Their shape and dimensions are determined by use of various shaped punches and dies. (Allen, Ansel and Popovich (2004)).

In the tablet-pressing process, it is important that all ingredients be fairly dry, powdered or granular, somewhat uniform in particle size, and freely flowing. Mixed particle sized powders can segregate during manufacturing operations, which can result in tablets with poor drug or active pharmaceutical ingredient (API) content uniformity. Content uniformity ensures that the same API dose is delivered with each tablet.

In early formulation studies, as a promising compound is characterized for biologic activity, it is also evaluated with regard to chemical and physical properties that have a bearing on its ultimate and successful formulation into

a stable and effective pharmaceutical product. This is the area of responsibility of pharmaceutical scientists and formulation pharmacists trained in pharmaceutics. When sufficient information is gleaned on the compound’s physical and chemical properties, initial formulation of the dosage form are redeveloped for use in human clinical trials. During the course of the clinical trials, the proposed product is developed further, from initial formulation to final formulation and from pilot plant (or small-scale production) to scale-up, in preparation for large-scale manufacturing.

The dose of the drug may be described as an amount that is enough but not too much; the idea is to achieve the drug’s optimum therapeutic effect with safety but at the lowest possible dose. The effective dose of a drug may be different for different patients. In a normal distribution sample, a drug’s dose will provide what might be called an average effect in most individuals. However, in a portion of the population the drug will produce little effect, and in another portion the drug will produce an effect greater than average. The amount of drug that will produce the desired effect in most adult patients is considered the drug’s usual adult dose and the likely starting dose for a patient. From this initial dose the physician may, if necessary, increase or decrease subsequent doses to meet the particular requirements of the patient. Certain drugs may produce more than one effect, depending on the dose.

Drug doses vary greatly between drug substances; some drugs have small doses, other drugs have relatively large doses. The dose of the drug is based on its biochemical and pharmacologic activity, its physical and chemical properties, the dosage form used, the route of administration, and various

patient factors. The dose of a drug for a particular patient may be determined in part on the basis of the patient’s age, weight, body surface area, general physical health, liver and kidney function (for drug metabolism and elimination), and the severity of the illness being treated. General dosing information for drug substances is provided in the monographs in the British National Formulary (BNF) as well as in the package inserts that accompany manufacturers’ pharmaceutical products. Again, these sources provide the prescriber and pharmacists with guidelines of usual dosage and usual dosage range. Optimally, appropriate drug dosage should resulting blood serum drug concentrations that are above the MEC and below the MTC for the period of time that drug effects are desired. For certain drugs, a larger than usual initial dose may be required to achieve the desired blood drug level. (Stoklosa and Ansel, 1996)

Active ingredients can be separated into two categories: low-dose and high-dose drugs. It should be technically possible to manufacture almost all drugs of low doses (less than 50 mg) by the direct compression process with a proper choice of excipients and tablet equipment. The term “ direct compression” is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required. The problems encountered in direct compression of low-dose drugs centre around uniform distribution of the drug (blending) and possible unblending during the compression stage.

Steps of Direct Compression

Source: http://inferenceforqbd. com/Solutions/Pharmaceutical%20R+D. aspx

Some granular chemicals, like potassium chloride, possess free-flowing and cohesive properties that enable them to be compressed directly in a tablet machine without need of granulation. For chemicals lacking this quality, special pharmaceutical excipients may be used to impart the necessary qualities for production of tablets by direct compression. These excipients include fillers, such as spray-dried lactose, microcrystals of alpha-monohydrate lactose, sucrose-invert sugar-corn starch mixtures, microcrystalline cellulose, crystalline maltose, and dicalcium phosphate; disintegrating agents, such as direct compression starch, sodium carboxymethyl starch, cross-linked carboxymethylcellulose fibers, and cross-linked polyvinylpyrrolidone; lubricants, such as magnesium stearate and talc; and glidants, such as fumed silicon dioxide. The capping, splitting, or laminating of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tableting is released, resulting in splits or layers in the tablets. Forced or induced feeders can reduce air entrapment, making the fill powder more dense and amenable to compaction. Capping also may be caused by punches that are not immaculately clean and perfectly smooth or by a granulation with too much fines, or fine powder. Fine powder, which results when a dried granulation is sized, is generally 10 to 20% of the weight of the granulation. Some fine powder is desired to fill the die cavity properly. However, an excess can lead to tablet softness and capping. Tablets that have aged or been stored improperly also may exhibit splitting or other physical deformations.

In low dose formulation, advances in pharmaceutical research have resulted in the development of high potency active ingredients, which can be difficult to formulate into capsules or tablets. The use of Starch 1500HYPERLINK “ http://www. colorcon. com/products/core-excipients/immediate-release/starch-1500″®HYPERLINK “ http://www. colorcon. com/products/core-excipients/immediate-release/starch-1500” partially pregelatinized maize starch as an active-premix in low dose formulations can provide consistent drug uniformity, which allows manufacturing by a direct compression process. Since many low dose medications are manufactured by a wet granulation method to assure each tablet contains the proper amount of active, switching to a direct compression process can result in substantial savings in total process time and cost.

Comparison of wet granulation and direct compression methods

Source: http://www. atacamalabs. com/technology_specialty

Spray-dried lactose is the earliest and is still one of the most widely-used direct compression fillers. It is one of the few such excipients available from more than a single supplier. In spite of many early problems, this material revolutionized tableting technology. Coarse and regular grade sieved crystalline fractions of a-lactose monohydrate have very good flow properties but lack compressibility. However spray drying produces an agglomerated product that is more fluid and compressible than regular lactose. In the production of spray-dried lactose, lactose is first placed in an aqueous solution which is treated to remove impurities. Partial crystallization is then

allowed to occur before spray-drying the slurry. As a result the final product contains a mixture of large a-monohydrate crystals and spherical aggregates of smaller crystals held together by glass or amorphous material. The fluidity of spray-dried lactose results from the large particle size and intermixing of spherical aggregates. The compressibility is due to the nature of the aggregates and the percentage of amorphous material present and the resulting plastic flow, which occurs under compaction pressure.

The problem of compressibility of spray-dried lactose is still real and troublesome. The compressibility of spray-dried lactose is borderline, and furthermore, it has relatively poor dilution potential. Spray-dried lactose is an effective direct compression filler when it makes up the major portion of the tablet (more than 80%), but it is not effective in diluting high-dose drugs whose crystalline nature is, in and of itself, not compressible. Furthermore, spray-dried lactose does not lend itself to reworking because it loses compressibility upon initial compaction. (Lieberman, Lachman and Schwartz).

For the binders, there are many excipients that can be used. these include hydroxypropylcellulose (HPC), methylcellulose (MC), povidone (PVP), hydroxypropylmethylcellulose (HPMC), and starches and their derivatives, such as pregelatinized and granulated starches. These polymers differ in their physico-chemical, mechanical and morphological characteristics. For direct compression, studies suggest highly compactable, plastic, fine particle size binders facilitate compression of drugs at relatively low filler-to-drug ratios, therefore representing ideal properties for tablet binders (Drug Dev Ind Pharm. 1999; 25: 1129-35) (Drug Dev Ind Pharm. 2001; 27: 181-924).

Tablet manufacturing by direct compression has increased steadily over the years. It offers advantages over the other manufacturing processes for tablets, such as wet granulation and provides high efficiency (Zhang et al., 2003). As direct compression is more economic, reducing the cycle time and straight forward in terms of good manufacturing practice requirements.

Amongst the techniques used to prepare tablets, direct compression is the most advanced technology. It involves only blending and compression. Thus offering advantage particularly in terms of speedy production. Because it requires fewer unit operations, less machinery, reduced number of personnel and considerably less processing time along with increased product stability.

Drugs characterized by high-dose, high bulk volume, poor compactibility, and poor fluidity (flow properties) do not lend themselves to direct compression. A typical sample would be paracetamol, an analgesic. The API of which is not easily compressed, then it require usually restricted to about 30% of direct compression formula hence tablet will costly and difficult to swallow. While it is possible to densify some drugs or formulations by preprocessing, there is some question as to whether the final tableting process could then be called direct compression.

Paracetamol is high dose at 500 mg, is highly elastic and requires tastemasking. The taste-masking system to use is important for the active ingredient. If a finished dosage form has great taste, the consumer may prefer your tablet to another tablet solely based upon taste. If the product has an unpleasant taste, the consumer may discount speed of delivery and

prefer better tasting slower tablets. The taste-masked API needs to survive the tabletting operation.

It is inherently a poor compressible drug and high dose formulation can show capping and lamination. This can be attributed to the elastic recovery and brittle nature of the drug. Good tablet hardness (17kP), friability (30%) and elimination of capping and lamination were achieved with 7% HPC EXF binder level in the IR granulation and employing a pre-compression force of 3kN in addition to a main compression force of 25kN.(www. aqualon. com). Magnesium stearate dihydrate (MgSt-D) is a more effective lubricant for a high dose product containing 90+% COMPAP™ L at a high tableting speed.

CONCLUSION

As shown, there is a big difference in the formulation of low dose and high dose tablet. For the low dose tablet, an example is digoxin which is a cardiotonic, it is manufactured under direct compression since the powder mixture of the active pharmaceutical ingredient (API) is compressed directly with its excipients. Low dose means having a small amount of API, since there is a small amount of it, direct compression is the best possible way because when compounding a tablet, it is unavoidable that there will have some residue or some particles that can be left in the containers or when triturating. For the high dose tablet, an example is paracetamol, direct compression can’t be use since high dose API are not easily compressed.