Duncan Hay

Drug formulation

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You wake up with an aching head. You scramble around the medicine cabinet, searching for a packet of painkillers. When you hold that little pill in your hand, do you ever stop to think what it's made of? Duncan Hay knows the answer.

Well, it's obvious, isn't it? A paracetamol tablet is surely made from paracetamol. This is partly true, but it's far from the whole story. Medicines rarely contain just one pure chemical substance. The vast majority are made of a complex mixture that contains an active ingredient (the compound that has the desired effect in the body) and compounds called excipients. This mixture is known as a formulation. But just what are these excipients, why are they there and how are these formulations designed?

Research

When new medicines are discovered, scientists spend years selecting a chemical compound that they hope will be able to treat a particular condition. This compound will hopefully form the active ingredient in the final medicine. Once they have selected this, one of the next steps is to design a formulation so that it can be administered to the patient in a safe, reproducible and convenient manner. In effect, this formulation will be a vehicle for getting the active ingredient into your body.

How do scientists go about designing a formulation that will show off the medicine to its full potential? One of the first things to consider is what will be the most appropriate method for administering the compound. For example, if the new compound is designed to treat asthma, it would be quite sensible to have an inhaled formulation that gets the compound directly into the lung. Other options include injections or applying the compound directly to the skin as a cream or ointment. In practice, most medicines are given orally, by swallowing or dissolving in the mouth, and the majority of oral medicines are in the form of a tablet, or a capsule. These provide a measured amount of the active ingredient in a convenient little package. It is also the preferred method for the patient. If your doctor offered you a choice of swallowing a small capsule or getting an injection, which would you choose?


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Would you prefer taking a tablet or having an injection?

Journey through the body

When designing oral formulations, it is important to consider what happens once the patient swallows. The medicine first travels down the oesophagus and into the stomach. Here is where it is likely to dissolve in the stomach acid before being passed into the small intestine. This is where most of the active ingredient is absorbed through the gut wall into the bloodstream, travelling first to the liver then round the rest of the body. The remainder of the compound in the gut passes to the large intestine. As it travels down the intestine, the pH rises and eventually becomes alkaline.

Buffers

A buffer keeps a solution at a constant pH even if small amounts of acid or alkali are added to it. The molecules of the buffer solution react with any acid or alkali and neutralise them. As there is no change in the amount of acid or alkali present, there is no change in pH. Buffer solutions are used to keep the pH constant in a wide variety of chemical applications and also occur naturally in living things.

Charles D. Winters/SPL

That's quite a journey for the medicine to take! How will it behave in the different conditions that it will encounter along the way? To help predict this, experiments are carried out to build a database of information about the properties of the compound. For example, it is important to know how well it dissolves in various solvents and buffers (see Box). These conditions will mimic what it is like in different parts of the body and so give a clue as to how soluble and stable the compound will be. Solubility is important as the compound must be in solution before crossing through the gut wall into the bloodstream. Also, if the compound is unstable, it could break down before it has a chance to act. It is also possible that it could break down to a toxic by-product.

Testing substances in the lab.

Chemistry in the body

After carrying out these studies, it may be found that the compound is poorly soluble, unstable, or that it doesn't pass through the gut wall into the bloodstream very well. This is where ingredients can be added to the formulation to help address these problems. These additives are the excipients. For example, if it is found that the compound is poorly soluble in alkaline environments, it may be helpful to add an excipient that resists changes in the pH. These are known as buffering agents and include compounds such as phosphate salts (K_2HPO_4 or KH_2PO_4). Alternatively, solvents such as ethanol or glycerine can be added to the formulation to help dissolve the compound.

How hydrophilic (polar and attracted to water) or hydrophobic (greasy and repelled from water) the compound is is likely to affect how well it passes through the gut wall. This is because the gut wall is quite hydrophobic itself. Excipients that help the compound get across include compounds that have detergent properties, such as sodium lauryl sulphate, a substance sometimes found in household cleaners and shampoos.

Soft shell capsules

Hard shell capsules

Once a foreign compound is in the bloodstream, the body will try to clear it away. One of the main ways the body does this is to use enzymes in the liver. These help alter the structure of the compound, making it more soluble in water so that it can be excreted. This is a natural and healthy defence to remove toxic compounds. However, if this happens too quickly, the active compound will not have a chance to have its effect. If the medicine is taken orally, the compound will have no choice but to pass through the liver. Excipients are unlikely to help you in this case. One method of avoiding these enzymes would be to inject the compound, which bypasses the liver. However, it is more likely that you would try to design a compound that was less likely to react.

Binding and coating

Other excipients that could be added to a formulation include binders to hold the ingredients together. Binders could be sugars, starches or cellulose. Obviously, it is important for the ingredients in a tablet to be bound together, but equally they need to break up in the stomach to make dissolving easier. Disintegrants can be added which expand and dissolve when wet. These include compounds such as water soluble polymers. Fillers can also be added to bulk out the formulation and make the tablet a more convenient size. Again, sugars and cellulose can be used, or salts such as calcium phosphate, calcium carbonate and magnesium stearate.

Many tablets are also coated to make them smoother and easier to swallow. The coating can also disguise an unpleasant taste and protect the ingredients from decomposing if they are sensitive to moisture or air. Coatings are often made from sugar, other carbohydrates or polymers.

Although the excipients are extremely useful, they cannot be added without first checking if they are compatible with each other and the active ingredient. Bringing together a useful formulation with all of the available options is a long and complicated process. This short article has just scratched the surface of the vast amount of work that is done formulating a chemical compound into what can actually be called a medicine. The scientists who carry out this formulation work are the unsung heroes in the discovery of new medicines, perhaps like the often unnoticed excipients contained in the medicines we use every day.

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