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Stability vs suitability of compounded preparations:

customisation with appropriate compromise

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

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

apc | ACCREDITED CPD

Accreditation Number: A1711AJP2
This activity has been accredited for 1 hour of Group 1 CPD (or 1 CPD credit) suitable for inclusion in an individual pharmacist's CPD plan which can be converted to 1 hour of Group 2 CPD (or 2 CPD credits) upon successful completion of relevant assessment activities.
Accreditation expires: 01/11/2019

The Pharmacy Board of Australia's *Guidelines on Compounding of Medicines*[1] 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.

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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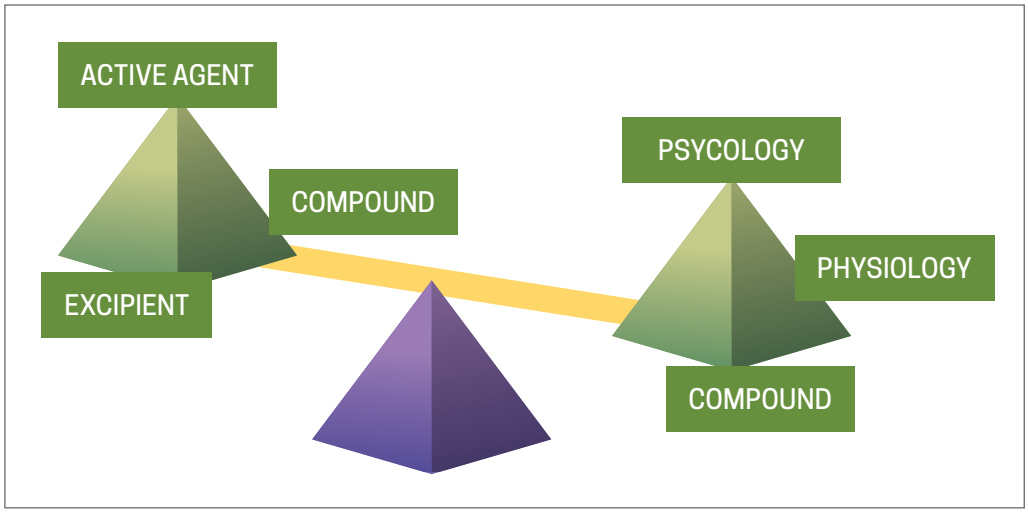

FIGURE 1: **BALANCING ACT OF STABILITY VS SUITABILITY[2]**

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:

- *The Art, Science and Technology of Pharmaceutical Compounding* by Loyd V Allen Jr*
- *The Handbook of Pharmaceutical Excipients*
- *Martindale: The Complete Drug Reference**
- *The Merck Index*
- *Trissel's Stability of Compounded Formulations* by Lawrence Trissel*
- *Australian Don't Rush to Crush Handbook* by The Society of Hospital Pharmacists of Australia*
- *The United States Pharmacopeia/ National Formulary*
- Safety Data Sheets (SDS)
- Certificate of Analysis (CoA)
- *International Journal of Pharmaceutical Compounding* (IJPC)*
- *Handbook on Injectable Drugs* by American Society of Health-System Pharmacists*
- *Pharmaceutical Calculations* by Howard C Ansel and Mitchell J Stoklosa*
- *Australian Injectable Drugs Handbook* by The Society of Hospital Pharmacists of Australia
- *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 prepration".[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.[4]

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.[3,10] The addition of sodium hydroxide solution will help increase the

TABLE 1: **FIVE TYPES OF STABILITY[5]**

TYPE OF STABILITY	CONDITIONS MAINTAINED
Chemical	Each active and inactive ingredient maintains chemical integrity and potency
Physical	Original properties including appearance, palatability, uniformity, dissolution, and suspendibility are maintained
Microbiological	Sterility or resistance to microbial growth is retained
Therapeutic	Therapeutic effect remains unchanged
Toxicological	No increase in toxicity

TABLE 2 : **FACTORS THAT AFFECT STABILITY**[2]

Absorption	Diffusion coefficient	Lipophilicity	Reactivity
Adsorption	Disintegration	Lubricity	Rectal retention
Affinity	Dispensing container	Melting point	Sedimentation
Bio-adhesion	Dispersion	Microbial proliferation	Solubility
Buccal retention	Dissolution	Molecular weight	Sorption
Buffering capacity	Ease of administration	Odour	Stability
Caking	Efflorescence	Organoleptic properties	Surface Area
Chelation	Flavour	Oxidation--reduction	Suspendability
Coloration/ discoloration	Flowability	Particle size	Taste
Consistency	Heat labile	Partition coefficient	Temperature Sensitivity
Creaming	Hydrophilic–lipophilic balance	pH; pKa and pKb	Texture
Crystalline form/ crystallisation	Hydrolysis	Phase inversion	Tonicity
Deliquescence	Hydrophilicity	Photosensitivity/light	Viscosity
Density	Hygroscopicity	Polarity	Washability
Diffusion	Ionization balance	Rate of absorption	Wettability

TABLE 3 : **PHYSICAL SIGNS OF INSTABILITY**[4]

DOSAGE FORM	SIGN
Capsules	Discolouration, distortion of capsule shell
Solutions	Discolouration, precipitation
Emulsions	Breaking, creaming
Suspensions	Caking, crystal growth
Ointments	Phase separation, drying
Creams	Phase separation, crystal growth, discolouration
Suppositories	Softening, hardening, change in shape
Gels	Shrinkage, phase separation, discolouration
Troches	Softening, hardening, crystallization, discolouration

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.

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Table 3 lists the physical signs of instability for different dosage forms.

The theoretical stability of a preparation can be determined using first principles. In Australia, as per the APF, a theoretical stability of a maximum of 28 days expiry date is utilised unless otherwise specified in the APF.[3] Alternatively, to assign a longer expiry date, a stability study should be conducted to support the extension, although extemporaneously compounded preparations should not have an expiry date of longer than six months applied.[3]

In summary, the customisation of an extemporaneously compounded preparation for an individual patient needs to consider factors that deem the commercially available drug unsuitable for the specific patient, balanced with factors which compromise the stability of the preparation. Without these considerations as part of the risk assessment, there is no confidence that patient outcomes are likely to be improved by the compounded preparation.

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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.[1] 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.[7] 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[10] 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.[11]

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.[9] 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,[3] the dilemma here is that melatonin is a light-sensitive API.[8] 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 are to be potent positive allosteric modulators of GABAA receptors, and produce sedative-like effects.[12]

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.

2 CPD CREDITS GROUP TWO

PRACTICE UPDATE

Stability vs suitability of compounded preparations: customisation with appropriate compromise

This unit attracts up to 2 Group Two CPD credits. Accreditation number: A1709AJP2. Accreditation expires: 01/11/2019. *Each question has only one answer.*

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

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