In customising preparations to the individual needs of the patient, compounding pharmacists need to find an appropriate compromise between suitability and stability.

Stability vs suitability of compounded preparations: customisation with appropriate compromise

The Pharmacy Board of Australia’s Guidelines on Compounding of Medicines state that pharmacists are permitted to prepare a compounded preparation when there is no appropriate commercial product available or the commercial product is unsuitable. Section 6 of the Guidelines, requires pharmacists to undertake due diligence to ensure that the compounded preparation meets requirements of quality, stability, safety and efficacy, while collaborating with the prescriber to ensure suitability for each patient. The compounding pharmacist’s search for an appropriate balance between suitability and stability leads to a discourse, in order to attain customisation with appropriate compromise (see Figure 1).

It is worth noting that formulation chemistry is a unique scientific field, and that drug manufacturers spend years developing and testing formulas. In contrast, compounding pharmacists have access to formulas based either on:
• first principles with relatively very short expiry dates; or on
• empirical research and any corresponding stability studies, which may include slightly longer expiry dates.

In either circumstance, the formulas used by compounding pharmacists must include references of chemical, physical and microbial stability, with compounding decisions supported by evidence of efficacy and safety.

Formulation databases are available via professional publications and bodies such as the Australian Pharmaceutical Formulary and Handbook (APF), United States Pharmacopeia (USP), British Pharmacopoeia (BP), TGA-registered compounding suppliers such as Medisca and PCCA; and the International Journal of Pharmaceutical Compounding (IJPC).

However, given the very nature of extemporaneous compounding, which aims to customise medication for each individual patient’s needs, these databases cannot provide a formulation for every possible preparation. In these circumstances, pharmacists will need to adapt existing formulas or develop their own formulas in light of the requirements of the individual patient. When developing a master formulation record, the pharmacist must consider the factors related to the suitability of the formulation for the specific patient, while also considering the stability of a compounded preparation in its entirety. All components of the formulation need to be assessed, including the Active Pharmaceutical Ingredient (API), excipients, base, storage and packaging.

After completing this activity, the learner should be able to:
• describe stability factors to be considered when formulating compounded pharmaceutical products;
• list physical signs of instability of pharmaceutical products.

The 2010 Competency Standards addressed by this activity include: 1.3, 1.4, 2.3, 5.1, 5.2
The 2016 Competency Standards addressed by this activity include: 1.2, 1.3, 1.6, 2.2, 3.4

Suitability

Suitability-related factors include dosage form, frequency of dosage, strength, application site, allergy or intolerance to excipients, and taste. A common barrier to compliance in the paediatric and geriatric populations are patients

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who are unable to swallow tablets or capsules. They may prefer a compounded oral liquid dosage form, for example, if there is no commercially available suitable equivalent. Patients whose oral dosage of medication is causing adverse events such as nausea or sedation may prefer a topical dosage form. Can the preparation simply be compounded into an oral liquid or topical emulsion by incorporating crushed tablets or the contents of capsules into the base?

There are numerous references available to compounding pharmacists that can be utilised to assist with this step of the formulation development, including:

- Remington: The Science and Practice of Pharmacy by David B Troy, Paul Beringer*
- Guide to Good Manufacturing Practice for Medicinal Products*
- Guidelines for Safe Prescribing, Dispensing and Administration of Cancer Chemotherapy*
- Ansel’s Pharmaceutical Dosage Forms and Drug Delivery Systems by Loyd V Allen Jr*

* These references are suggested in the Guidelines on Compounding of Medicines. The references used to develop the formulation need to be recorded in order to meet the requirements of Standard 5: Compounding of the PSA’s Professional Practice Standards, Version 5.6

**Stability**

Loyd Allen Jr describes stability as “the extent to which a product retains, within specified limits, and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its preparation”.4

The physical stability of a preparation is generally the most commonly thought of as organoleptic properties (meaning involvement of the sense organs) are used. However, in reality the stability of a compounded preparation should encompass the five types of stability: chemical, physical, microbiological, therapeutic and toxicological (see Table 1).5

The stability of a preparation can be affected by external environmental factors, for example temperature, oxygen, and light, as well as physical properties of the components, including molecular weight, melting point, particle size and solubility. When developing a master formulation record, pharmacists can limit factors which affect stability through the considered choice of base, addition of excipients, adjusting storage requirements and changing the packaging in which the formulation is dispensed (see Table 2).

One of the most important factors affecting the stability of an aqueous preparation is pH. Several published documents provide the pH stability profile of different APIs, which the pharmacist can use to determine the target pH range that improves stability. Buffers are then used to increase or decrease the pH of the preparation until it is within this range.6

A common example of an oral extemporaneously compounded preparation where pH is pertinent is omeprazole suspension, a commonly prescribed medication for paediatric patients who are unable to swallow the commercially available capsules. Omeprazole exhibits maximum stability at pH 11 and rapidly decomposes below pH 7.8.10 The addition of sodium hydroxide solution will help increase the stability.

### TABLE 1: FIVE TYPES OF STABILITY6

<table>
<thead>
<tr>
<th>TYPE OF STABILITY</th>
<th>CONDITIONS MAINTAINED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical</td>
<td>Each active and inactive ingredient maintains chemical integrity and potency</td>
</tr>
<tr>
<td>Physical</td>
<td>Original properties including appearance, palatability, uniformity, dissolution, and suspendibility are maintained</td>
</tr>
<tr>
<td>Microbiological</td>
<td>Sterility or resistance to microbial growth is retained</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>Therapeutic effect remains unchanged</td>
</tr>
<tr>
<td>Toxicological</td>
<td>No increase in toxicity</td>
</tr>
</tbody>
</table>
alkalinity of the suspension to above 7.8. Alternatively, there are several pre-made proprietary bases on the market that contain an alkaline buffer system, which can be used for APIs such as omeprazole. This is a classic example of the stability versus suitability dilemma, as preparations with alkaline pH are more irritating for patients, yet for stability reasons the preparation cannot be compounded with a pH of 7; despite the neutral pH being more comfortable for the patient.

Rebecca O’Grady has worked in both community and compounding pharmacy, completing her internship in one of Sydney’s largest compounding pharmacies. She has been with Medisca Australia since 2016 as a part of the Technical Support Services Division, working on the development, accreditation and facilitation of CPD training activities.
**Case Study 1**
A prescription is received for metronidazole suspension 200mg/5mL, dose 150mg twice daily for a 4-year-old child. At this time, the commercially available product is out of stock. The tablets are unsuitable as the child is unable to swallow them. After a discussion with the physician, it is agreed that an extemporaneously compounded liquid will need to be prepared, as there is no other bulk-manufactured therapeutically appropriate option for this child.

To meet patient suitability, the preparation must be a palatable oral liquid. The oral solid dosage form, such as the commercially available tablet, is more stable than the compounded oral liquid. Despite this consideration, stability needs to be balanced with suitability for the specific patient.

The Guidelines require a pharmacist to use pure powders of APIs when available, rather than modifying a commercial product. When crushing a tablet, the compounder adds another uncertainty to stability, since the unintended inclusion of the excipients from the bulk-manufactured product can affect both the composition of the preparation and bioavailability of the active. When determining a suitable vehicle for the preparation, the solubility of the API(s) should be considered. Metronidazole is sparingly soluble in both alcohol and water. Metronidazole inhibits alcohol metabolism, hence alcohol would not be a suitable solvent for this formulation, due to the increased risk to the patient. Since metronidazole is only sparingly soluble in water, an aqueous solution would not be an appropriate formulation type. A suspension would be the most appropriate formulation. Metronidazole is available in the free base form and the salt form, metronidazole benzoate.

When developing a formula, pharmacists need to take into consideration which form of the API they are using. In this case, metronidazole is a very bitter API, which would affect compliance. The benzoate salt form has a bland taste and therefore should be used. The conversion factor between the two forms also needs to be calculated. The pharmacist should flavour the suspension with a flavour appealing to the child to improve compliance. This is an example where the customisation of the formulation outweighs the compromise to the stability of the formulation in order to improve compliance and patient outcome.

**Case Study 2**
An adult patient has requested that you compound for them an oral liquid of aspirin (acetyl salicylic acid) as they are unable to swallow the tablets. If stability is ignored and only suitability is considered, an oral liquid would be suitable for the patient, given the ease of swallowing a liquid compared to a tablet. Among the many variables that would affect the stability of the preparation, aspirin is known to undergo hydrolysis to salicylic and acetic acids in an aqueous environment.

This is an example where the compromise to the stability of the preparation outweighs the customisation benefit for this patient. There are several commercial products available on the Australian market, which would meet the suitability requirements of this patient including effervescent and chewable tablets, without compromising stability. In addition, this situation does not meet the circumstance requirements set out in the Guidelines on compounding of medicines to permit the extemporaneous compounding of this preparation. Oral liquid aspirin should not be compounded.

**Case Study 3**
A patient presents with a prescription for a melatonin suspension 5mg/mL; 5mg before bed, provide six months’ supply. The patient lives on a rural property, which is approximately a 2-hour drive from the closest compounding pharmacy. In the absence of a stability study, the maximum length expiry date that can be assigned to an oral liquid is 28 days as per the APF. While it may be suitable for the patient to have six months of their medication dispensed at once, in the absence of a stability study, it is unknown whether this preparation would be stable for this length of time.

There are stability-studied formulations for extemporaneously compounded melatonin 2mg/mL suspensions which, when followed exactly, would provide a 90-day expiry date. These stability-studied formulas need to be followed without any deviation in preparatory steps, packaging and storage conditions, otherwise the APF expiry dates prevail. Although a 6-month expiry date can be assigned to oral powder-containing capsules, providing all components used have an expiry of six months or longer remaining, they are stable in air and are not hygroscopic, the dilemma here is that melatonin is a light-sensitive API. The APF does not provide guidance on how to assign expiry dates in these circumstances. This is again a balance between stability and suitability. Even if the oral powder capsules have a longer expiry date, the patient may find that an oral liquid is more suitable for them to swallow. The pharmacist will need to consult with both the prescribing physician and the patient.

**Case Study 4**
A middle-aged female presents to the pharmacy to have her prescriptions filled, who reveals that she does not always take her oral progesterone capsules, as she finds she experiences daytime drowsiness. She asks whether there are alternatives.

When considering compounding, if stability is neglected a transdermal cream or sub-buccal troche may be compounded, which will aim to reduce the adverse effects by reducing first pass metabolism. If suitability is neglected, oral capsules may be compounded, as they are the most stable dosage form. The oral capsules have proven not to be the most appropriate dosage form for this patient as she is non-compliant. This is not surprising given that progesterone metabolites, such as allopregnanolone, are known to be potent positive allosteric modulators of GABAA receptors, and produce sedative-like effects.

The pharmacist will need to have a discussion with the prescribing physician to determine the extent to which the stability may be compromised in order for the medication to be suitable for the patient to improve compliance.
1. When considering the stability of a compounded preparation, which of the following components need to be assessed?
   i. Active Pharmaceutical Ingredient
   ii. Packaging
   iii. Excipients
   iv. Base

   A i.
   B i, ii
   C i, iii, iv
   D i, ii, iii, iv

2. Identify the INCORRECT statement below regarding stability of compounded preparations.
   A Theoretical stability can be determined using first principles.
   B Pharmacists should only consider the physical stability of compounded preparations.
   C Stability needs to be considered of the entire formulation including active pharmaceutical ingredient(s), excipients, base, storage and packaging.
   D There are measures a pharmacist can take when formulating to help decrease instability of compounded preparations.

3. Which of the following is not an organoleptic sign of instability?
   A Odour
   B Discolouration
   C Heat labile
   D Consistency
   E Texture

4. Which of the following are physical signs of instability in dosage forms?
   A Discolouration of a capsule
   B Phase separation of an ointment or cream
   C Hardening and change of shape of suppositories
   D Growth of crystals in a suspension
   E All of the above

5. Which of the following are suitability factors when considering extemporaneously compounding medications for patients?
   A Dosage form
   B Route of administration
   C Allergy
   D Strength
   E All of the above

5. USP <1191> Stability considerations in dispensing practice, August 2017.