

## **EXTEMPORANEOUS COMPOUNDING PRACTICE BY PHARMACISTS: A SYSTEMATIC REVIEW**

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### **ABSTRACT**

**Objective:** To identify the frequency and scope of extemporaneous compounding practice reported in community and hospital pharmacies.

**Methods:** A systematic literature review was undertaken to identify the prevalence of extemporaneous compounding practice in community and hospital pharmacies, including the reasons of providing compounding services.

**Results:** Nine studies were identified and evaluated in which extemporaneous products prepared by pharmacist could be identified. Most of the studies record that prevalence of extemporaneous compounding practice is very low (less than 5%). Prescribing of compounded medicines occurs more frequently in paediatrics and for special patients' need. The major types of extemporaneous compounding products were dermatological dosage forms and followed by oral solutions and oral suspensions. Reasons for providing compounding practice were to make a customised products that not available commercially and to provide full pharmaceutical care to patients. Issues about the stability of compounded products, accuracy in dose strength and lack of standardised protocol in extemporaneous compounding need to be addressed.

**Conclusion:** Extemporaneous compounding practice are an essential part of pharmacist' competency. These unique skills need to be preserved and regulations that cover rationalised compounding practice is necessary.

**Keywords:** Extemporaneous compounding, Pharmacists, Practice, Pharmaceutical care

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### **INTRODUCTION**

Extemporaneous compounding describes the use of traditional compounding techniques to manipulate chemical ingredients to produce appropriate dosage forms when no commercial medicines form is available [1]. Pharmacists providing compounding services can assist the patients with the access to special medications and dosage forms that can be helpful in providing a suitable therapeutic plan for the patients [2, 3].

Most available medicines are formulated as solid dosage forms such as tablet and capsules. However, many of medicines prescribed and administered to patients have not meet with patients' need in terms of strength and dosage forms [4]. Compounded products are needed for patient-specific conditions and can contribute to pharmaceutical care for tailored patients [5]. For example, pharmacists prepare suitable preparation extemporaneously by crushing the licensed tablet or opening the capsule. The powder content of tablet or capsule may be dissolved or suspended with various excipients to produce an oral liquid medicine or may be reformulated in a smaller dosage strength with lactose. Tablets are sometimes cut into halves or quarters in the pharmacy to obtain appropriately sized dosage unit for children [6]. For centuries, compounding was an elementary core task of pharmacists. The skill to compound extemporaneous is one of the competencies required of entry-level pharmacists for registration with the Pharmacy Council in several countries [7, 8]. In addition, pharmacists are required to demonstrate these skills prior to registration and to maintain them as registered pharmacists [9]. However, in several Western countries, compounding practice was dramatically decreased. An estimate by Food and Drug Administration (FDA) that 1-10% of all prescriptions require compounding was not supported by evidence data [10]. Data on the current status of compounding in are lacking. Therefore, identification of pharmacists who are compounding is an essential step to establish the further actions related to enhancing pharmacist competence. The compounding practice has become a justification for increased efforts to regulate the practice. Thus, effort at increased regulation of pharmaceutical compounding are apparently based on assumptions that the practice represents a significant,

increasing, fraction of pharmaceutical services and that the quality of compounded products cannot be assured. Since data to support these assumptions are clearly lacking, an understanding of the prevalence of compounding in community pharmacy practice is needed. The goal of this review was to determine the scope and frequency of extemporaneous compounding practice among pharmacists, including the reasons in providing such service.

### **MATERIALS AND METHODS**

A systematic literature review of studies that analysed the extent of extemporaneously prepared medicines and dispensed by pharmacists was undertaken.

#### **Literature retrieval**

Searches were conducted of the following electronic databases, PUBMED (1996-2015) and Google Scholar (1996-2015). Search terms included 'extemporaneous', 'compounding', 'compounded', 'drug formulations', and 'pharmacies', 'pharmacists'.

#### **Inclusion criteria**

Articles were included in the review if the information on the prevalence of all compounded products, including dosage form, volume and quantity prepared was provided. Primary reports of compounding of special products relative to all prescriptions to enable comparisons between speciality areas and countries will be made. The review was restricted by English language papers only.

#### **Exclusion criteria**

Articles were excluded if only specific extemporaneous product was reported, e. g. off-labeled use of medicines totals parenteral nutrition or only oral liquids. Reviews, editorials, letters, guidelines, and studies only available in abstract were also excluded.

### **RESULTS AND DISCUSSION**

Twenty-four published studies were identified, and nine of them were excluded. Seven studies were excluded because the study was

a focus on reported an unlicensed and off-label drug use in paediatrics, and a further eight studies were excluded because they involved total parenteral nutrition incompatibilities. Table 1 summarises the studies included in this review.

### Study design and respondent characteristics

The majority of included studies performed retrospective data analysis. Five studies used a questionnaire to identify the current practice of compounding [7, 11-14], with various way of delivering questionnaire include self-administered, face to face interviews [13], or mailed questionnaire. Richey used a combination of questionnaire and direct observation and compared the results of data [11]. Two studies conducted data records in practice including logbook of

compounding [15] and prescription record [16]. One study performed secondary data analysis from multicenter survey gathered in the previous study with focusing on compounding activities [17]. Only one study using prospective nested case-control study where some number of controls are selected for each case from that case's matched risk set [18].

Most of the studies use a purposive sampling approach for maximum variability for the observational study and a sample of convenience for the questionnaire study. Only one study use a random sampling in selected areas [13]. Since data were collected retrospectively, the interpretation of the data may be limited by the documentation available. In addition, modification to compounding drugs in the pharmacy may not be captured all in retrospective analysis.

**Table 1: Characteristics of published studies of extemporaneous compounding by pharmacists**

Author, Year	Country	Method	Respondent (N)	Patient group	Extemporaneous (%)	Most types of compounded product	Reason for compounding (or not compounding)	Source of compounding information, (Identified potential risks of compounding)
Richey et al, 2013[11]	United Kingdom	Questionnaire and observation	Pharmacist and paediatric nurse (21 areas)	paediatrics	54 (17%)	Tablet (61.6%), sachet (9.7%), transdermal patch (3, 2%).	NA	NA, (Accuracy of the dose. Lack of practice guideline)
Kairuz et al, 2007[15]	New Zealand	Data retrieved from compounding logbook	Pharmacists (32 hospitals)	paediatrics	152 per month	Oral dosage form (152), topical (100)	NA	NA, (Not all batch sheet had a record of the 'beyond-use date')
Brion et al., 2003[7]	EU (Belgium, France, Germany, Switzerland)	Questionnaire	Pharmacist (41 hospitals)	paediatrics	<10%	Oral preparations	Allow flexibility in dosage form	NA, (Palatability and physical, chemical, and microbial stability. Excipient may produce adverse reactions)
Pappas et al., 2002[12]	Australia	Questionnaire	Physicians (1138 general practice)	Not classified	32%	Most prescribed: Topical (31%), eye/ear/nose (16%)	Worked well for certain conditions and the product was not available commercially (lack of product knowledge, items not being listed in insurance)	Experience, medical school curriculum, (NA)
Lindblad et al., 1996[16]	Sweden	Prescription record	Physicians (2,154 physicians)	Not classified	1,043 (1.7%)	Most prescribed: Dermatologicals preparation	No commercial products	NA, (Doubt inappropriateness)
Zaid et al., 2011[13]	Palestine	questionnaire	Pharmacists and physicians (260 pharmacists and 179 physicians)	Not classified	1.55%	Topical preparations, oral solution, oral suspension	Providing pharmaceutical care to their patients, unavailability of required dosage forms (do not receive prescriptions that require compounding, lack of trust in the quality of compounding)	NA, (Lack of quality data of compounding products)
McPherson et al., 2006[14]	United States	questionnaire	Community pharmacists (370 pharmacists)	Not classified	2.3%	NA	(not receiving prescriptions that required compounding, compounding is not cost-effective)	NA
Martin et al., 2009[17]	United States	Previous survey data	Community pharmacists (1,643)	Not classified	NA	Dermatological preparations, oral solution,	NA	From pharmacy school courses. PharmD curricula

Buurma et al., 2003[18]	Netherland	Prospective nested case-control study	Community pharmacists (79 pharmacists)	Not classified	3.4%	oral suspension Dermatological dosage form, oral solution, ear/nose/throat products	Meet patients' need	should include compounding, NA, (Non-standardized protocol)
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Most of the studies were using pharmacists in hospital or community practice as a target of respondents [13, 14, 17, 18]. Two studies are invited hospital pharmacists for data source [11, 15]. Richey *et al.* [11], Pappas *et al.* [12] and Lindbald *et al.* [16] invited physicians served as a respondent for the source of information [11, 12]. In regards with types of patient, four studies focusing compounding practice for paediatric patients in the clinics, hospital, and pharmacies [5, 15, 18] and rest studies used non-classified patients (both adults and children) [7, 12-14, 16-18].

#### The prevalence of extemporaneous compounding

Most of the studies record the prevalence of extemporaneous compounding practices among pharmacists was under 5% of total prescription. Buurma *et al.* noted that the overall frequency of prescriptions for pharmacy-compounded medicine in relation to the total number of prescription was 3.4% [18]. Zaid *et al.* found that 1.55% of pharmacists provided compounding services based on prescriptions requested by doctor [13]. A study by Pappas found that only one-third of physician prescribed extemporaneous product [12]. According to McPherson's data, a prescription that required compounding represented less than 1% of total prescription [14].

#### Types of extemporaneous products compounded

The majority of studies found that dermatological product is the most frequent compounded products by pharmacists [12, 16, 18]. Burma *et al.* observed that a huge share of dermatological dosage forms among compounded medicines (62.1%) was found [18]. Lindblad *et al.* also found that the therapeutic area with the highest percentage of extemporaneous prescriptions was dermatological drugs [16]. In contrast, Kairuz *et al.* stated that topical preparations were compounded less frequently than oral formulations [15]. Some examples of ointment compounded included cocaine ointment and salicylic acid in the emulsifying ointment. Aspirin in the chloroform paint was compounded at five hospitals, the only lotion compounded was menthol 0.5% in DP lotion [15]. Compounding products in second rank frequency were an oral solution and oral suspension [12, 18] and followed by ear-nose-throat (ENT) products [18] and tablet modification [11]. Richey *et al.* study provided the details of tablet modification, that of the 40 tablet modification, 25 (62.5%) of the tablet were cut, 12 (30%) dispersed, one (2.5%) crushed, one (2.5%) was broken by hand [11]. When comparing the trend of compounding product across country, Brion *et al.* found that in England, Ireland, Norway, and Sweden prepared mainly oral solution (60%) [7]. Finland, Italy, and Scotland prepared mainly powder, while Belgium, Croatia, France, and Switzerland prepared mainly capsules. Practice in Germany, Spain, and Slovenia involved preparation of a less well-defined combination of liquid, powders, and capsules [7]. It can be seen that the same drug may be prepared in several different dosage forms, reflecting the different preference for types of extemporaneous preparation between countries.

With respect to patient-related determinants, children under 12 y of age received relatively more compounded medicines than other age groups [7, 11, 15]. This might be explained by the fact that children need patient-tailored therapy more frequently, for which commercial products are not available, because of a special dose or dosage form is needed. On the other hand, there is the risk that pharmacy compounding thereby supports the use of drugs in children which have not yet been evaluated in an appropriate way and which may give rise to considerable adverse drug reactions [11].

#### Reasons of extemporaneous compounding

The reasons listed in the review were mostly to meet special needs of the patient. Richey *et al.* [11] and Pappas *et al.* [12] reported that

the reason for the compounding practice was that there was 'no suitable preparation or strength available'. Further reasons given for compounding were a patient preference (reported 13 (6.9%) compounding) and usual practice 23 (12.2%) [11]. Based on pharmacists' perspective, using more extemporaneous prepared products could also make sense economically. "The significant therapeutic improvement and some cost savings may be gained" by the rational use of extemporaneously prepared medicines [12]. Pharmacists that did not provide compounding service cited by the main reason as not receiving prescriptions that required compounding (63.6% of non-compounder pharmacists) [14]. In about 33% of the compounded products, they indicated patient-specific reasons. In about 10% this reason concerned a strictly defined pharmaceutical care issues [18]. Zaid *et al.* conclusively said that 73.2% pharmacists reported their goal in providing full pharmaceutical care to their patients was the most important motivator [13]. The main reasons for the decision to provide compounding service were want to provide full pharmaceutical care to patients (73.8% of compounder pharmacist) and responding to requests by prescribers. Most community pharmacists (69%) accepted compounding as a component of pharmaceutical care.

In most of the studies, major reasons stated by physicians for prescribing extemporaneous products were that they worked well for certain conditions and that the product was not available commercially [12]. Conversely, the most significant factor which limits prescribing of compounded medicines was that patients did not want products due to these products were not covered by the national insurance [12]. Furthermore, for doctors not prescribing these products, the major barrier to prescribing was their lack of knowledge of the products [12]. Most responding doctors do not prescribe medications that require compounding because they lack trust in the quality of the compounded formulations [13]. However, most of the doctors expressed a desire to learn more as shown in having access to information about the usefulness of extemporaneous products [12].

According to Martin *et al.*, sources of compounding knowledge and skills were from other pharmacists on the job (68.2%), from text or reference books (67.6%), self-taught (56.1%), and from continuing education program (34.6%). The survey shows how each respondent's pharmacy school compounding exposure was structured. The vast majority (95.3%) of the pharmacists graduated from a program that included required course with a laboratory component [17].

#### Concerns about the potential risks of extemporaneously compounded products

All studies in this review highlight that issues about the stability of compounded products, accuracy in dose strength and lack of standardised protocol in extemporaneous compounding were needed to be acknowledged [7, 11, 13]. Pharmacists felt low efficacy when performing compounding practice. In Dutch community pharmacies, pharmacists did not use a standardised protocol in 42% of cases [18]. Contrary with pharmacists' argument, concerns about safety, stability, or efficacy were considered limitations by less than 10% of doctors [12].

Richey *et al.* argued that every compounded products need for caution when splitting tables with short half-lives or low therapeutic indices [11]. Thirty-five percent of respondents to the questionnaire reported concerns with the accuracy of the dose achieved following manipulation. Respondents also noted the importance of good communication between health care professionals and the need for availability of clear drug preparation and administration protocols and/or policies for such scenarios [11]. Segments from tablets are

quick to cut and probably have similar stability to the original tablet, but cannot be cut with a great accuracy of dose. In general, if stored under suitable conditions away from moisture, powders should have greater stability than oral liquids but are more time to consume to prepare [7]. The accuracy of dividing tablets into other fractions is even more unclear than halves or quarters. The potential lack of accuracy during manipulations implied by a prescription may mean that the actual dose delivered to the patient is not known. It seems likely that prescribers are often unaware of the dosage form (and strength) that will be used to administer the dose required or the potential for inaccuracy that arise from their prescribed doses [11].

Oral liquid are comparatively quick to prepare and allow flexibility in the dosage form in a single strength preparation by accurately measuring the volume required using a spoon designed for oral administration. However, oral liquids may be difficult to formulate to ensure palatability, and physical, chemical, and microbial stability. The formulations may contain excipients (especially preservatives) that produce adverse reactions in some babies or children. The short expiry period generally assigned may be an inconvenience for patients [7]. In addition, not all batch sheets had a record of the 'beyond-use date'. The average 'beyond-use date' was seven days for oral dosage forms [15]. Most products were assigned short 'beyond-use dates', which is in accordance with the good pharmaceutical practice in New Zealand. The variation in assigned beyond-use dates in this study could be due to the use of different formula at the various hospitals.

The results of this review showed that the incidence of extemporaneous prescribing and compounding is very low. This is an important consideration regarding any estimates of the extent of compounding, as some studies with pharmacists respondent might unconsciously underreport compounding activity since 'Compounding' is specifically not clearly defined. This inquiry was intended to provide a foundation for further study on the outcomes of compounding within the context of pharmaceutical care [2].

Our results demonstrate that modifications of dosage forms are integral to pharmacy practice. However, it is not entirely clear who is responsible for compounding. There are two relevant situations, firstly, when the compounding is conducted because a suitable dosage form is not available. This situation may arise because there is no suitable dosage form on the market. Secondly, the pharmacist makes a professional judgment to meet a patient's preference when a dosage form is available [3]. Pharmacists performed a range of extemporaneous compounding indicating that this skill is essential for the practising pharmacist.

In the present study, the most frequently cited statements as reasons for providing compounding service is the motivation to serve the patients' needs and to provide pharmaceutical care for patients. These suggest that a primary motivation for compounding might be related to pharmaceutical issues. It can be a highlight that most reasons for not offering compounding service were a lack of prescriptions requiring compounding, lack of time, and lack of training. Perhaps non-compounders might provide compounding service if they perceived their patients needed it and that they were sufficiently skilled [10].

Need to be considered that extemporaneous compounding is not without risk. There are no published standards for the process. If the process procedure is applied, this will often comprise a worksheet of recorded data. Errors in preparation, some of them with potentially serious consequences, have been noted [5, 19]. It is important that all concerned recognise extemporaneous preparation as a necessary and important method of making appropriate medicine available. However, it is important that they are also aware of the potential problems. Pharmacists and physicians should work together to ensure that suitable licensed preparations are used when available. Extemporaneous preparation should only be used if there are no alternatives [20].

Extemporaneous preparation may be in accordance with a formulation published in a pharmacopoeia or some other published work of reference, or the formulation may have been developed locally. Medicines prepared extemporaneously should be

rationalised for formulation and strength and their standards assured by monographs in official publications such as European Pharmacopoeia [8]. The research undertaken to established the suitability of the formulation and its physical, chemical and microbial stability may be extensive, but such work may not be undertaken at all [21]. In an unpublished UK survey, it was noted that 54% of 112 paediatric extemporaneous formulations had an inadequate date on shelf-life. If there are insufficient data to support the formulation or its stability, these data should be gathered in a way that avoids duplication of effort. Data, once available, should be published in all countries and should lead to a monograph in a pharmacopoeia [7].

Time, expertise, and facilities in hospital pharmacies limit the type of preparations prepared extemporaneously. Pharmaceutical companies have appropriate facilities and should be encouraged to make modern dosage forms available for children. When considered on a European scale, the market for paediatric pharmaceutical is large [7]. It is encouraging to note that pharmaceutical manufacturers may soon be given incentives to manufacture and distribute medicines for a common paediatric market, according to a recent European memorandum [8]. We suggest developing policies and procedures to cover compounding practice performed by pharmacists. Pharmacists should have access to the relevant information and the support from their institution to make a professional judgment about compounding practice. Organisations and regulatory bodies should be a focus for improving the availability of appropriate compounded medicines especially for children and ensuring that extemporaneous preparation is a high standard in quality [6].

These findings provide a timely opportunity for collaboration between the pharmacy and medical professions. Hepler and Strand argued that pharmaceutical care has evolved within the profession of pharmacy in which pharmacist collaborates with patients and other professionals in designing, implementing, and monitoring that will produce intended therapeutic outcomes and higher quality of life for the patient [22]. By enhancing prescribing knowledge of doctors in this area, they are more likely to utilize extemporaneous products in the clinical setting [12]. This will enable pharmacists to maintain their compounding skills and ultimately benefit the patient with greater choice in treatment. Our results have implications for contemporary pharmacy practice. First, most pharmacists provide compounding service, but at low prescription volume. As such, any regulations that cover compounding practice must take this into account. Physicians and the general public look to the community pharmacy to provide compounding services and that view is accepted by a majority of pharmacists [2].

## CONCLUSION

Extemporaneous compounding practice in a pharmacy setting is still exists aimed at providing suitable dosage forms for patients with special needs. Prescribing of extemporaneous medicines to meet this unmet medical need is accepted part of pharmacy practice, and it seems likely that pharmacists will continue to be required to prepare extemporaneous products. Medicine regulatory agency efforts to create appropriate standard need to be initiated and implemented. Furthermore, pharmacists need to have access to stability, compatibility, and formulation information as well as appropriate training to ensure patients are supplied with high quality, safe, and effective preparations.

## CONFLICT OF INTERESTS

All authors have none interest to declare

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