

THE PHARMACEUTICAL INDUSTRY

The pharmaceutical industry in New Zealand takes the active ingredients of drugs (which are imported from overseas) and converts them into a form that can easily be given to a patient. This involves mixing the active ingredient with various other ingredients with appropriate chemical properties, then either compressing the mixture into a tablet, filling a gelatine capsule with it or dissolving it in an appropriate solvent.

Tablets

The active ingredient is mixed with other dry ingredients to dilute it and make it compress more easily into tablet form. The mixture is then either made into a dough (by wetting with water or some other solvent), pressed into small granules and dried or simply sieved in dry form. The granules are then compressed into a tablet and, if necessary, coated with a thin, protective film.

Capsules

Capsules are processed in an identical manner, except that they are poured into empty gelatin capsules rather than compressed into tablets.

Liquids

Liquid pharmaceuticals are either creams/ointments that are spread onto the skin, or medicines for swallowing or injecting. For all of these liquids production consists of dissolving the active ingredient in an appropriate solvent, often with various preservatives and other additives, mixing the ingredients completely before packaging.

All factories dealing with pharmaceuticals have to follow a code of practice set down by the Ministry of Health. This ensures that the products are exactly what they are labelled to be, and ensure that all items from a given batch of medicine can easily be traced if a problem develops. The tests that are carried out to ensure that these standards are met are done by the laboratory of the company concerned.

INTRODUCTION

Pharmaceutical products used in New Zealand may have been processed in this country or overseas. Many of the large international pharmaceutical companies had in the past their own manufacturing plants in New Zealand but due to the economic reforms that have been enacted over the last 10-12 years the majority of those plants have been closed down. The only ones remaining are those that are principally involved in the manufacture of generic products for sale in the domestic market or for export.

Manufacturing companies that remain in New Zealand are:

- Douglas Pharmaceuticals
- Pacific Pharmaceuticals
- Apotex
- Stevens Chem Industries

The production of a pharmaceutical involves the initial research that identifies an appropriate active ingredient, and the trials that follow (see cancer article). After this, the active ingredient has to be manufactured on an industrial scale, and then processed into a form in which it can conveniently be administered to a patient. Only the last of these steps is carried out in New Zealand: there is no chemical synthesis of medicines carried out in this country and hence all active raw materials have to be imported from various sources throughout the world. Inactive raw materials, otherwise known as excipients, which are used to aid the processing of active ingredient into a finished dose form may be purchased from overseas or manufactured within New Zealand.

Medicines

A medicine is defined in the Medicines Act 1981 as “any substance or article other than a medical device that is manufactured, imported, sold or supplied wholly or principally for administering to one or more human beings for a therapeutic purpose where therapeutic purpose is defined as treating, preventing or diagnosing disease”. A large selection of tablets, capsules and liquid preparations fall within the scope of this definition. The liquid preparations can be subdivided into three groups; those that can be taken orally, those that can be taken intravenously, and those that are for application on the skin.

Some of these products and their methods of manufacture will be discussed here.

TABLETS

A tablet is the most common means of administering a medicine. Tablets are compressed powder, formulated so as not to break up or chip before being taken, but to disintegrate in the digestive tract and release the drug in a consistent and predictable manner. This requirement, and the requirement that the drugs be of a suitable size to be taken, means that there is more involved in tablet making than simply taking a powder and compressing it, and the process used is described below.

Step 1 - Dispensing

Sufficient active ingredient to make up a batch is weighed out, and at the same time the first of the excipients¹ to be used is added to the mixture. The excipients used at this stage are fillers (to dilute the active) and binders: either lactose or polyvinyl pyrrolidone (both of which act as both fillers and binders).

Step 2 - Granulation

This is the stage in which the tablet ingredients are thoroughly mixed, and prepared for compressing. Two different methods are used, with the choice of method based on particle size and shape.

¹*Excipients* are biologically inactive compounds that are added to tablets either to dilute the active ingredient so that the tablet is big enough to be conveniently taken, or to lubricate the powder so that it compresses easily, or to ensure that the tablet doesn't break up before it is taken, but does do so in the digestive tract. The quantity of excipient required in any tablet can vary considerably depending upon the active ingredient, the tablet size required and the dose; e.g. aspirin tablets are only approximately 10% excipient, while other tablets are more than 99% excipient.

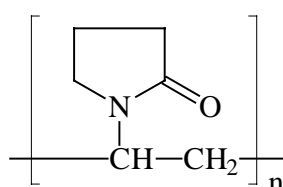
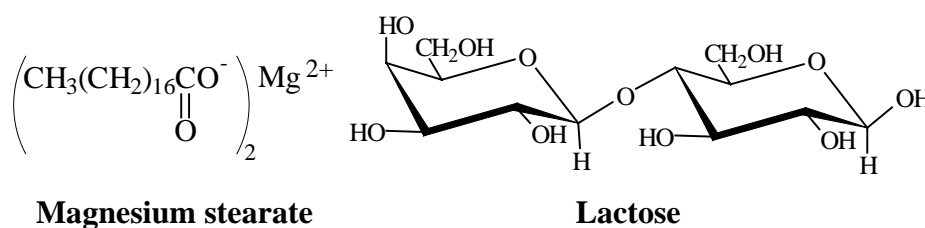
Dry granulation

This is the simpler of the two methods, and is suitable for tablets where the particle size of both the active and the excipients are the same. The active ingredient and the excipients are sieved through a fine mesh and thoroughly mixed. If particle sizes differ, desegregation can occur in the tablet hopper during the compression stage leading to non-uniform dispersion of active in the tablets.

Wet granulation

This method is more complicated, but it is more commonly used. It is necessary for tablets in which the active ingredient and excipients have different particle sizes. It also helps tablets with very spherical particles to bind together, by making them more lumpy in shape.

Here the dry mixed ingredients from the dispensing stage are mixed with liquid - usually a paste made of maize starch (a further excipient that acts as a filler and binder) and water, but sometimes water or alcohol. This is mixed to form a dough, and then cut into very small pieces with knives. These pieces are dried below 60°C either in a hot air oven or a fluid bed drier until they are less than 2% moisture. The dried pieces are then milled into very small granules and blended with magnesium stearate (the salt of a fatty acid) or talc (a mixture of magnesium silicates). This powder coats the granules of the other ingredients, and acts as a lubricant to reduce friction during the compression and ejection of the tablets. Unfortunately, lubricants also reduce the rate at which tablets disintegrate and dissolve in the digestive tract.



Polyvinyl pyrrolidone

Step 3 - Compression

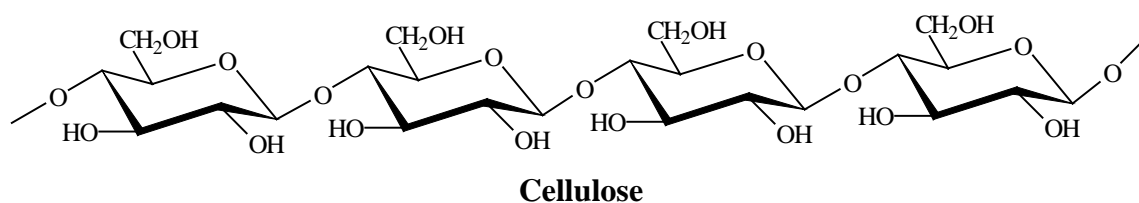
Tablets are compressed on machines that can usually produce either 16, 32 or 64 tablets per rotation. The weight and, therefore, strength of the tablet is controlled by adjustment of the volume of the die into which the powder for each individual tablet is fed immediately prior to compression. The compression machine is loaded with dies that either simply compress the powder into a tablet of suitable size and shape, or that also emboss them with various identification marks or put a groove in them so that they can be broken in half (e.g. for medicines in which a child dose is half a tablet). Tablet production may be finished at this stage or if required they can proceed on to being coated.

Step 3 - Tablet coating

Tablets may be coated to improve the stability (by protecting the tablet from exposure to light, moisture or air) and appearance, to mask an unpleasant taste, or to protect the tablet

from the acid in the stomach. In addition, outside coatings are sometimes coloured, either to improve their appearance, or to enable them to be easily identified.

Sugar coating used to be the most common type of coating used, however, this was a very cumbersome process requiring application of up to 27 coats of different sugar, sealing and polishing coats. The majority of coated tablets nowadays use film coating. Here the polymer to be used (hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose or carboxymethylcellulose sodium - all of which are cellulose polymers with different functional groups in place of some or all of the -OH groups) is simply mixed with water or another appropriate solvent. This solution is sprayed onto the tablets as they are turned in a large rotating bowl, the solvent evaporates off, and a layer of film remains on each tablet. As well as being simpler to apply than sugar coatings, film coatings have the advantage that they can be applied to embossed tablets without the embossing being filled up with coating solution.



A small number of tablets on the New Zealand market are coated with what is known as an enteric coating - one that doesn't dissolve in the acid conditions of the stomach. This is important for patients whose stomach lining must be protected from contact with the drugs being administered, or the drugs themselves must be protected from contact with stomach acid. Enteric coatings are produced from cellulose acetate phthalate (CAP), which only dissolves in the more alkaline conditions of the small intestine. This means that the tablet core only disintegrates, and hence the active is only released for absorption, in the small intestine. Unlike the other coatings mentioned above, CAP has to be dissolved in a non-aqueous solvent, rather than in water.

CAPSULES

Manufacture of capsules involves a similar process to that of tablets. The major difference is that after mixing of the formulation ingredients, instead of being compressed, the mixture is filled into gelatin capsules that may be either hard or soft in texture.

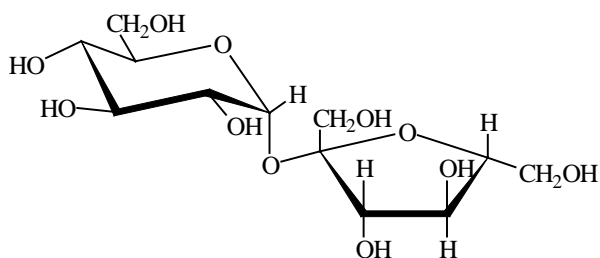
LIQUIDS

These fall into three main categories: liquids for oral administration, liquids for injections and liquids applied topically (i.e. creams and ointments).

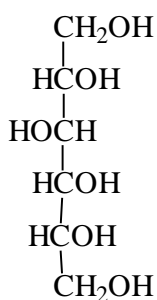
Liquids for oral administration

These are usually the simplest formulations available, as the ingredients are simply mixed in a suitably sized tank. The most important aspect of manufacture is to ensure all ingredients are fully dissolved and well mixed before packing and that the formulations contain suitable effective preservatives. Where the liquid is a suspension, mixing of the bulk must be continued during packing to ensure even dispersion of the active at all times. These liquids generally include, in addition to the active ingredient and the solvent (usually water, although

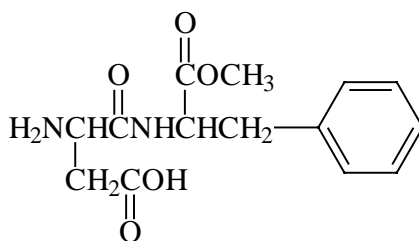
alcohol sometimes used as a solvent or cosolvent²), antimicrobial agents to prevent the growth of molds and yeasts, and often include sweeteners such as sucrose, sorbitol, aspartame and glycerin. In addition, a variety of other substances are sometimes used to alter such properties as solubility, flavour and viscosity.



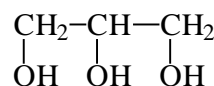
Sucrose



Sorbitol



Aspartame



Glycerin

Liquids for intravenous administration

Liquids for injections are also usually simple to prepare, however, manufacture must occur under aseptic conditions using methods that ensure the finished injection is sterile. Injections are usually rendered sterile by autoclaving³; however, some medicines cannot be autoclaved and so must be sterilised by filtration during the manufacturing process.

As well as being available in liquid form, injections may, for stability purposes, be prepared in powder form, either freeze dried or as pure powder, for reconstitution immediately prior to use. Injections may also be prepared for intramuscular or subcutaneous administration often using oils as the vehicle rather than water. Injected liquids sometimes also contain small amounts of additives, the most common of these being sodium chloride (table salt) - used in aqueous solutions to make the injected solution isotonic⁴.

Liquids for topical application

Liquids for topical application are usually prepared as either ointments or creams. The general difference between these forms is that ointments in the majority of cases are dispersions of water in oils while creams are the opposite. The method of manufacture is, however, the same. It involves preparation of separate oil and water phases containing the required ingredients, heating each phase to between 60-70°C, mixing and then cooling the mixture with stirring until the cream or ointment is formed. The bases used are substances

² A *cosolvent* is a second solvent, generally used in smaller quantities than the first solvent.

³ *Autoclaving* is sterilising something using super-heated steam.

⁴ An *isotonic* solution is one having the same concentration of dissolved salts as the solution inside a living cell.

such as hydrocarbons and lanolin. Depending on the base used, the cream/ointment may wash off or easily absorb into the skin, or it may remain on the surface, and thus protect the skin underneath.

GOOD MANUFACTURING PRACTICE

It is an essential requirement in manufacture of pharmaceuticals that the manufacturer must comply with the New Zealand Code of Good Manufacturing Practice published by the Ministry of Health. Since inception, considerable efforts have been made in the manufacturing pharmaceutical industry to establish procedures and facilities that decrease the occurrence of any mishap in manufacture and packing that might adversely affect the health of the public. The New Zealand Code of Good Manufacturing Practice is based on manufacturing principles established internationally, and details the standards that must be maintained by each manufacturer. Compliance with the Code is monitored by annual audit carried out by the Ministry of Health. The main points covered by the code are as follows:

- The manufacturing premises must be kept clean and must be designed to allow a product to be made in complete isolation from any other product being made at the same time.
- Equipment must be cleaned before use with all traces of the last product removed.
- The operator is issued with a set of batch records for each separate batch of product to be prepared. The batch records detail the product formula, and the manufacturing steps required to be followed in preparation of that product. The operator enters appropriate information on the batch records during manufacture, such as the identifying numbers of raw materials, the results of in-process checks etc. Once manufacture is complete, these records are retained as they constitute a complete record of the batch and must be readily accessible if required for either audit purposes or investigation of any product complaints.
- Each batch of a product is given a unique identifying number which is written on the batch records and identifies the product throughout manufacture and is then used as the batch number on all labelling of product filled from the batch during packaging.
- Samples of each batch must be kept for the shelf-life of the product plus one year.
- Each raw material and finished product must comply before use or upon packaging with standards that are set down for each product. Such standards may be found in either the British Pharmacopoeia, United States Pharmacopoeia, or the European Pharmacopoeia, or may be standards that are set by the manufacturer and agreed to by appropriate regulatory authorities such as the New Zealand Ministry of Health before the product is allowed for sale. Such standards detail the tests and analytical methods which have to be performed to confirm the identity; determine the concentration of active drug; and ensure the absence of any undesirable contaminants prior to release of the product to market.

THE ROLE OF THE LABORATORY

In the pharmaceutical industry in general, the laboratory carries out three important functions: quality control; development of new, more appropriate mixtures of excipients; research into new active ingredients. The first two are covered here, the third (which is not done in the commercial sector in New Zealand) was covered in the cancer article.

Quality control

Quality control is of crucial importance to the pharmaceutical industry, and for this reason numerous checks are made at every stage of production to ensure that quality is not compromised and that the Code of Good Manufacturing Process is adhered to. Quality control procedures include:

- *Sampling of raw materials.* All incoming raw materials are initially quarantined, and samples are taken and tested to ensure that the material meets strict purity guidelines. This testing involves both microbiological and chemical testing, as is laid out in the relevant Pharmacopeia (a reference book on the preparation of pharmaceuticals. Three are published - the British, United States and European Pharmacopeia).
- *In-process checks.* The manufacturing staff carry out checks on such things as tablet weight and size at frequent intervals. At hourly intervals the quality control staff take samples to check for contamination and to ensure that composition is as expected.
- *Final product checking.* Checking similar parameters to those measured during production.
- *Monitoring cleaning.* When a batch of a certain drug has been made, all equipment that has been used must be cleaned. When the next pharmaceutical to be made on that line is going to be different, this cleaning must be particularly thorough to prevent contamination. In this instance, after cleaning the quality control staff take swabs off each piece of equipment, and test them to see if they can detect the presence of the active previously used. Only when the equipment is so clean that the previous active is undetectable can the production of the next pharmaceutical commence.

The results of all of these tests are recorded on the batch records for the pharmaceutical, as well as the name and batch number of the pharmaceutical made immediately prior on the same production line.

In terms of laboratory testing, over the past 10 years there has been a major change in the equipment that is used. Ten years ago the laboratory was normally equipped with a visible-UV spectrophotometer, analytical balance, tablet disintegrator and analytical glassware. Nowadays pharmaceutical laboratories will also include high pressure liquid chromatography, gas liquid chromatography, infra-red spectrophotometers, and dissolution testing apparatus as standard items.

Development

The laboratory staff are also involved in research to discover new blends of excipients that result in better tablets (i.e. easier to take, more predictable release of active etc.) and new manufacturing techniques. This latter role is carried out in conjunction with the

manufacturing staff, with the goal of improving compliance with the Code of Good Manufacturing Practice.

Written by Roger Smart, Director - Regulatory Affairs, Douglas Pharmaceuticals, updating an article from volume one of edition one by Dr. R.F. Armishaw, Chem Industries. Edited and expanded by Heather Wansbrough with reference to:

The United States Pharmacopeia 1995 (USP 23); United States Pharmacopeia Convention Inc.; 1994