ELSEVIER

Extemporaneously prepared controlled release formulations for accelerating the early phase development of drug candidates

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Extemporaneous drug preparations, which are compounded by a pharmacist at a clinical site, are commonly used in early clinical studies to evaluate the performance of drug candidates. However, the types of formulations compounded have been limited to relatively simple preparations such as solutions, suspensions and active ingredients filled into capsules. This article describes the preparation of advanced formulations, specifically extemporaneously prepared matrix tablets and osmotic capsules, which can be used to evaluate the feasibility of controlled release for exploratory new drug candidates or new formulations of existing drugs with a differentiated medical advantage. Extemporaneously prepared dosage forms enable the rapid assessment (i.e. reduced cycle time) of new formulation ideas with minimal quantity of the active pharmaceutical ingredient needed to demonstrate proof-of-concept.

Introduction

Extemporaneous preparations (sometimes referred to as pharmaceutical compounding) are drug preparations that are compounded by a pharmacist pursuant to a prescription [1]. In the USA, compounding can be performed when there is a valid patient–physician–pharmacist relationship. There are FDA, US Pharmacopeia (USP), State Board of Pharmacy and Pharmacy Society policies and guidances that govern compounding. The laws and regulations governing extemporaneous preparations are given in Box 1. Several resources are available to pharmacists [2–4] that provide formulation and preparation instructions.

Historically, compounding has been an integral part of pharmacy practice and a traditional role of pharmacists until the expansion of the pharmaceutical industry and the availability of manufactured medicines, although a re-emergence of compounding has been noted [5]. Compounding is important in pediatric practice because it has the potential to provide age-appropriate dosage forms when manufactured medicines are not available [6–10]. Compounding is also applicable in dermatology for diseases for which pharmaceutically prepared products either do not exist or lack the desired therapeutic ratio [11–14]. These preparations can also help physicians individualize treatment to the specific needs of a patient [15]. For example, administration of oral anticancer drugs can be challenging for patients that have difficulty swallowing a tablet or capsule, in these cases oncology pharmacists frequently extemporaneously prepare oral liquid formulations [16].

Extemporaneous preparations in drug development

For the clinical phase of drug development there are two basic processes used to supply clinical trial materials (CTMs): (i) GMP manufacture in a clinical dosage form manufacturing facility; and (ii) extemporaneous preparation (EP; see Glossary) by the pharmacist. EP techniques are widely used in small, in-patient, Phase I clinical or first in human (FIH) studies. A majority of Phase I studies conducted by Pfizer utilize EP formulations. EP formulations offer several advantages: they enable rapid development of a candidate drug and allow stopping the development program earlier for candidates that will not be developed further; they enable the clinical evaluation of formulation options before full development and GMP supply; and as such offer upfront manufacturing cost avoidance. Additionally, they generally require fewer resources compared with traditional GMP manufacture. They allow flexibility in dose selection because doses can be adjusted based on real-time cohort data. EP formulations allow precise dose control which is important

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GLOSSARY

Active pharmaceutical ingredient (API) also referred to as 'active ingredient' or 'drug substance' – any component that is intended to provide a pharmacological activity (inactive ingredients or excipients are components other than the API).
b.i.d. bis in die (twice a day).
Controlled release (CR) the science that deals with dosage forms intended to provide a therapeutic amount of drug to a specific site or location at the desired rate. Often used interchangeably with modified release (MR). MR dosage forms include delayed release (DR) (i.e. those that release drug at a time other than immediately after oral administration) and extended release (ER) (i.e. those that make the drug available over an extended period).
Extemporaneous dispensing record (EDR) a Pfizer-specific term for a document that describes the steps required to prepare the subject or patient doses. The EDR instructions are verified by an analyst and it is approved by the formulator, analyst and PharmSci QA.
Extemporaneous preparation (EP) also referred to as pharmaceutical compounding. A drug preparation compounded under the supervision of a pharmacist based on the pharmacist–patient–prescriber relationship. In the context of drug development, EP refers to compounding at a clinical research unit in accordance with a clinical protocol and dose preparation instructions.
First in Human (FIH) a clinical trial where a drug candidate is tested on human subjects for the first time.
Immediate release (IR) dosage forms such as solutions and conventional tablets or capsules that allow the drug to dissolve in the gastrointestinal (GI) tract with no intention of delaying or prolonging the dissolution or absorption of the drug.
New chemical entity (NCE) a new drug that has not been previously approved by the FDA.
Occupational exposure band (OEB) a classification system for a compound's hazard, which dictates the way it should be handled. OEB is typically used in an R&D setting to protect employees from known or unknown hazards of experimental compounds.
Pharmacokinetics (PK) the study of the absorption, distribution, metabolism and excretion of drugs.
Proof of concept (POC) clinical studies aimed at validating the mechanism of action of the drug candidate providing initial data on efficacy and safety.
t.i.d. ter in die (three times a day).

for early clinical evaluation where the therapeutic index is still being established.

EP-tablet

An extemporaneously prepared tablet (EP-tablet) is a compressed tablet formulation that is compounded in the onsite pharmacy at a clinical research unit (CRU). It is prepared individually for each subject under the supervision of a trained pharmacist. EP-tablet provides the ability to test a tablet formulation quickly (i.e. reduced cycle time) and with minimal API (see Glossary) usage in a clinical study to evaluate proof-of-concept. Tablets that are manufactured conventionally [i.e. by a solid dosage manufacturing (SDM) facility] require development of the formulation and manufacturing process followed by manufacture of clinical supplies, and then by packaging and labeling. The drug product is tested according to analytical methods that have been developed and validated, and then it is released for clinical use. A formal stability program is also initiated with the tablets. By contrast, EP-tablet is prepared by two appropriately trained individuals in the pharmacy, one of whom is a qualified pharmacist. The tablets are prepared in advance before dosing (depending on stability). In the USA, compounding an EP-tablet is a practice of pharmacy, not manufacturing, and requires formulation development with an abbreviated stability program to support the in-use period. As a result of these differences, the lead time for EP-tablet is much shorter than conventional manufacturing.

EP-tablet is particularly useful in exploring product enhancement (PE) opportunities. The goal of PE is to develop new dosage forms with differentiated medical advantage. However, there can be uncertainty about the commercial value of a new formulation because of generic competition, second-generation new chemical entities (NCEs), US–Europe (US–EU) formulary changes post-loss of exclusivity and the value of the product could be sensitive to approval and launch timing. Also, the probability of technical and regulatory success (PTRS) can be low because of pharmaceutical sciences (PharmSci), clinical and regulatory factors. In such cases, EP-tablet provides the ability to test new formulation ideas quickly in clinical studies to determine proof-of-concept (POC) or to optimize the formulation.

Exploratory candidates (pre-POC or post-POC) that might need a controlled release (CR) formulation present another opportunity for EP-tablet. For example, compounds that have a short half-life and require frequent dosing (b.i.d. or t.i.d.) can compromise a POC study as a result of compliance issues. They can also jeopardize post-POC development because the market expects once-daily dosing. Compounds with undesirable dose-limiting side-effects related to high and rapidly rising peak plasma levels could also benefit from a CR formulation. Additionally, CR could also be

BOX 1

Laws and regulations governing extemporaneous preparations

The laws and regulations governing extemporaneous preparations vary by country. A summary of regulations, guidance and practices of compounding in the USA, where Pfizer has a clinical research unit (CRU), is provided below.

- FDA Compliance Policy Guides Manual, Section 460.200 Pharmacy Compounding (http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm).
- USP <795> Pharmaceutical Compounding – Nonsterile Preparations (http://www.uspnf.com/uspnf/login).
- USP <797> Pharmaceutical Compounding – Sterile Preparations.
- USP <1075> Good Compounding Practices.
- USP <1160> Pharmaceutical Calculations in Prescriptions Compounding.
- USP <1163> Quality Assurance in Pharmaceutical Compounding.
- USP <1191> Stability Considerations in Dispensing Practice.
- Connecticut Comprehensive Drug Laws (http://www.ct.gov/dcp/cwp/view.asp?a=1620&Q=275966&dcpNav=|&dcpNav_GID=1541).
- American Society of Health-System Pharmacists (ASHP) Policies and Guidance (http://www.ashp.org/s_ashp/doc1c.asp?CID=485&DID=2214).