CHAPTER 5

Information Regarding Modification of Oral Solid Medicines in Written Drug Information: Potential Consequences for Patient Safety

Daniel Horst Zeiss & Linda Amundstuen

Faculty of Nursing and Health Sciences, Nord University, Namsos, Norway

Abstract: Oral solid medicines (oral solid dosage forms, OSDFs) are among the most used medications, and have various pharmaceutical designs ranging from relatively simple uncoated tablets with immediate-release properties, to advanced modified-release preparations slowly releasing the active ingredient. Taking medicines correctly is essential to preserve intended effects and avoid adverse effects. Still, modification of OSDFs is a common practice among patients and health care personnel, due to for example, swallowing difficulties. Modifications such as crushing tablets and opening capsules should only be done with a careful assessment of potential risks and benefits. In this study, we systematically reviewed the information relating to modification of OSDFs in the monographs of a commonly used source of medicine information in Norway, Felleskatalogen®. A total of 31 different OSDFs were identified. Results show that information on whether the medicines should be swallowed whole, could be divided, crushed, chewed, or opened, varied widely. Medicines with modified-release characteristic generally had more and stricter recommendations concerning modification than medicines with immediate-release characteristic. Recommendations varied largely between monographs, and different recommendations such as "shall", "should" or "must" may be interpreted differently among readers. Furthermore, a relatively small proportion of the monographs contained descriptions of the potential consequences of modification.

Based on our observations, a necessary risk-benefit assessment on dosage form manipulation for health care personnel and patients is possibly being impeded. Explicit and unambiguous information, or the development and implementation of

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a "traffic light model" for dosage form manipulation might reduce the risk of medication errors, and thereby increase patient safety.

Keywords: Oral solid dosage forms, modified-release, immediate-release, medicine safety, drug modification, medicine information

According to the World Health Organisation (WHO, 2017), medication errors are one of the leading causes of avoidable harm from medicines, and often occur during their administration. Solid medicines taken by mouth, so-called oral solid dosage forms (OSDFs), are most common, and vary widely in pharmaceutical form and design (Logrippo et al., 2017). Modifying the pharmaceutical form of a tablet or a capsule, for example, may alter the effect of the medicine due to changes in the rate and extent of absorption of the active ingredient (Anonymous, 2014; Logrippo et al., 2017). Thus, the correct handling and administration of each specific OSDF is essential to avoid medication errors and the risk of harm to the patient. However, a correct administration of OSDFs includes not only the intake of the unaltered dosage form, but also other factors, like an adequate amount of fluid during intake (Fuchs, 2009; Schiele et al., 2013) and correct head posture (Lau et al., 2018; Schiele et al., 2013).

Several sources of information, such as the package, the package label printed at the pharmacy, and the package leaflet, contain information on how to handle and administer medicines. In Norway, a frequently used source of information for nurses administering drugs is Felleskatalogen® (Johansen, 2019; Kirkevold & Engedal, 2010). Felleskatalogen® is a catalogue with monographs containing pharmaceutical preparations available in Norway. It is available online (www.felleskatalogen.no), as a version available for downloading, and as an application for smart phones and reading boards. The monographs are developed by pharmaceutical companies and the editorial staff at Felleskatalogen®, and based on the summary of product characteristics (SPC) (Felleskatalogen, 2021c). Information on administration and recommendations concerning manipulation of medicines are given under the dosing chapter for each medicine in Felleskatalogen®.

OSDFs, such as tablets, capsules and granules, have several advantageous features for both patients and manufacturers, including: a high degree of

self-administration, increased adherence, good stability attributes, and cost-effective production. OSDFs offer a large variety of products with different technological designs to fulfill various objectives, like a certain mode of drug release (immediate-release vs. modified-release) or managing a drug's stability issues (Logrippo et al., 2017). Conventional, immediate-release, solid dosage forms contain a single dose of a drug, and are designed to release its total amount within minutes into the gastrointestinal tract (GIT). Depending on the absorption rate following release, and the mechanism of action, a rapid pharmacological response is expected.

Modified-release solid dosage forms, on the other hand, are designed to release their contents in an either extended (i.e., continuously steady release over an extended period of time) or delayed manner (i.e., release with a time gap following intake) (Alderborn & Frenning, 2018). Extended-release dosage forms are intended to reduce the dosing frequency, that is, the number of drug doses per day, ideally to a once-daily or twice-daily dosage regimen (McConell & Basit, 2018). Less frequent dosing, compared to immediate-release dosage forms, needs to be compensated through a higher amount of the drug in an extended-release dosage form, in order to attain comparable drug levels in plasma within the extended dosing interval. Among delayed-release dosage forms, are OSDFs with a gastro-resistant release mechanism. The purpose of such dosage forms is to prevent the release of the drug into the stomach, thereby preventing either chemical degradation, with a subsequent loss of the drug, in the acidic environment, or gastrointestinal side effects from local irritation by the drug (Logrippo et al., 2017). Although many OSDFs should be swallowed whole due to the stated reasons, modification of medicines may be considered necessary because of swallowing difficulties (Logrippo et al., 2017; Solberg et al., 2021) or, as in the case of children, inappropriate dosage forms and/or strengths of commercially available medicines (Bjerknes et al., 2017).

The Extent of and Reasons for Manipulation of Oral Solid Dosage Forms

Manipulation of solid oral dosage forms is common and occurs in different settings and for different reasons. Schiele et al. (2013) reported

that 59% of patients in a German general practice population, taking at least one OSDF for a period of four weeks or more, reported having modified their drugs to facilitate swallowing. A self-reported study done in Australian hospitals, found that modifications occurred at the bedside for 79% of responding hospitals (Nissen et al., 2009). Modification occurred for both adults and children, and the most common reason for modification was the inability to swallow the OSDF (82%). Other reasons were lack of the correct dose in commercially available products and the need for drug administration through, for example, nasogastric tubes. Furthermore, a Norwegian cross-sectional study carried out in hospital paediatric wards, found that 17% of administrations of oral medicines involved manipulation. Unacceptable dosage form, inappropriate strength, or a combination of these, were the most frequent reasons for manipulations (Bjerknes et al., 2017). A study performed in 19 Norwegian nursing homes, showed that crushing tablets occurred in all nursing homes. Difficulty swallowing was the most common reason for crushing tablets. Others were preventing tablets from being spat out, kept or hidden in the mouth, and the need to administer the drug through a probe (Wannebo, 2009). Solberg et al. (2021) recently reported that modifications were done in 56 (21%) of 273 dispensing episodes. In addition to swallowing difficulties, lack of understanding by the patient, routines, and the patient's own wishes were the most common reasons reported for modification. For a specific patient, both the formulation, size, shape, and surface characteristics of the tablet/capsule, may contribute to swallowing difficulties. Fear of patients choking on medication may also contribute to modifying oral medicines (Mc Gillicuddy et al., 2019).

Potential Consequences of Modification

The consequences of modifying OSDFs depend on the pharmaceutical design of the specific medicine (Anonymous, 2014; Logrippo et al., 2017). Most worrying are cases of modifying extended-release solid dosage forms, which might lead to the release of the total amount of the drug, possibly causing severe adverse effects depending on the nature

of the drug itself (Cleary et al., 1999). The consequences of manipulating gastro-resistant dosage forms depend on the reason for formulating a gastro-resistant dosage form in the first place. For chemically susceptible drugs, drug loss through degradation may occur, resulting in a lower amount of the drug being absorbed, reducing the pharmacological response (e.g., proton pump inhibitors). For drugs showing gastrointestinal side effects due to, among other things, local irritation, like NSAIDs, these effects might be more pronounced (Anonymous, 2014).

Manipulating immediate-release solid dosage forms by means of crushing or chewing, might not necessarily have an impact on their intended release profile. Such dosage forms are supposed to disintegrate rapidly, releasing the drug immediately in the stomach, and one could argue that crushing or chewing such dosage forms would accelerate the disintegrating process, resulting in earlier onset. Lippert et al. (2005) revealed no significant differences in the area under the curve (AUC) and the maximum concentration (C_{max}) of immediate-release telithromycin tablets, administered as either intact or crushed tablets, and thereby assessed both administrations as bioequivalent. Nonetheless, manipulating immediate-release solid dosage forms might be unacceptable due to drug properties rather than release profile, like unpleasant taste or safety issues handling the medicine (e.g., chemotherapeutic agents).

The appearance of OSDFs do not in general reveal the purpose of their design, but since the intake of certain dosage forms in an unaltered way is crucial for their intended mode of action, so is comprehensible written information on how to handle and administer such dosage forms for the success of the medical treatment.

The aim of the study underlying this chapter is to describe the extent and content of information and advice given relating to manipulation (e.g., crushing and dividing) of OSDFs in the Felleskatalogen®. The research questions were: To what extent is information on manipulation given in the monographs? What information concerning manipulation is given for immediate-release and modified-release preparations, respectively? Based on specific examples, what could be the implications of (not)

following the advice concerning manipulation of oral solid medicines given in the monographs?

In this study, OSDFs include all different types of tablets, capsules, granules, powder, gums, pastilles/lozenges as well as powder and granules intended to be dissolved or dispersed in water by the patient before administration.

Methods

We exported trade names of all pharmaceutical preparations available in Felleskatalogen® (www.felleskatalogen.no) on 4 March 2021, n = 2,555 monographs. Written consent was given by Felleskatalogen® to store and use the data for the purpose of this study. Data were further handled and analyzed using IBM SPSS version 27.0. and 28.0.

The monographs were screened to identify the total number of individual pharmaceutical preparations. Medicines available as two different dosage forms, for example both tablets and capsules, were counted as two preparations. Medicines containing the same active substances having different names, (e.g., Cozaar Comp® and Cozaar Comp Forte® by Organon, both containing hydrochlorothiazide and losartan), were registered as two different preparations. A total of 2,915 individual pharmaceutical preparations were identified, representing 41 different oral dosage forms, in addition to preparations not intended for oral administration.

As shown in Figure 1, we excluded oral liquid preparations, and preparations not intended for oral administration. Thus, a total of 1,387 monographs relating to OSDFs were included in the study. From 4 March until 22 July 2021, we reviewed the monographs of these OSDFs on www.felleskatalogen.no. The following variables were registered: the dosage form; whether the preparation had its "own" monograph in Felleskatalogen®, and if not, which monograph the reader was referred to; the recommendations given under "Administration" for the manipulation of drugs (e.g., advice on crushing, dividing, and chewing the drugs); and whether the reasons for the recommendations were given. Dosage forms were registered based on the descriptions in Felleskatalogen®. In the analysis,

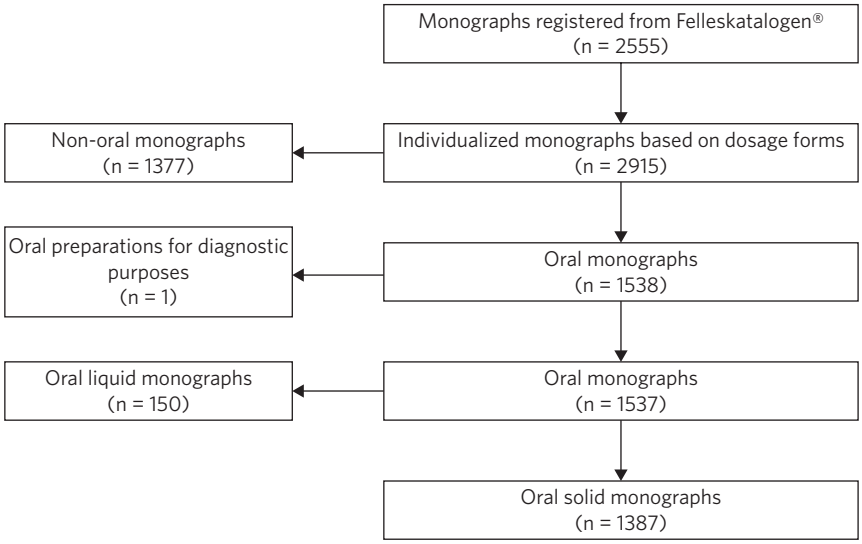

Figure 1. Flow Diagram Showing the Number of Monographs Registered in Felleskatalogen®. The monographs were reviewed to obtain the number of individual dosage forms. Monographs for non-oral medicines and oral liquid medicines were excluded

we categorized extended-release, delayed-release and gastro-resistant tablets, capsules, and granules as drugs with modified-release characteristics. All other drugs were categorized as immediate-release drugs.

We categorized the recommendations for medicines that "shall not", "should not" and "cannot be divided" as "cannot be divided". Medicines that "can be divided", "can be divided in two similar doses", "should only be divided once", "cannot be divided in two similar doses" and medicines for which different recommendations were given for different doses were categorized as "can be divided". For capsules, medicines were categorized in "shall not be opened", and "can be opened". For recommendations concerning crushing, medicines that "should not", "shall not" and "must not be crushed" were categorized as "cannot be crushed", whereas medicines that "should be" and "may (if necessary) be crushed" were categorized as "can be crushed". For chewing, medicines that "should not", "shall not" and "must not" be chewed were categorized as "cannot be chewed", whereas medicines that "can be" or "should be" chewed, were categorized as "can be chewed".

Results

Table 1 shows the frequency of different OSDFs in Felleskatalogen®, representing 33 different types of dosage forms. 1,200 (86,5%) of the preparations had dosage forms with immediate-release-characteristics, whereas 187 (13,5%) had modified-release characteristics. Of the 187 modified-release preparations 122 (65,2%) were tablets, 56 (29,9%) were capsules, and 9 (4,8%) were granules.

Table 1. Frequency of Different Oral Solid Dosage Forms in Felleskatalogen® (www.felleskatalogen.no)

Dosage form	Number of preparations (%)
Dosage forms with modified-release characteristics	**187 (13,5)**
Modified-release tablets	91 (6,6)
Gastro-resistant tablets	29 (2,1)
Gastro-resistant capsules	26 (1,9)
Modified-release capsules	30 (2,2)
Gastro-resistant and/or modified release granules	5 (0,3)
Others**	6 (0,4)
Conventional dosage forms with immediate-release characteristics	**1068 (77,0)**
Coated tablets	607 (43,8)
Conventional tablets	294 (21,2)
Hard capsules	133 (9,6)
Soft capsules	34 (2,5)
Alternative dosage forms with immediate-release characteristics	**132 (9,5)**
Powder or granules for liquid preparation (prepared by patient)	27 (1,9)
Orodispersible tablets (lyophilisates, "melting tablets")	27 (1,9)
Chewable tablets	17 (1,2)
Effervescent tablets	16 (1,2)
Dispersible tablets	9 (0,6)
Sublingual tablets	9 (0,6)
Granules	8 (0,6)
Lozenges	7 (0,5)
Others*	12 (0,9)
Total	**1387 (100,0)**

*Soluble tablets (n = 3), chewing gums (n = 2), powders (n = 4), granules in capsules to be opened (n = 1), pastils (n = 1), and dispersible/soluble tablet (n = 1).
**Gastro-resistant granules for liquid preparation (n = 3), gastro-resistant modified-release tablets (n = 2), modified-release granules for liquid preparation (n = 1).

Information and recommendations concerning administration varied largely between dosage forms and within similar dosage forms. We will further focus on information concerning modified-release tablets and capsules, and conventional immediate-release dosage forms. Table 2 shows the information and recommendations given on whether to swallow these drugs whole.

Table 2. Information and Recommendations in Monographs in Felleskatalogen® This relates to whether oral solid modified-release (tablets and capsules) and the conventional immediate-release dosage forms should be swallowed whole. Soft capsules are not included in the table

Dosage form/ To be swallowed whole?	No information N (%)	Can be swallowed whole N (%)	To be swallowed (primarily) whole N (%)	Should be swallowed whole N (%)	Shall be swallowed whole N (%)	N (%)
Tablets with modified-release characteristics	10 (8,2)	0 (0,0)	12 (9,8)	5 (4,1)	95 (77,9)	122 (100,0)
Capsules with modified-release characteristics	1 (1,8)	4 (7,1)	10 (17,9)	14 (25,0)	27 (48,2)	56 (100,0)
All coated tablets	297 (48,9)	1 (0,2)	97 (16,0)	79 (13,0)	133 (21,9)	607 (100,0)
Conventional tablets	227 (77,2)	3 (1,0)	25 (8,5)	13 (4,4)	26 (8,8)	294 (100,0)
Hard capsules	23 (17,3)	3 (2,3)	31 (23,3)	6 (4,5)	70 (52,6)	133 (100,0)

Of the 11 OSDFs with modified-release characteristics lacking information on whether to be swallowed whole, all had other specific recommendations on how to handle the drug. Recommendations were, for example:

- Should be swallowed with a glass of water. Shall not be chewed. Shall not be divided or crushed (Cortiment® modified-release tablets (budesonide, Ferring Legemidler AS))
- One gastro-resistant capsule is to be taken with cold or lukewarm water (not over 37°C) on an empty stomach, and at least one hour before the next meal. Shall not be chewed, and is to be swallowed as soon as possible after being put in the mouth (Vivotif® gastro-resistant capsules (typhoid vaccine, Emergent)).

Six of the 11 medicines with modified-release characteristics lacking recommendations to be swallowed whole, could, however, be divided, (e.g., Tegretol Retard®, carbamazepine, Novartis). Selo-Zok® modified-release tablets (metoprolol, Recordati) could also be divided. Yet, for 50, 100 and 200mg doses, dividing should only take place to make them easier to swallow. In comparison, dividing 25mg tablets results in two similar doses.

Information on whether the medicine should be swallowed whole, could be divided, crushed, chewed, dispersed in water, or sucked was lacking for all variables for 143 coated tablets (23,6%), 45 (15,3%) conventional tablets, and 11 (8,3%) capsules. This does not necessarily mean that no information was given on how to administer these medicines, as some mentioned that the drug was to be swallowed (but not, specifically, whole) and gave other recommendations which did not fit into these pre-defined categories. No OSDFs with modified-release characteristics were among these.

Table 3 shows information and recommendations on dividing, crushing and chewing oral solid dosage forms with modified-release characteristics and the conventional immediate-release dosage forms.

Only a few monographs explained the reasons for recommendations relating to modifying the medicine. One explicit reason given for the recommendation on why one should swallow the drug whole, was that the taste of the drug was bitter or bad. Another stated reason to swallow the drug whole, was an increased risk of side effects if the drug was divided, crushed, or chewed. Side effects could occur due to local effects, such as irritation of the gastric mucosa (e.g., Albyl-E® gastro-resistant tablets (acetylsalicylic acid, Takeda)), and discoloration of the teeth and mouth cavity (e.g., Vanquin® tablets (pyrvin, MEDA)), or due to increased systemic effects of the drug, such as an increased risk of bleeding caused by Pradaxa® capsules (dabigatran, Boehringer Ingelheim). For some drugs, dividing, chewing, or crushing tablets may result in rapid release and absorption of potentially lethal doses of the drugs, such as for Reltebon Depot® (Actavis) and OxyContin® (Mundipharma), both containing the opioid analgesic drug oxycodone in a modified-release dosage form. Furthermore, some cytostatic drugs, such as Sprycel® tablets (dasatinib,

Table 3. Information and Recommendations. This relates to dividing, crushing, and chewing oral solid modified-release (tablets and capsules), and the conventional immediate-release dosage forms. Soft capsules are not included in the table

Dosage form	N (%)	Dividing/opening*			Crushing			Chewing		
		No information	Can be divided**	Cannot be divided	No information	Can be crushed	Cannot be crushed	No information	Can be chewed	Cannot be chewed
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Tablets with modified-release characteristics	122 (100,0)	38 (31,1)	16 (13,1)	68 (55,7)	31 (25,4)	0 (0,0)	91 (74,6)	25 (20,5)	0 (0,0)	97 (79,5)
Capsules with modified-release characteristics	56 (100,0)	23 (41,1)	29 (51,8)	4 (7,1)	18 (32,1)	0 (0,0)	38 (67,9)	12 (21,4)	0 (0,0)	44 (78,6)
All coated tablets	607 (100,0)	351 (57,8)	154 (25,4)	102 (16,8)	419 (69,0)	60 (9,9)	128 (21,1)	496 (81,7)	0 (0,0)	111 (18,3)
Conventional tablets	294 (100,0)	93 (31,6)	175 (59,5)	26 (8,8)	222 (75,5)	49 (16,7)	23 (7,8)	262 (89,1)	8 (2,7)	24 (8,2)
Hard capsules	133 (100,0)	78 (58,6)	20 (15,0)	35 (26,3)	100 (75,2)	2 (1,5)	31 (23,3)	96 (72,2)	0 (0,0)	37 (27,8)

*For capsules, the presented data concerns opening the capsules.
**Includes preparations for which different recommendations are given for different strengths of the drug.

Bristol-Myers Squibb), were recommended to be swallowed whole to ensure correct dosing and minimize the risk of skin exposure. Similarly, Valganciclovir® tablets (valganciclovir, Accord; Sandoz), an antiviral drug, should not be divided or crushed as it is potentially teratogenic and carcinogenic.

Discussion

Different OSDFs and Recommendations Concerning Modification

We identified a great variation in OSDFs (Table 1) in Felleskatalogen®. As a consequence, recommendations concerning handling and administration of the medicines varied to a large degree. Some drugs are intended to be modified before or as they are administered, such as chewing tablets and orodispersable tablets. Others, such as medicines with modified-release characteristics are primarily intended to be swallowed whole. For OSDFs with modified-release properties, recommendations to swallow the medicines whole were more common than for OSDFs with immediate-release properties (Table 2). In addition, the monographs for these medicines generally contained recommendations to ensure their safe administration, and avoid potentially harmful modification. Modifying OSDFs with modified-release properties by crushing or chewing tablets, opening, or chewing capsules is of particular concern, as this may increase the risk of adverse effects (Cleary, et al., 1999), underdosing (for gastro-resistant medicines) and overdosing (for sustained-release medicines) (Anonymous, 2014). Approximately 20–30% (Table 3) of the monographs for OSDFs with modified-release characteristics lacked explicit recommendations as to whether these tablets or capsules should not be crushed or chewed. The phrase "to be swallowed whole" might be interpreted as a recommendation not to crush or chew the drug. Although OSDFs with modified-release properties require special caution regarding modifications, few rules of thumb exist for identifying whether a drug with a specific dosage form may or may not be modified, without checking information for the specific drug. Even though a large percentage

(78%) of tablets with modified-release characteristics *shall* be swallowed whole according to Felleskatalogen®, some may be divided, at least under specific circumstances, such as when both parts of the tablet are taken, or for specific strengths of the medicines.

The most common OSDFs in Felleskatalogen® were coated and conventional tablets. We would expect fewer restrictions concerning the modification of these medicines, compared to modified-release medicines. As shown in Tables 2 and 3, recommendations on modifying medicines were often missing for coated and conventional tablets. However, a significant number of tablets and capsules were recommended to be swallowed whole. There may be many reasons why it is preferable to swallow drugs whole, as presented in this study, thus decreasing the risk of local adverse effects, masking bitter taste, as well as avoiding contact with the skin, and to risk exposure to potentially carcinogenic and teratogenic medicines. Interestingly, the reasons for recommendations concerning modification were given in only a few monographs. For OSDFs where modification of the medicine could affect their properties, having explicit information available as to: a) whether a specific type of modification (e.g., crushing) of a medicine can be done, and b) what happens if the medicine is modified this way, may help prevent inappropriate or potentially hazardous modification of drugs.

Using and Interpreting the Available Information

For some health care personnel, crushing tablets may be a routine procedure on which they do not reflect (Wannebo, 2009). Lack of knowledge for both patients and health care personnel concerning modification of OSDFs, in combination with a lack of explicit information related to medicine modification, may result in reliance on informal information and the continuation of previous practices (Mc Gillicuddy et al., 2017b). Several studies have reported crushing of drugs with modified-release characteristics (Bjerknes et al., 2017; Nissen et al., 2009; Solberg et al., 2021; Wannebo, 2009). While recommendations concerning the modification of many OSDFs are available in Felleskatalogen®, this information has limited value to patients, carers or health professionals preparing

and administering the drugs do not seek the information, cannot find it or interpret it (Kirkevold & Engedal, 2010; Wannebo & Sagmo, 2013), or choose, for various reasons, to deviate from the recommendations.

To administer and modify an OSDF safely three factors are crucial. Firstly, the person responsible needs to check whether the medicine can be modified using reliable sources of information. Studies have shown that health care personnel do not always check for information before modifying and administering medicines (Karttunen et al., 2020; Kirkevold & Engedal, 2010). In a Finnish cross-sectional study (Karttunen et al., 2020), one-third of 492 nurses working in long-term elderly care, reported that they did not always follow the guidelines for preparing medication, and only 59% checked for information before crushing tablets. Furthermore, only 66% and 67% of nurses followed guidelines on not to crush enteric-coated and sustained-release tablets, respectively, although the SPC did recommend not doing so.

Secondly, when seeking information, one must know where to look. In Felleskatalogen® information concerning modification of medicines is now given under the same paragraph for all medicines and should be relatively easy to look up. As shown in this study, information is available for many OSDFs, whereas it is lacking for others.

Thirdly, the information – if there – needs to be easy to understand for the reader. Earlier studies have criticized information concerning modification of medicines in Felleskatalogen® in terms of both availability and understandability (Kirkevold & Engedal, 2010; Wannebo & Sagmo, 2013). These studies are quite old and may not reflect how this source is evaluated today. However, according to Table 2, many immediate-release drugs lack information on whether to swallow the drugs whole. On the other hand, many monographs stated that the drugs should be "swallowed" or "taken", often with a glass of water or fluid (results not shown). We do not know whether health care personnel interpret to be "swallowed" or "taken" significantly differently from "to be swallowed whole". Explicit, and unambiguous information is, however, preferable. Table 2 also shows that nuances exist between different monographs on whether drugs "should be (primarily)" swallowed whole, "should be" swallowed whole or "shall be" swallowed whole. These may not be considered or interpreted identically.

Consequently, the variation in phrasing might be confusing. Lack of descriptions of possible consequences regarding modifying OSDFs makes weighing potential risks and benefits of a specific medicine difficult.

Lastly, when looking up, finding, and interpreting information, this must still be applied to the specific patient. The need and the reasons for modifications vary largely between patients (Mc Gillicuddy et al., 2017a; Mc Gillicuddy et al., 2017b; Mc Gillicuddy et al., 2019). Administering the medicine may be considered more important than following recommendations concerning modification. Mc Gillicuddy et al. (2017a) found that modifications may be considered a "necessary evil " to meet individual patient's needs. A recent systematic review (Mc Gillicuddy et al., 2017b) highlighted the complexity involved in balancing the advantages and disadvantages concerning modification of oral dosage forms to individual patients, for health care personnel and patients making these decisions. Concerns related to the effects and safety of medicines being modified are only one of many issues involved in this decision-making process. For example, facilitating the administration of important medicines and overcoming concerns regarding choking or discontinuation of therapy, are others. In many cases, however, alternative forms may be available, including OSDFs as effervescent or orodispersible tablets or oral liquid dosage forms (Schiele et al., 2013; Thong et al., 2018). The use of a similar medicine from the same class might also be an option, as well as the discontinuation of unnecessary medicines (Anonymous, 2014; Mc Gillicuddy et al., 2017b).

In addition, even though tablets could be crushed from a pharmaceutical point of view, crushing and dividing tablets are not standardized procedures, being further complicated by for example, splitting techniques that affect drug loss (Gharaibeh & Tahaineh, 2020; Thong et al., 2018), or mixing crushed tablets or the contents of capsules into food or liquid before administration (Manrique-Torres et al., 2014).

Implications and Further Studies

Information on how to administer and handle OSDFs is available in Felleskatalogen® as well as other sources of information, such as the SPC and the package leaflet. Based on the apparently common practice

to modify OSDFs in Norway (Bjerknes et al., 2017; Solberg et al., 2021; Wannebo, 2009), information on whether a specific medicine should be swallowed whole, can be divided, crushed, chewed and/or dispersed in water before administration needs to be readily available, explicit, and preferably with explanations for the given recommendations, as well as the consequences for each type of modification. We are not familiar with any gold standard for the organization or phrasing of this kind of information to ensure its readability and understandability. Mullen et al. (2018) reviewed best practices for written patient-oriented medication information. They found that plain, behavior-oriented and explicit text, standardized format and typographic cues (e.g., headings and bullet points) could be considered best practice, however, outcomes differed significantly between studies, as did their design.

One way to increase the understandability of information relating to the manipulation of OSDFs, is to design a traffic light model comparable to the ones used for classification of drug interactions: "Green light" might represent medicines for which all kinds of modifications could be done without risking a loss or increase in effect; "yellow light" could represent medicines for which some modifications can be made, such as dividing the tablet in two to ease intake; and "red light" could represent medicines for which all modifications would risk the patient being deprived of its effect or experiencing adverse effects. Information included in such a model would need to be explicit. For example, for OSDFs with modified-release characteristics which cannot be modified at all, it should be specified that these can neither be crushed, divided, nor chewed, and that they must be swallowed whole. In Australia, the Society of Hospital Pharmacists of Australia (SHPA) has published a book called, *Don't Rush to Crush,* which gives answers to whether medicines can be crushed, dispersed, opened, and whether liquid formulations are available (SHPA, 2021). In Norway, Oslo University Hospital has developed the crushing/opening/dissolving list ("knuse-/åpne-/løselisten") which summarizes information on whether one may modify many OSDFs on the Norwegian market (Oslo Universitetssykehus, 2021). The list is to be used in combination with the guidelines for crushing/opening/dissolving tablets and capsules at the hospital, although explanations for the recommendations concerning each

specific medicine are not included. We are not familiar with to what degree this source of information is used by health care personnel outside the hospital.

Strengths and Weaknesses of the Study

We chose to use Felleskatalogen® as the source of information in this study, as this is a familiar and frequently used source of drug information for health care personnel handling and administering drugs in Norway (Johansen, 2019; Kirkevold & Engedal, 2010). Earlier studies have reported that nurses experience the information in Felleskatalogen® relating to crushing and dividing tablets as difficult to find and/or understand (Kirkevold & Engedal, 2010; Wannebo & Sagmo, 2013) However, these studies are quite old, and Felleskatalogen® has gone through major changes both in lay-out, as well as in content in recent years. Importantly, it is no longer available in book form. The monographs are based on the approved SPC, and has its own structure (Felleskatalogen, 2021a). Under the chapter "Dosing", a tag called "Administration" exists for all drugs with a few exceptions, including some parallel-imported drugs. This makes information and recommendations relating to manipulation readily available if you know where to look. We could have chosen to use the SPC and/or the package leaflets for information on how to administer drugs. Felleskatalogen® however, is based on the SPC. Our impression is that Felleskatalogen® is used more, and is easier to search than the SPC and the digital package leaflets. Felleskatalogen® might be more familiar to health care personnel than to lay people, and future research could compare information and recommendations relating to administration and manipulation of drugs in these sources.

Drugs were categorized as immediate-release and modified-release based on their description under the paragraph "Administration" in Felleskatalogen® only. Some drugs may have properties causing them to belong to both categories. Lanzo Melt® (lansoprazole, Pfizer), for example, is designed as orodispersible tablets, intended to dissolve rapidly in the mouth cavity, and could therefore be categorized as immediate-release tablets. The active ingredient lanzoprazole on the other hand

is particularly sensitive to gastric acid, which is why the tablet consists of drug-loaded microgranules with a gastro-resistant coating. Drug release from these granules happens as a delayed-release process (Felleskatalogen, 2021b).

We focused on oral solid dosage forms, and exclusively on the information and recommendation in relation to the manipulation of these. Other given recommendations, like procedures encompassing the use of beverages (amount/type) and concurrent food intake would be interesting, but were not within the scope of this study.

Conclusion

Information on modification of OSDFs is commonly available in Felleskatalogen®. As expected, information was more common for medicines with modified-release than immediate-release characteristics. However, recommendations regarding the modification of immediate-release dosage forms were surprisingly numerous. Moreover, the information was not unambiguous, and the reasons for the given recommendations, as well as the possible consequences of modifications, were rarely included. This may result in medication errors and possible harm to the patient.

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