ARTICLE

Extemporaneously compounded medicines

SUMMARY

Extemporaneously compounded medicines may be useful when a required dose or dose form is unavailable commercially, or for individualised dosing.

There are numerous established compounding formulae available, and new formulae may be developed with the help of formulation guidelines and professional advice.

Unlike registered medicines, compounded preparations have not generally been assessed for safety and efficacy. Their use is off label and is based on extrapolation from the component ingredients.

Short-term expiry dates are provided for compounded products unless their stability has been assessed.

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Introduction

Extemporaneous compounding is the preparation of a therapeutic product for an individual patient in response to an identified need.[1] It is a practical way to have medicines supplied when there is no other option. For example, compounding may be useful for patients with dysphagia who are unable to swallow solid medications whole, when an appropriate dose or dosage form is not commercially available, when patients require an individualised dose, or when medicines must be delivered via nasogastric or gastrostomy tubes.[2]

Active pharmaceutical ingredients can be incorporated into a wide array of products including creams, eye drops, nasal sprays, oral dosage forms or intravenous infusions. In Australia, products may be classified into simple or complex compounding (Table 1). Simple compounding can be performed by any pharmacist and is a core competency of pharmacy training. Complex compounding requires additional training and evidence, as described by the Pharmacy Board of Australia's guidelines on compounding.[1]

Regulation

The final medicine produced by compounding is regulated according to the component's schedule in the Poisons Standard (the SUSMP).[3] For example a topical progesterone (S4) cream requires a

Table 1 **Classification of simple versus complex compounding**

Compounding type	Explanation	Examples
Simple	All pharmacists have training during their undergraduate degree to prepare these products. Involves well-established preparations published in reputable literature, e.g. the Australian Pharmaceutical Formulary and Handbook, or formulae for which some data are available regarding quality, stability, safety, efficacy and rational design.	Topical creams, ointments, lotions, gels, e.g. steroids, hormones, coal tar, cholestyramine Oral liquids (solutions, suspensions, emulsions, mixtures, elixirs), tinctures, e.g. omeprazole suspension Capsules, tablets, powders, e.g. boric acid capsules Suppositories, pessaries, e.g. paracetamol, clotrimazole
Complex	Pharmacists require further postgraduate training in association with self-assessment of relevant competencies and documentation of the specific competencies in a continuing professional development plan. Specialised facilities (sterile room with positive pressure) and equipment (laminar flow isolator, dry heat sterilisation oven) are also required.	Parenterals, e.g. morphine, clonidine Ingredients with a safety hazard, e.g. cytotoxics, hormones Single unit micro-dose (<25 mg of drug or no more than 25% w/v of a dosage form), e.g. naltrexone Modified-release dosage forms, e.g. levothyroxine (T4), progesterone capsules Ophthalmic preparations, e.g. phenylephrine, tropicamide, ciprofloxacin

Source: Reference 1

prescription whereas dithranol (S3) ointment can be supplied without instructions from a medical practitioner. In contrast, a pharmacist must have been instructed by a veterinary surgeon to compound medicines for an animal irrespective of the scheduling of the active ingredient. All components of a compounded product, that is the active ingredient and the excipients, are subject to quality standards set out in the *Therapeutic Goods Act 1989*, and are sourced from compounding supply companies that undertake rigorous quality-assurance testing.

The Therapeutic Goods Administration (TGA) specifies that all medicinal products must meet the PIC/S* Guide to Good Manufacturing Practice for Medicinal Products, which is an international standard.[4] However, it is important to be aware that the final medicine produced by extemporaneous compounding is exempt from assessment by the TGA.

Commercially available medicines must be listed or registered in the Australian Register for Therapeutic Goods (ARTG) (see Box), unless exempt by the Therapeutic Goods Regulations. They are manufactured by TGA-licensed manufacturers and undergo extensive testing to ensure an accurate dose of active drug will be delivered in a reasonably reproducible manner. Commercially available medicines are also tested for stability so an expiry date can be provided. Extemporaneously compounded medicines are not listed or registered, and no assessment of the final medicinal product in terms of quality, stability or efficacy is required.

Where are compounded products made?

Extemporaneous compounding takes place in community and hospital pharmacies. There are usually specialist compounding pharmacies in major towns and cities, but any pharmacy may undertake compounding as long as they have appropriate facilities according to state-based legislation (e.g. allocated clean bench, specific compounding equipment).

Complex compounding is performed in a pressurised clean room using a laminar flow cabinet, cytotoxic drug safety cabinet or an isolator.[1] Many public and private hospitals maintain large aseptic compounding facilities to provide individualised dosing or commercially unavailable formulations.

* Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

Box Commercially available and compounded medicines in Australia

Commercially available medicines

These products must be listed (AUST L) or registered (AUST R) on the ARTG. Listed medicines are evaluated for quality and safety by the TGA and include vitamins and mineral supplements and herbal medicines. Registered medicines are evaluated for quality, safety and efficacy by the TGA and include all prescription medicines, most over-the-counter medicines (e.g. analgesics) and some complementary medicines (e.g. high-dose calcium supplements).

Extemporaneously compounded medicines

These products are prepared according to PIC/S Guide to Good Manufacturing Practice for Medicinal Products. However, they are not listed or registered on the ARTG and assessment of the quality, stability and efficacy of the final product is not required.

ARTG Australian Register of Therapeutic Goods
TGA Therapeutic Goods Administration
PIC/S Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

How is compounding performed?

The active ingredient may be derived from commercially available medications or the pure chemical. Sometimes compounding is as simple as mixing a crushed tablet or the contents of a capsule in water to form a solution or suspension. However, this may not be suitable and depends on the solubility of the active ingredient. For example, insoluble tablet excipients can lead to blockages in enteral feeding tubes.[5] In the majority of compounded products, additional non-active components (excipients) are included to ensure the active ingredient dissolves or remains suspended, or to adjust palatability or viscosity.[6]

A range of proprietary bases and excipient mixes are available commercially through compounding suppliers to create preparations such as capsules, rapidly dispersing tablets, creams, gels, ointments, oral liquids, lozenges, troches and suppositories. This can simplify the preparation protocol and provide some background research, development and quality control for the base. All pharmacies are required to document the compounding protocol used and maintain records of all compounded products dispensed.

Compounding formulae

It is preferable to use standardised formulae, especially when some stability information is available. Formulae and associated preparation

protocols are available for some of the more commonly compounded products, for example the current edition of the Australian Pharmaceutical Formulary and Handbook[7] describes approximately 130 formulae. Over 1000 other formulae may be found in older editions.[8] Formulae may also be found through specialist journals and websites. Pharmacies that regularly compound, particularly hospital and compounding pharmacies, often have their own compendium of formulae for products that they dispense on a regular basis. The formulae are documented in the form of a batch sheet that precisely describes the compounding method and allows for documentation of the ingredients used.

Advice is available from experienced pharmacists that work for the companies that supply the raw materials in Australia, such as the Professional Compounding Centers of America (membership required), Medisca and Bella Corporation (no membership required). They can help to develop formulae that will theoretically optimise drug delivery and minimise instability.

Stability of products

In most instances, the actual stability of the drug in the final compounded medicine is not known. Larger compounding companies or hospitals may undertake or outsource stability testing for a particular product, and will reference published stability information when preparing their batch sheets. Information regarding the chemical stability of the active ingredients can inform product design and expiry date. Active ingredients may degrade when exposed to oxygen and water, with reactions being initiated and accelerated by light, heat or certain trace metals (see Table 2).[9,10] For example, active ingredients containing an ester functional group, such as aspirin and penicillins, are susceptible to breakdown by hydrolysis, while those containing aldehyde or hydroxyl groups, such as testosterone and dopamine, undergo oxidative decomposition. A 10°C increase in temperature can result in a 2–5-fold faster rate of degradation.

It is essential that the active ingredient does not interact with any excipients originating from the dosage form being crushed for reformulation (e.g. tablet lubricants and fillers), or from additives in the new formulation (antioxidants, preservatives, suspending agents, colourants, emulsifiers). Interactions with other ingredients can result in physical instability of the product, such as precipitation of the active drug or phase separation ('cracking') of a cream, affecting drug solubility, absorption and bioavailability.

To minimise the risk of a compounded medicine degrading, short-term expiry dates are used (e.g. 28 days for oral and topical products, or 24 hours for parenteral formulations), unless stability studies have been conducted and indicate otherwise.

Sterility of products

Microorganisms may grow if the water content is high enough so exposure to an aqueous environment can cause medicines to 'spoil'. Contamination can cause instability of the formulation or drug degradation, or both.

Microorganisms could potentially be introduced during reformulation of non-sterile products. For example, if *Candida albicans* is inadvertently introduced into freshly prepared multi-dose citric acid solutions that are to be used orally for cough reflex testing, immunocompromised individuals could become infected.[11] Including a preservative is the most common approach for non-sterile water-based compounded products, especially when storage for more than a few days is required. Many factors affect the choice of preservative, such as dosage form and pH of the product. Refrigerated storage can help delay deterioration.

Table 2 **Common degradation pathways of active drugs in compounded products**

Pathway	Factors determining degradation rate	Susceptible functional groups	Examples[9,10]
Oxidation (O_2 dependent)	Concentration of drug, temperature, catalysts, solvents, light and excipients	Aldehydes, alcohols, phenols, alkaloids, unsaturated alkyl chains, carboxylic acids	Paracetamol, progesterone, testosterone, quinine, oils (unsaturated fats) such as soybean and corn oil, essential fats, atorvastatin, atenolol
Hydrolysis (H_2O dependent)		Esters, amides, lactones, ethers, lactams, imines, acetals, anhydrates, sulfonamides	Aspirin, vigabatrin, norfloxacin, omeprazole, simvastatin (statins), baclofen, diphenoxylate, methylphenidate, lignocaine, sildenafil, penicillins, cephalosporins, diazepam, digoxin, heparin, captopril, hydrocortisone

Note: drug molecules with more than one functional group can be more easily degraded. In fact, many drugs contain more than one functional group, being susceptible to both oxidation and hydrolysis, e.g. atenolol (contains amide and alcohol groups).

Parenteral products are compounded by appropriately trained staff using aseptic techniques. Multiple-use products will contain a suitable preservative, while single-use syringes or infusions rely on good aseptic practice. Regular monitoring of the environment, equipment and procedures is essential to ensure quality and sterility is maintained. The consequences of failure can be catastrophic, for example methylprednisolone injections from a single compounding pharmacy in the USA resulted in 137 cases of *Aspergillus fumigatus* meningitis and 12 deaths.[12]

Conclusion

Medicines are commonly prepared by extemporaneous compounding in Australia and around the world when commercial preparations are unavailable or individualised dosing is required. They do not have to be listed or registered on the ARTG because they are prepared for an individual patient. The quality of the components are assured by purchase from reputable suppliers, and quantities used and the formulation method are thoroughly documented within the pharmacy. The preparation of compounded medicines is subject to strict international standards, but they are generally dispensed without any testing for content, consistency, stability and sterility.

There is published information regarding chemical degradation of the active drug and for many compounding formulae. However, usually there are no data to inform the pharmacist or patient about a specific product's quality or stability. Products are typically freshly prepared with a relatively short-term expiry date based on guidelines in the Australian Pharmaceutical Formulary and Handbook [7] to limit the risk of degradation or contamination by microorganisms. <

Conflict of interest: none declared

REFERENCES

1. Pharmacy Board of Australia. Codes, guidelines and policies. Guidelines on compounding medicines. 2015. http://www.pharmacyboard.gov.au/Codes-Guidelines.aspx [cited 2017 Jan 9]
2. Burridge N, Deidun D. Australian don't rush to crush handbook. 2nd ed. Melbourne: The Society of Hospital Pharmacists of Australia; 2015.
3. Therapeutic Goods Administration. The Poisons Standard (the SUSMP). 1 November 2016. https://www.tga.gov.au/publication/poisons-standard-susmp [cited 2017 Jan 9]
4. Therapeutic Goods Administration. PIC/S guide to good manufacturing practice for medicinal products PE 009-8 - 15 January 2009. http://www.tga.gov.au/publication/manufacturing-principles-medicinal-products [cited 2017 Jan 9]
5. British Association for Parenteral and Enteral Nutrition (BAPEN) and British Pharmaceutical Nutrition Group. Administering drugs via enteral feeding tubes: a practical guide. 2004. http://www.bapen.org.uk/resources-and-education/education-and-guidance/clinical-guidance#guidanceDrugAdmin [cited 2017 Jan 9]
6. Haywood A, Glass BD. Pharmaceutical excipients – where do we begin? Aust Prescr 2011;34:112-4. http://dx.doi.org/10.18773/austprescr.2011.060
7. Pharmaceutical Society of Australia. Australian pharmaceutical formulary and handbook (APF): the everyday guide to pharmacy practice. 23rd ed. Canberra: PSA; 2015.
8. Kairuz TE, Laksmana I, Steadman KJ. History of extemporaneous compounding in Australia: changes and developments in the Australian Pharmaceutical Formulary. J Pharm Prac Res 2013;43:117-21. http://dx.doi.org/10.1002/j.2055-2335.2013.tb00233.x
9. Aulton ME, Taylor KM, editors. Aulton's pharmaceutics: the design and manufacture of medicines. 4th ed. London: Churchill Livingstone Elsevier; 2013.
10. Snape TJ, Astles AM, Davies J. Understanding the chemical basis of drug stability and degradation. Pharm J 2010;285:416.
11. Falconer JR, Wu Z, Lau H, Suen J, Wang L, Pottinger S, et al. An investigation into the stability and sterility of citric acid solutions used for cough reflex testing. Dysphagia 2014;29:622-8. http://dx.doi.org/10.1007/s00455-014-9558-1
12. Centers for Disease Control and Prevention (CDC). Multistate outbreak of fungal infection associated with injection of methylprednisolone acetate solution from a single compounding pharmacy - United States, 2012. MMWR Morb Mortal Wkly Rep 2012;61:839-42.

FURTHER READING

Glass BD, Haywood A. Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products. J Pharm Pharm Sci 2006;9:398-426.

Marriott JF, Wilson KA, Langley CA, Belcher D. Pharmaceutical compounding and dispensing. 2nd ed. London: Pharmaceutical Press; 2016.