# Excipient selection for compounded pharmaceutical capsules: they're only fillers, right?

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Excipients are not merely inert fillers and, in contrast, may affect bioavailability to the extent of causing significant patient harm.

## Function of excipients in pharmaceutical formulations

Pharmaceutical excipients offer compatibility for the specific needs of the patient, as they address patient adherence. They also have a significant role in maintaining stability of the active pharmaceutical ingredient (API) over time, such as protecting the API from degradation. Essentially, excipients function to regulate or balance the electrochemical and physical properties of the dosage form thus contributing to the creation of environments that affect stability, solubility, permeation and absorption. Excipients are functional ingredients that facilitate the therapeutic function of the API, not just inert ingredients in a formulation.

Factors compounding pharmacists must consider when selecting the most appropriate excipients[1] include the:

- stability of the active ingredient, such as hygroscopicity, oxidation, hydrolysis;
- physical properties of the active ingredient, such as the powder flowability, suspendability, colour, flavour, smell and texture;
- pH of solubility and pH of stability of the active ingredient within the formulation base, for aqueous solutions and suspensions;
- solubility of the active ingredient in the biological environment in which it is to be delivered;
- potential interaction between the API and excipients;
- potential interaction between the excipient and the intended packaging;
- bioavailability of compounded formulation compared to the commercial formulation, pertinent in cases when the compounding rationale is to address proprietary drug shortages;
- physical, chemical and microbial stability of the overall formulation;
- desired onset of action, duration of action and therapeutic intent; and
- patient-specific allergies and intolerances.

## Types of excipients used in powder-filled oral compounded capsules

This article will focus on excipients specific to oral compounded capsules, particularly diluents. Far more than being 'just a filler', an appropriately chosen diluent, in an appropriate concentration, can alter the bioavailability of active pharmaceutical ingredient, influencing whether a drug dose is:

- within the therapeutic window;
- below it, in which case efficacy is by definition unachievable; or
- above it, in which case adverse events are more likely and toxicity may occur.

A dramatic example where a change in the capsule excipient blend altered efficacy, is given by Lloyd Allen.[2] A change in the excipients in a phenytoin formulation of a commercially manufactured product in the 1960s in Australia lead to cases of toxicity. Following the cases of toxicity, the capsules' potency was analysed and found to contain the labelled amount of phenytoin, which confirmed that the correct amount of active was included in the manufacturing process.

In addition, the investigation determined that:

- all the affected patients had received the same brand of 100mg phenytoin capsules;
- the new formulation had replaced calcium sulfate with lactose; and
- the new formulation had slightly increased amounts of magnesium silicate and magnesium stearate.

**AFTER COMPLETING THIS ACTIVITY, THE LEARNER SHOULD BE ABLE TO:**

- describe types of excipients used in powder-filled oral compounded capsules;
- describe factors to consider when choosing excipients for capsule formulations;
- explain the significance of the Biopharmaceutical Classification System (BCS) of active pharmaceutical ingredients and its relevance to the selection of excipients;
- understand factors to consider when compounding slow-release capsules.

The 2010 Competency Standards addressed by this activity include (but may not be limited to): 5.1, 5.2

The 2016 Competency Standards addressed by this activity include (but may not be limited to): 3.4

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Considering the solubilities of the excipients for which the amounts were significantly altered:

- calcium sulfate is listed as "slightly soluble in water";
- lactose is listed as "freely soluble in water".

Since the API phenytoin (the active) is "freely soluble in water", the lactose (excipient filler) would serve to increase the "wetting" of the active, thereby enhancing the dissolution of the active, which consequently lead to increased absorption and the systemic toxicity in patients. This was confirmed when the production of the capsule returned to the previous formula containing the calcium sulfate instead of lactose, as the patients' serum levels returned to normal.

This example demonstrates that excipients are not merely inert fillers and, in contrast, may affect bioavailability to the extent of causing significant patient harm.

Table 1 identifies types of excipients and the reasons for their use in capsules. Table 2 lists specific excipients and their respective function in powder-fill capsules.

When selecting only one excipient as the filler, such as the commonly used microcrystalline cellulose, the potential beneficial attributes of other excipients are foregone. Lactose monohydrate, which is also a commonly used filler in compounding, exhibits poor flowability and interacts with various drug actives.[3] In contrast, a considered combination of excipients ameliorates the formulation. An ideal capsule powder blend for compounded capsules may have the following properties:

- lactose-free to accommodate patient-specific intolerance;
- gluten-free to accommodate patient-specific intolerance;
- neutralise electrostatic repulsion of highly static APIs;
- increase chemical stability;
- increase drug dissolution;
- assist with disintegration, if necessary;
- provide bulk; and
- increase compounding efficiency.

## Selecting excipients for compounded capsules using biopharmaceutical classification system

In 1995, Amidon *et al* introduced the concept of the Biopharmaceutical

TABLE 1: **TYPES OF EXCIPIENTS AND THE REASONS FOR THEIR USE IN CAPSULES**

| EXCIPIENT TYPE | REASONS FOR USE |
|---|---|
| **Diluent** | Fill empty space; increase accuracy |
| **Glidant** | Reduces a powder's adherence to plastics |
| **Electrostatic neutralizer** | Reduce electrical charge; prevents running up metal |
| **Adsorbent** | To reduce or prevent two chemicals from undergoing sorption |
| **Flow agent** | Reduces powders from sticking to surfaces and/or to itself |
| **Slow-release agent** | Retards the bioavailability of active agent |
| **Chelating agent** | Binds to and neutralizes trace metals |
| **Antioxidant** | Prevents oxidation |
| **Tracer Dye** | Quality assurance measure; visible test |

TABLE 2: **SPECIFIC EXCIPIENTS AND THEIR RESPECTIVE FUNCTION IN POWDER-FILLED CAPSULES**

| FUNCTION | EXCIPIENT |
|---|---|
| **Adsorbent** | Bentonite |
| **Diluent** | Acidophilus |
| **Diluent** | Calcium carbonate |
| **Diluent** | Lactose, anhydrous |
| **Diluent** | Lactose monohydrate |
| **Diluent** | Mannitol |
| **Diluent; Adsorbent** | Magnesium carbonate |
| **Diluent** | Magnesium oxide |
| **Diluent** | Microcrystalline cellulose |
| **Diluent** | Sorbitol |
| **Diluent** | Starch |
| **Diluent; Glidant** | Talc |
| **Diluent** | Tapioca powder |
| **Flow agent** | Sodium bicarbonate |
| **Glidant** | Magnesium stearate |
| **Neutralise electrostatic repulsion** | Silica gel |
| **Neutralise electrostatic repulsion** | Sodium lauryl sulphate |
| **Slow-release agent** | Hydroxypropyl methylcellulose |

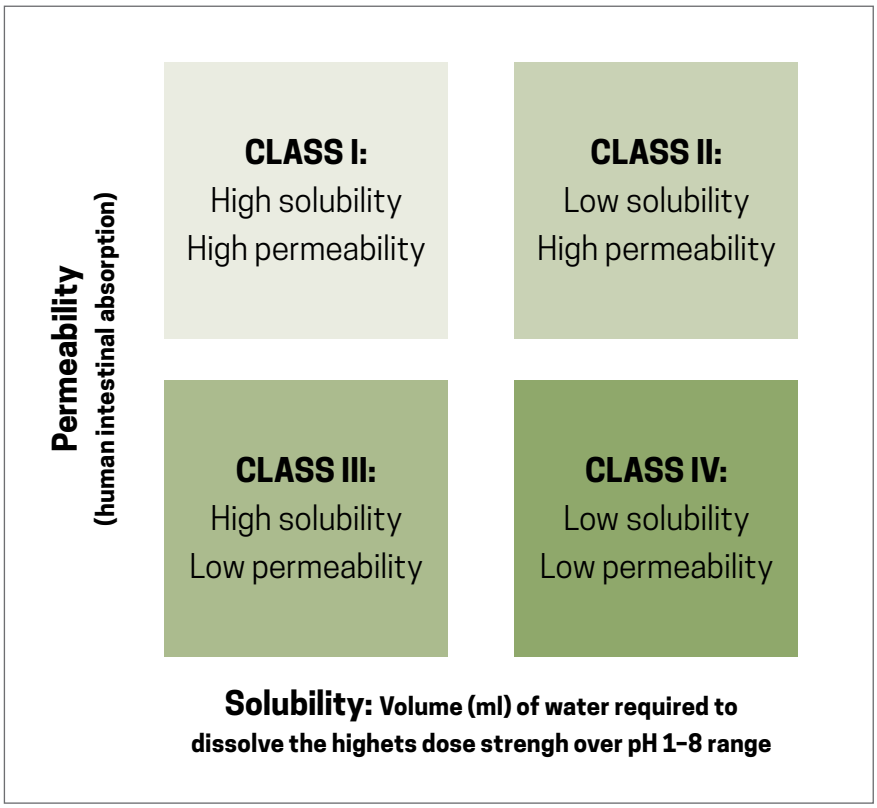


FIGURE 1: **THE FOUR CLASSES OF THE BIOPHARMACEUTICAL CLASSIFICATION SYSTEM**

Classification System (BCS).[4] The BCS was developed as a means to provide a scientific approach for drug classification based on aqueous solubility and intestinal permeability. For instance, a drug is considered highly permeable when the extent of absorption in humans is more than 90% and highly soluble when the highest dose is soluble in 250mL or less of buffer, ranging between a pH of 1 and 7.5.

Hence, the BCS covers the three main factors which govern the rate and the extent of drug absorption from immediate release solid oral dosage forms (e.g. tablets, capsules). These factors are:

- dissolution rate;
- solubility; and
- permeability.[5]

The four classes of the BCS shown in Figure 1 are Class I, Class II, Class III and Class IV.

Class I medications normally have few bioavailability challenges; hence suitable excipient blends need to offer flowability and disintegration without impeding dissolution. Class II medications are limited in their absorption capabilities; hence ingredients need to aid dissolution and act as wetting and disintegrating agents. Class III medications require absorption-enhancing excipients. Class IV medications may have serious bioavailability obstacles, requiring absorption-enhancing excipients.[6]

The BCS provides an insight into properties of active pharmaceutical ingredients and consequently the properties of the excipients required in formulations. The BCS is used by the pharmaceutical industry to select excipients for manufactured immediate release capsule and tablet products.[7,8,9] It may be used by compounding pharmacists such as when compounding immediate-release capsules. To address the needs of each biopharmaceutical class, a blend containing different excipients could be used in the compounded formula.

When compounding capsules, selecting an excipient powder blend that provides protection of the active ingredient(s) from degradation is the first priority. Oxidation and light sensitivity may be managed when considering choice of storage, the handling and packaging of the active(s) and the compounded preparation.

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If the active is hygroscopic, protecting it from degradation due to hygroscopicity is the priority, for which specific powder blends are available or may be developed. For non-hygroscopic APIs, the blend should be based on the solubility of the drug at the prescribed dose in a volume of 250mL. A compounding pharmacist should choose a blend based on the considerations shown in Figure 2.[10]

The Dose Number concept developed by Amidon assists in understanding whether the drug has a high solubility or low solubility considering the dose and the volume of fluid with which it will be taken.

According to Ferreira in 2008, to determine the Dose Number, use the equation:[11]

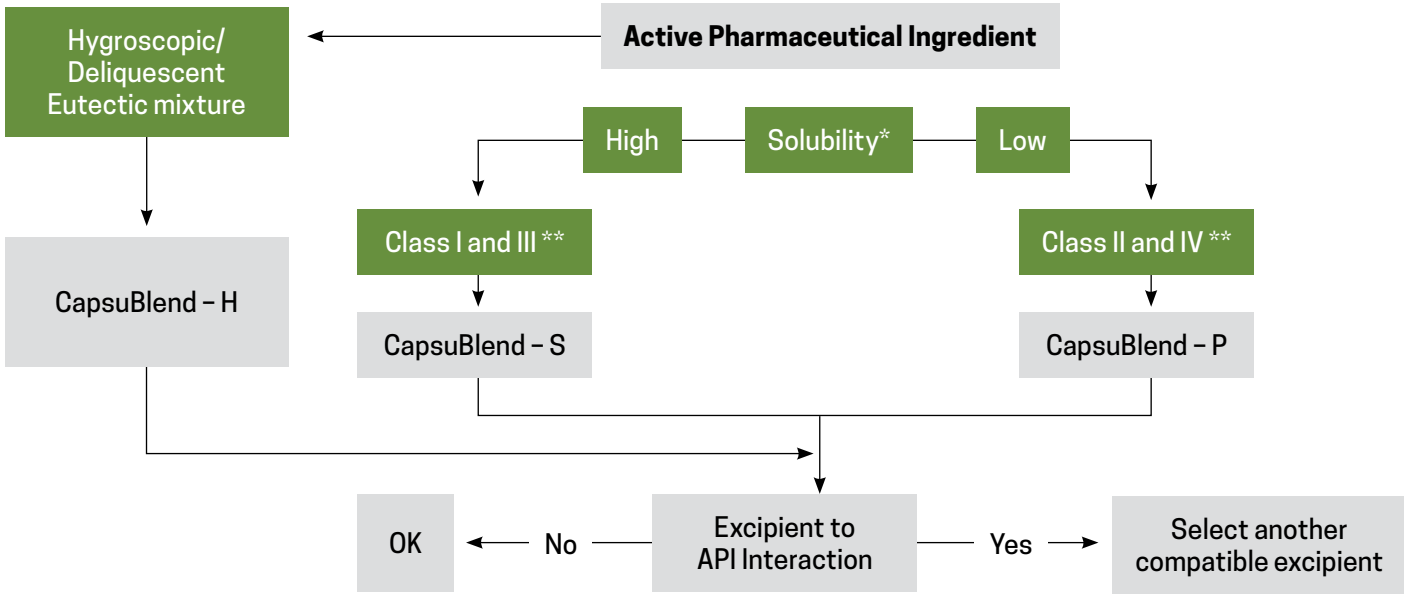
$$\text{Dose Number} = \frac{\text{Highest Usual Dose (mg)} \div 250\text{mL}}{\text{Solubility of API (mg/mL)}}$$

$$\text{Do} = \frac{\text{Mo} \div \text{Vo}}{\text{So}}$$

Where: **Do** is the Dose Number
**Vo** is the volume of water with which the dose should be taken (250 mL)
**So** is the aqueous solubility of drug (refer to *Merck Index*, *Martindale*).

Where Do is <1, use an excipient blend suitable for highly soluble actives.*
Where Do is >1, use an excipient blend suitable for poorly soluble actives.*
* Solubility concept according to BCS developed by Amidon, not according to API solubility.[3]

Pharmacists may refer to the BP Solubilities Table[10] in order to convert word definitions of solubility, into numerical values, which can be inserted into the above equation.




*Volume (mL) of water required to dissolve the highest dose strength over pH 1–8 range.

**Biopharmaceutical Classification System.

FIGURE 2: **FLOWCHART FOR SELECTION OF PREMIXED EXCIPIENTS FOR ORAL COMPOUNDED CAPSULES**[10]

## Melatonin capsule example in the BCS

Melatonin 5mg capsules, 1 nocte. Melatonin is slightly soluble in water and not hygroscopic. The BP Solubilities table defines slightly soluble as "from 100 to 1000 parts". Meaning solubility ranges from 1000mg/100mL to 1000mg/1000mL. In the worst case scenario, solubility is 1000mg/1000mL, which equates to 1mg/mL.

This example emphasises that BCS considers more than the aqueous solubility of the drug. Although melatonin is slightly soluble in the water, the DO number is <1, which classifies it as a highly soluble active.* The reason being, that considering a volume of 250 mL of water and a very low therapeutic dose, this drug is highly soluble as per Amidon's concept.

$$\text{Number of Doses} = \frac{\text{Usual Dose} \div 250\text{mL}}{\text{Solubility of API (mg/mL)}}$$

$$\text{Do} = \frac{5\text{mg} \div 250\text{mL} = 0.02}{1\text{mg/mL}}$$

Since Do <1, use excipient powder blend suitable for highly soluble actives.*

## Naltrexone capsule example in the BCS

Naltrexone capsules 3mg, 1 daily, solubility 100mg/mL; hygroscopic active

$$\text{Number of Doses} = \frac{\text{Usual Dose} \div 250\text{mL}}{\text{Solubility of API (mg/mL)}}$$

$$\text{Do} = \frac{3\text{mg} \div 250\text{mL} = 0.00012}{100\text{mg/mL}}$$

Irrespective of solubility, since it is a hygroscopic API ➔ use the excipient blend suitable for hygroscopic actives.

There are a number of proprietary pre-mixed excipient blends on the market. The Capsublend range, developed by Medisca is based on the BCS to meet the specific requirements of drugs within BCS classes.[11] The range contains various combinations of glidants, diluents, electrostatic repulsion neutralisers and disintegrants in three different excipient blends:

1. Capsublend-H, for hygroscopic drugs
2. Capsublend-P, for drugs identified as poorly soluble in the BCS by Amidon
3. Capsublend-S, for drugs identified as highly soluble in the BCS by Amidon.

LoxOra is a powder blend to improve the dissolution of actives and reduce static[12] developed by PCCA. This one excipient blend is designed to be used in any oral capsule formulation and with most APIs according to PCCA.

## Compounding slow-release capsules

Compounding pharmacists are often asked to compound hard gelatin capsules with a slow-release component in order to improve patient adherence and pharmacotherapy.[13,14] This kind of preparation is suitable for APIs that require frequent dosing within a 24-hour period due to their short half-life.[3,6] A consequential benefit when compounding slow-release oral capsules is the advantage of minimising a high peak blood level that is sometimes associated with untoward effects. "The onset is a little slower and the release is a little prolonged, but not within narrowly defined limits. This aids in patient adherence and is one aspect of pharmaceutical care."[15]

There are a number of terms that should not be used for compounded formulations as the terms have specific definitions in the pharmaceutical industry and the United States *Pharmacopoeia*, which could imply that

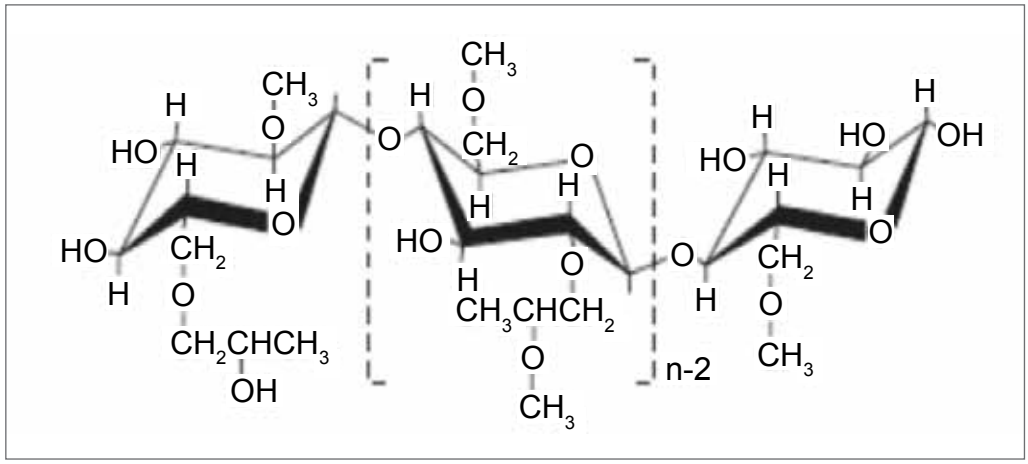



FIGURE 1: **TYPICAL CHEMICAL STRUCTURE OF HYDROXYPROPYL METHYLCELLULOSE (HPMC)[13]**

the compounded preparation is the same as the commercially available product. These terms are as follows:[13]

**1.** Controlled release
**2.** Delayed release
**3.** Extended release
**4.** Long acting
**5.** Modified release
**6.** Prolonged action
**7.** Sustained action
**8.** Sustained release
**9.** Targeted release

Unless there are supportive studies, only the term 'Slow Release' may be used on labels of extemporaneously prepared capsules designed to release slowly. In the absence of bioavailability studies and clinical research giving rise to a plasma-drug concentration profile, the claims attributed to a compounded delivery system need be conservative. In the context of pharmacy compounding where there is an absence of appropriate experimental testing procedures, the base used with a compounded dosage form (composed of the excipients) should not be thought of as having the status of that developed by a research laboratory.

Under no circumstances can a compounded medication be labelled with the proprietary name of the original brand, as the pharmacokinetic features cannot be assumed to be the same. Moreover, intellectual property laws abide, aside from misleading representations.

The mechanism which slows drug release relies on the powder mixture forming a hydrophilic gel system. When the slow-release polymer comes into contact with an aqueous medium, a strong viscous gel is formed.[16] The gel layer formed within capsules tends to be weaker than that provided in tablets due to the low compaction of the contents. The dissolution rate and API delivery is then determined by the diffusion of the API through this gel layer.

Drug solubility is a very important factor which needs careful consideration on a case-by-case basis. Different drug characteristics, such as high or low solubility, affect gel characteristics and drug release. High-solubility drugs can dissolve by diffusing through the gel matrices and this is considered to be the main pathway for their release. However, release also occurs through erosion of the gel matrix. It is said that highly soluble drugs also act as pore formers with the formation of micro-cavities and make the gel structure more porous and weaker, hence leading to increased drug release rates.[17]

In order to slow the release of active drugs, compounding pharmacists prepare capsules that contain a mixture of the API and specific celluloses at a set percentage and a secondary diluent such as microcrystalline cellulose,[13] which is not known to affect the release rate. Trituration, geometric dilution and uniformity in the preparatory procedures are required. Quality compounding also requires validation and quality assurance measures.

Hydroxypropylmethylcellulose (HPMC), more commonly known as hypromellose,[18] is a water soluble, hydrophilic, non-ionic polymer derived from cellulose[17,19] used to retard release of compounded APIs. It is enzyme resistant and stable over a pH range of 3–11.

HPMC is considered a stable non-toxic, non-irritating material, widely used in the pharmaceutical industry, compatible with most APIs apart from some oxidizing agents.[18] It is non-ionic, and thereby has minimal interaction with acidic, basic, or electrolytic systems, and is suitable with soluble and insoluble drugs at high and low concentrations. HPMS provides the release of a drug in a controlled manner, effectively increasing the duration of release of a drug to prolong its therapeutic effect.[17]

The solution viscosities of celluloses are given in millipascal-seconds (mPa.s) measured at 2% concentration in water at 20°C. The viscosity of an aqueous solution of the Methocel cellulose ethers, products of Dow Chemicals, is proportional to the molecular weight or chain length of the specific Methocel product used. Methocel cellulose ethers are available in various viscosity grades, ranging from 3mPa.s to 20,000mPa.s. For example, Methocel E4M is a HPMC, which is commonly used in slow-release compounded capsules, has a viscosity 4000 mPa.s; while Methocel E10M is a HPMC with a viscosity of 10,000 mPa.s.

The concentration of the cellulose also determines the viscosity of the solution. Although some researchers report wider ranges in the order of 10% w/w to 80% w/w,[18] there is much evidence that 30% w/w to 40% w/w of specific types of hydroxypropylmethylcellulose result in reliable and consistent drug systems.[13,17,20]

Two slow-release extemporaneously compounded niacinamide capsule preparations containing 40% and 60% v/v hypromellose respectively, were studied in comparison to an immediate release proprietary product. The release rates were 80% of the API released at 6 hours, 7 hours and less than 20 minutes

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PRACTICE UPDATE

## Excipient selection for compounded pharmaceutical capsules: they're only fillers, right?

This unit attracts up to 2 Group Two CPD credits. Accreditation number: A1708AJP1. Accreditation expires: 01/08/2019.

*Each question has only one CORRECT answer.*

**1. Select the TRUE statement regarding the Biopharmaceutical Classification System (BCS):**

A The BSC is used by the pharmaceutical industry and compounding pharmacies in consultation with the FDA.
B The BSC categorises APIs according to their dissolution rate, solubility and permeability at its highest dose in 250mL of buffer.
C According to the BSC, an API which is highly insoluble in water will always require excipients to improve its bioavailability.
D Excipient selection is unimportant when considering the electromagnetic properties of an API.

**2. When determining the choice of excipients for a capsule which of the following factors need/s to be considered?**

A The hygroscopicity of the API is the first factor to consider.
B The taste and smell of the API.
C The BCS class that the specific dose of the API falls into.
D All of the above

**3. Which excipients are commonly used in pharmaceutical compounding to slow the release of the active in an oral compounded capsule dosage form?**

A Hydroxypropylmethylcellulose
B Microcrystalline cellulose
C Methocel E4M
D A and C
E All of the above

**4. Identify the FALSE statement(s) below in relation to the amount of the excipient intended to slow the release of an API in compounded capsules.**

A The amount varies depending on the solubility properties and dose of the API.
B Capsule fill volumes in the order of 30-40% are commonly used.
C Ranges of 10% w/v to 80% w/v have been used.
D NONE of the above statements are FALSE.

**5. Identify the TRUE statement(s) below in relation to the claims which can be made in relation to compounded capsules with impaired release properties.**

A Pharmacists may use the term "control release" in reference to capsules that have been compounded with polymers that retard the release of the API.
B Pharmacists may make a definitive claim about the duration of action of the slow-release formulation based on first principles.
C Pharmacists may use the trade name of a slow-release drug compounded only during a drug shortage.
D None of the above statements are TRUE.

respectively. The results suggest that slow-release niacinamide capsules can be compounded using hypromellose as the sole release modifier and that the release mechanism is comparable to hydrophilic polymer matrix-based systems.[21]

While numerous studies have shown that hypromellose attenuates the release of APIs from capsules, compounders need to be cognisant to avoid making claims about the time frame over which an API will be released from a compounded slow-release capsule[1,3] unless they have conducted appropriate dissolution studies for their specific formulation. As illustrated above, the release rate for a specific slow-release formulation cannot be specified with certainty unless studied, irrespective of whether the formulation was compounded or otherwise. As with all quality management systems monitoring is required, in this case the response of the patient needs to be monitored.

In summary, the choice of excipients in a compounded capsule will directly affect bioavailability and the pharmacokinetic profile of the compounded medication. The properties of particular inert cellulose will determine the rate of release of the active agent. Therefor the choice of excipients requires careful consideration for improved patient outcomes and in order to manage potential harm to the patient. ●

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1. Jouyban A. Handbook of solubility data for pharmaceuticals. CRC Press, 2009; 2.
2. Loyd V Allen Jr, Clinical pharmaceutics and compounding, Part V. Compounding Today. 2014 Oct 10; 11(40).
3. Ferreira AO, Guia practico da farmacia magistral, Vol 1, ed 3. Sao Paulo, Brazil: Pharmabooks, 2008;106-16.
4. Amidon GL, et al. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995 Mar;12(3):413-20.
5. Bock U, et al. Validation of the Caco-2 cell monolayer system for determining the permeability of drug substances according to the Biopharmaceutics Classification System (BCS). Across Barriers. 2003 Jul:1-7.
6. Pinheiro V, et al. In vitro evaluation of extemporaneously compounded immediate-release capsules. Int J Pharm Compd. 2013 Sept/Oct; 17(5):424-31.
7. Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Guidance for Industry. FDA, May 2015.
8. www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm128219.htm.
9. Waiver of Bioequivalence Study. FDA, Aug 2000.
10. Woods DJ. Formulation in pharmacy practice. 2nd edn. Available at www.pharminfotech.co.nz/manual/Formulation/mixtures/pages/solubilities.html.
11. www.medisca.com.au/Pages/ProductDetails.aspx?StockCode=2595&C=B&C2=112.
12. www.pccarx.com.au/products/pcca-exclusives/bases.
13. Zur E. Compounding slow-release capsules: a comprehensive review and an excel spreadsheet for faster calailtaions of excipients. Int J Pharm Compd. 2013 Jan/Feb; 17(1):10-22.
14. Vu N, et al. Compounding slow-release pharmaceuticals. Int J Pharm Compd. 2009 Mar/Apr;13(2):144-5.
15. Allen L. Prescription. Int J Pharm Compd. 2003 Nov/Dec;7(6):418.
16. Tiwari S, et al. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS PharmSciTech. 2003;4(3):Article 31.
17. Li C, et al. The use of hypromellose in oral drug delivery. J Pharm Pharmacol. 2005;57:533-46.
18. Rowe RC, et al. Hypromellose. In: Handbook of pharmaceutical excipients. 7th edn. London: Pharmaceutical Press, 2012:373-76.
19. https://pubchem.ncbi.nlm.nih.gov/compound/57503849.
20. Pinheiro V, et al. Development and in vitro evaluation of extended-release theophylline matrix capsules. Braz J Pharm Sci. 2007 Apr/Jun;43(2).
21. Radojkovic B, et al. Compounding of slow-release niacinamide capsules: feasibility and characterization. Int J Pharm Compd. 2012;16(5):434-7.