Excipients

After completing this tutorial, you will be able to:

- Identify the excipients in a medicine.
- Decide whether a patient's allergy, intolerance or other reaction is caused by an excipient.
- Adopt a practical approach to managing reactions to excipients, and be able to advise other professionals about them.

Why this subject matters...

Medicines contain one or more pharmacologically active compounds which are responsible for the product's therapeutic potential. Excipients, or pharmaceutical additives, are all the other parts of the formulation. Although excipients are not the principal 'active' constituents of a medicinal product they do, in many cases, have pharmacological activity. This means they can occasionally cause side effects in their own right. Sometimes an unexpected reaction to a medicine can be explained by considering the potential effects of excipients. Alternatively, a patient or healthcare professional may know about a problem with a specific excipient and ask you to check new medication to ensure that the excipient is not present.

What are excipients for?

Collectively, excipients stabilise a medicine, help with the manufacturing process, aid dispersion of the drug or make the product more appealing to the patient. Two oral formulations are described in detail below, showing you what all the ingredients actually do:

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Ciproxin tablets	Lanoxin PG elixir
The body of the tablet contains: • Ciprofloxacin *(the active ingredient).* • Microcrystalline cellulose *(used as a binder which holds tablet together, and as a diluent which bulks up the tablet).* • Crospovidone *(disintegrant, which helps tablets break up in the stomach).* • Maize starch *(binder, diluent, disintegrant)* • Silica colloidal anhydrous *(improves flow of powder through tabletting machine).* • Magnesium stearate *(lubricant in tabletting process).* The film coat consists of a mixture of: • Hypromellose *(main ingredient of coat).* • Macrogol 4000 *(makes the coating more soluble so it dissolves in the stomach).* • Titanium dioxide *(white pigment).*	The elixir contains: • Digoxin *(the active ingredient).* • Methyl hydroxybenzoate *(preservative).* • Sucrose or syrup BP *(sweetener and thickener).* • Citric acid monohydrate *(lowers pH, to where formulation is most stable).* • Anhydrous sodium phosphate *(a buffer – helps to maintain desired pH).* • Quinine yellow *(colour).* • Ethanol *(solvent).* • Propylene glycol *(solvent with some preservative properties).* • Purified water *(solvent and diluent).* • Lime no. 1 NA *(flavour).*

Note that patients may ask to avoid excipients of animal origin for personal or religious reasons. For example, some vegans request medicines that do not contain gelatin, and Jehovah's Witnesses may seek to avoid products containing albumin from a human source. SPS has a review of what you should consider when advising vegan patients about excipients. There is also a review of the implications of cultural and religious beliefs on selecting medicines in Drug & Therapeutics Bulletin Apr 2016 (subscription required).

Excipients and 'E' numbers

Some excipients found in medicines are also used in foods, where they are usually called 'food additives'. The 'E' number system was devised by the EU so that there would be a standard way of identifying additives across Europe.

Examples of pharmaceutical excipients that might also occur as food additives include sorbitol (E420), titanium dioxide (E171), sodium benzoate (E211) and tartrazine (E102). If a patient has allergy or intolerance to an 'E' number then you should check to see if it is in any of their medicines. The Food Additives and Ingredients Association provides a comprehensive list of E numbers.

Excipients and patients

Excipients can occasionally be the cause of a medicine's side effects. Many healthcare professionals are unlikely to know much about this subject or to consider it clinically, so adverse reactions to excipients can be overlooked. As a pharmacist you need to be able to offer advice about it.

Reactions to excipients

It can be difficult to find out about adverse reactions to excipients and how frequently they occur, although one of the reasons for a substance being selected as an excipient is that it should not commonly cause side effects. In addition, the amounts of excipients in medicines are usually small.

However, occasionally, excipients can cause dose-related adverse reactions. Persistent administration of sugar-containing medicines might cause tooth decay, for example, and the popular sweetener sorbitol used in some liquid medicines can cause diarrhoea because it acts as an osmotic laxative. Another example is the sodium content of medicines. Sometimes this is high enough for a medicine not to be recommended for patients on a restricted salt diet (e.g. those with hypertension). A number of antacids contain quite high amounts of sodium.

In practice, the commonest side effects of excipients tend to be due to **intolerance**, which is often dose-related, and **allergy**, which is not dose-related. In these situations it is important to help patients to avoid further exposure.

Factors influencing risk

Some excipients are not absorbed from the gut, and so are particularly unlikely to cause systemic reactions after oral administration (e.g. talc). Certain other common excipients are natural to the human body and in the amounts used in pharmaceuticals are unlikely to cause side effects (e.g. citric acid). Many excipients also occur naturally in food (e.g. starches).

Some excipients can potentially cause problems in both adults and children such as sorbitol which is commonly found in liquid medicines. However, certain excipients can present **special problems in children** such as those in the table below. Exposure to these agents should be minimised as far as possible but occasionally a medicine containing a problem excipient may be indicated after a careful risk-benefit assessment (e.g. amiodarone containing benzyl alcohol).

Excipient	**Linked with**
Glucose and sucrose	Obesity, and tooth decay if taken orally
Benzyl alcohol	A gasping syndrome in neonates
Ethanol	CNS effects
Aspartame	A source of phenylalanine in patients with phenylketonuria
Polyoxyl castor oils	Severe anaphylactoid reactions
Propylene glycol	CNS effects especially in neonates and children under 4 yrs
Colourants (e.g. tartrazine)	Hypersensitivity and behavioural disturbances

This table is not a comprehensive list and exclusion does not indicate safety

A more detailed assessment of the risks posed by excipients to children is presented by the NPPG and the Welsh Medicines Information Centre here (see p 2).

As already noted, the commonest reason you may be asked about excipients is that a patient has a known allergy or intolerance to it. In this situation you need to find out the

history and nature of the reaction in order to best help the patient. We examine this aspect in more detail below.

Allergy and intolerance

A range of excipients can produce **allergic** reactions such as skin rashes which have an immunological mechanism. Other excipients can trigger **intolerance** which has a non-immunological basis and can be caused by, for example, deficiency of a human enzyme. Part of the pharmacist's role when optimising a patient's medicines is to help ensure that further exposure to these excipients is avoided.

Lactose

Lactose intolerance is caused by a deficiency of the gut enzyme lactase which normally breaks lactose down into simple sugars. Deficiency may be a temporary situation (e.g. after gastroenteritis) or permanent (genetic deficiency). In the absence of lactase, the undigested lactose reaches the colon where it osmotically draws in fluid and is fermented by enteric bacteria. This results in symptoms such as diarrhoea, flatulence and abdominal pain. Lactose is commonly used in tablets and capsules as a diluent. It is used in small amounts, and as such it does not usually cause a significant problem for patients with lactose intolerance, but it may need to be avoided by patients with severe intolerance. SPS has produced a document that discusses this subject in more detail.

Gluten

This is a protein found in wheat and barley which exacerbates the gastrointestinal symptoms of coeliac disease. Wheat starch is occasionally used in pharmaceuticals but only contains very low amounts of gluten so most patients with coeliac disease are able to tolerate it. It is often possible to find an alternative product for patients who wish to avoid wheat completely because substitute excipients such as maize (or 'corn') starch do not contain gluten. Coeliac disease is often associated with intestinal symptoms such as diarrhoea and bloating, but there may be other effects such as tiredness, weight loss, and skin disease. You can read more about coeliac disease at Coeliac UK.

Phenylalanine

This, and the chemically-related aspartame, should be avoided in patients with phenylketonuria. These patients are unable to metabolise phenylalanine and suffer a range of symptoms including learning disabilities and behavioural difficulties as a consequence of its accumulation. The NHS website has more information about phenylketonuria.

Preservatives

Allergy to these can sometimes be demonstrated and further exposure should subsequently be avoided if possible. An example is the methyl-, ethyl- and propyl- hydroxybenzoates used in oral liquids and topical products. Preservatives in eye drops can cause stinging and itching as well as keratitis, which is why preservative-free varieties are sometimes requested.

Peanuts

Arachis oil comes from peanuts. One study has suggested that the refined type of arachis oil in pharmaceuticals may not contain enough protein to cause reactions in those allergic to peanuts, which is helpful if a patient is exposed accidentally. However, given the severity of the reaction in many patients and the fact that arachis oil is usually easy to avoid, patients with peanut allergy should be offered products free of arachis oil. There are helpful Q&As on the SPS website about arachis oil and peanut allergy and about cross-sensitivity between peanuts and soya.

Latex

In patients with allergy, contact with latex can cause a range of reactions from dermatitis to anaphylaxis. Latex is sometimes used as part of the bung, plunger or entry port in parenteral medicines so they should be avoided in those with latex allergy. However, latex might be found in all sorts of other health-related products including medical gloves, resuscitation equipment, and condoms.

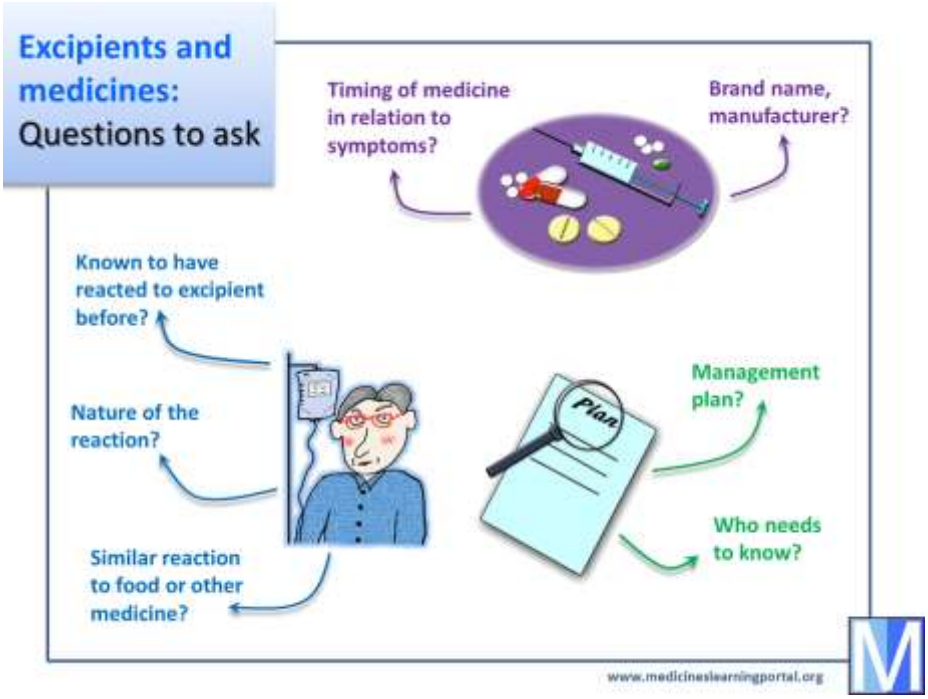
Colourants

Some patients discover a link between colourants in foods and behavioural illness (e.g. hyperactivity in children) or physical illness (e.g. eczema) and should therefore avoid further exposure.

Suggested questions

Sometimes you'll be asked about excipients directly by patients because there are substances they know that they can't take. On other occasions you might be raising the question yourself: 'If it's not the drug causing this reaction, could it be an excipient?'

If you're being asked about use of a specific medicine you'll need the indication, dose, frequency, route of administration and expected duration of treatment. There are some general questions to ask when problem solving; in particular, you should ask about other medicines being taken because a patient may be taking a suspect excipient in another medicine. But what else do you need to know that's specific to excipients?



The Medicine

- Timing of medicine administration related to any symptoms? *Has a new medicine, or a new brand of an existing medicine, been started shortly before new symptoms were reported?*
- What is the brand name or manufacturer? *You need to know this for all medicines suspected to be involved, because excipients vary between different brands and formulations of the same drug.*

The Patient

- Is the patient *known* to react to a particular excipient, or is the reaction suspected? *Patients will often know about problems they have experienced with certain additives or medicines in the past. Has the patient taken other brands or formulations before without any problems?*

- What is the nature of any known or suspected reactions to excipients? *You'll need a clear description, as you would for any adverse reaction.*
- Has the patient had a similar reaction with any other medicine, food or drink? *Excipients and additives will be found in other medicines or foods so the patient may have encountered the reaction before.*

Going Forward

- What is the management plan? *Don't just identify the potentially causative excipient. Advise about suitable alternative brands/formulations, or a different medicine that does not contain the excipient.*
- Who needs to know? *Make sure that any problems related to excipients are clearly communicated to the patient, the ward medical team, and the patient's GP so that the offending medicine is not re-prescribed and further exposure to the excipient is avoided. You must also document a potential allergy or intolerance in a patient's notes, to help the patient avoid exposure in the future.*

Information sources

When using any information source, do be careful that some excipients have **more than one name** so make sure you check them all. For example, PEG, polyethylene glycol, E1521, macrogol, and polyoxyethylene glycol can all be terms for the same thing.

Manufacturers' SPCs are the single most helpful source for identifying the excipients in a particular medicine. You can access them via the eMC, but many SPCs missing from here are available via the MHRA site (e.g. some generic medicines). Generally, the information required is in **section 6.1 of each SPC**. However, note that occasionally an SPC does not list every excipient: those present in 'trace' amounts may not be declared. If it is crucial to be sure about excipient content, the only option is to ring manufacturers individually.

Remember that you can use the eMC to help you find a formulation that doesn't contain a particular excipient. If you don't know how to do this, then look at our Guide to the eMC, and particularly pages 3 to 5.

To best manage patients, and to understand the safety of an individual excipient, there are a variety of useful sources:

- The SPS website has a number of Q&As to help you, including:
  - Using excipients in vegans.
  - Arachis oil in medicines and peanut allergy, and also soya-containing medicines and peanut allergy.
  - Lactose intolerance and medicines.
  - Gluten and wheat starch in medicines.
- Expert sites about allergy may offer valuable advice on caring for patients. Examples include the American Academy of Allergy Asthma and Immunology and the British Society for Allergy and Clinical Immunology.
- The book Pharmaceutical Excipients (Pharmaceutical Press) describes the chemical properties of excipients and their safety. Your MI centre may have a subscription.
- Finally, **Medline** and **Embase** enable retrieval of case reports and reviews of excipient side effects.