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Research Article

Assessment of oral solid dosage forms administration manner and acceptability

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Abstract

Taking oral solid dosage forms (OSDFs) safely and effectively is particularly important. This study aimed to determine the pattern and knowledge about the proper criteria of OSDF administration and the consumers' preferences toward OSDF characteristics. The aims of this study were achieved by cross-sectional survey through open and closed-ended questionnaires, and the presence of the main OSDF administration recommendations of a sample of 32 OSDF drug leaflets was assessed. Based on a simple random sample of 250 volunteers, we found inadequate compliance with the OSDF medicine administration criteria. We also found an absence of the main recommendations of OSDF drug administration on most of the investigated OSDF drug leaflets. Conventional white, round tablets were found to be the most preferred type of OSDF drug. These findings can be valuable to pharmaceutical manufacturers, regulatory agencies, and pharmacists to enhancing patient awareness and compliance with OSDF administration for safe and effective drug administration.

Keywords

Tablets preferences, drug leaflets, Medication adherence , PIL, Drug Labeling

Introduction

Since the nineteenth century to date, the oral solid dosage form (OSDF), such as tablets and capsules, has been the most predominant and frequently used medication form (Almukainzi et al. 2014a). This is not only because of the convenience of OSDF administration for patients but also because of their cost-effectiveness in manufacturing for pharmaceutical companies (Forough et al. 2018). Hence, taking OSDF safely and effectively is particularly important.

Important factors affect the OSDF medication adherence and taking tablet and capsule formulation correctly (FDA 2009). The successful esophagus passage and the transit time of OSDF depend significantly on the body position at swallowing time, even in subjects without an esophageal motility disorder (Osmanoglou et al. 2004; Perkins et al. 2008; Marquis et al. 2013). One study showed that the overall rate of successful esophageal passage of a tablet, such as a barium sulfate drug, was only 17% among 20 healthy participants who swallowed the tablets in a supine position (Gallo et al. 1996). However, this passage rate of the tablets was significantly increased to 66.5% when swallowed in a 45° upright position of the upper body and to 69.7% when swallowed in a vertical position(Gallo et al. 1996). Although the transit time of tablets in the upright position was the shortest, the study also showed that the passage of the tablets was improved by increasing the amount of water intake with the tablets in all three body positions (Gallo et al. 1996).

Therefore, the volume of the concomitant water intake is another significant factor that affects the smooth

and effective passage of OSDF drugs. It is well established that most OSDFs, with some formulation exceptions (May Almukainzi et al. 2019), are designed and tested to be administered with a full glass of water (which is approximately 250 ml) (Zuo et al. 2013; Almukainzi et al. 2019). However, most patients do not follow these recommendations when they are taking their medications (Fuchs 2009).

Moreover, many patients tend to drink beverages other than water with their medications. Common examples of these beverages are fruit juices, milk, coffee, tea, carbonated drinks, or, in more extreme cases, alcoholic beverages (Odou et al. 2001; Chuong et al. 2010; Zuo et al. 2013; Garin et al. 2014). These beverages that are taken to aid the swallowing of medications may affect their efficacy and/or safety by triggering drug disintegration, dissolution and/or absorption (Odou et al. 2001; Zuo et al. 2013). Studies have also shown that many OSDF drugs are not taken intact as patients tend to crush tablets or open capsules before administration (Manrique et al. 2014).

Limited studies have investigated the pattern of administration of OSDF and patient compliance with OSDF administration recommendations to ensure safe and effective administration. Pharmaceutical companies have different shapes and colors of OSDF, which can be used for medication differentiation and for practical purposes during drug manufacturing. The characteristics and physical appearance of an OSDF, such as the size, shape, and surface texture, also have an impact on the ease of medication swallowing and can improve patient acceptability (Overgaard et al. 2001; Ibrahim et al. 2012; Fang Liu et al. 2015). Although OSDF characteristics are critical to ensure patent adherence and therapeutic outcomes (Delamater 2006; Fang Liu et al. 2014), an inadequate number of studies have investigated consumer preferences and perceptions (Ibrahim et al. 2012).

This study aimed to determine the consumers' knowledge about the proper criteria of OSDF administration and their preferences toward OSDF characteristics. Additionally, the study aimed to assessed the presence of the OSDF administration recommendations on leaflets of the most common local medications.

Materials and methods

A cross-sectional survey using questionnaires distributed online to the public through social media websites and applications. The survey began with a consent statement for participation to be able to continue the survey. The questions were mainly multiple choice answers, and a couple of questions were designed as open-ended. The merits of the proposal and its alignment with national regulations were evaluated, and the study received "exempt" status from the Institutional Review Board (Registration Number# 20-0328) of Princess Noura University, Riyadh, Saudi Arabia.

The survey was made available online through a Google Docs link in the Arabic language and targeted individuals who are 18 years old and over. The questions started with demographical questions about gender, age, and education level, followed by questions that were developed around three major topics to assess the participants' practice and perception about that topic. The first topic (3 items) included questions about the OSDF swallowing ability of the participants and the prevalence of OSDF consumption. The second topic evaluated the participants' patterns in taking OSDF (positions at swallowing time, concomitant kind and amount of liquid intake, modifying the OSDF before intake, and changing the primary packaging before administration of OSDF). The last topic was about the participants' acceptability and preference toward OSDF in terms of form, shape, and color.

The second aim of this study was achieved by scanning a sample of 32 OSDF drug leaflets that are manufactured nationally and in the Middle Eastern region to investigate the presence of the main OSDF administration recommendations criteria (Table 1). This included the administration mode, water noted as the liquid that should be taken with the OSDF, amount of water intake, and storage conditions.

Abbreviations

EMA	European Medicines Agency;
FDA	Food and Drug Administration;
GIT	gastrointestinal tract;
IM	Immediate release;
OSDFs	Oral solid dosage forms;
OTC	over-the-counter drugs;
PIL	Patients information leaflet;
PR	prolonged release;
SAHPRA	South African Health Products Regulatory Authority;
US	United States.

Results

A simple random sample of 250 volunteers was used: 79% were women and 21% were men. Most of them had a university degree or above. Table 2 presents the characteristics of the volunteer sample.

A total of 3.6% of the participants reported that they always faced OSDF swallowing difficulties, and 25.8% of them sometimes faced swallowing difficulties with OSDF. Ninety-six percent of the participants had taken OSDF at least once in their lives. Figure 1 presents the frequency of taking OSDF medications.

In this study, 26% of the participants were taking beverages other than water with their OSDF medications. A total of 8.5% of the participants believed that taking beverages other than water had no impact on OSDF medications, whereas 15% said they did not know. Only 27% of the sample was taking a full glass of water with their OSDF medications, while the rest of the participants were taking less water, as presented in Figure 2. Approximately 15% of

Table 1. OSDF drugs used to evaluate the presence of administration criteria on the leaflets.

Active constituent	Drug name	Company name	Origin
Folic acid	Folic acid	Riyadh pharma	KSA
Loratidine	Lorinase	Spimaco	KSA
Diclofenac pottasium	Rapidus	Tabuk	KSA
Quetiapin	Adazio	Riyadh pharma	KSA
Omeprazole	Gasec	Batterjee pharma	KSA
Mebeverine hydrochloride	Meva	Jamjoom pharma	KSA
Levofloxin	Levoflox	National Pharmaceutical Industries Co (SAOC)	Oman
Clarithromycin	Clarixin	Pharma International Company (PIC)	Jordan
Loratadine	LoraS	Dammam Pharma	KSA
Rantidine hydrochloride	Zydac	Jamjoom pharma	KSA
Prednisolone	Predo	Jazeera phrma	KSA
Azithromycin	Zocin	The Arab Pharmaceutical Manufacturing Company (APM)	Jordan
Telmisartan	Nizortan	Tabuk pharma	KSA
ferric hydroxide polymaltose complex) and folic acid	Ferose-F	Spimaco	KSA
Amoxicillin	Megamox	Jazeera pharma	KSA
Oseltamivir	Oselta	Jamjoom pharma	KSA
Cetrizine	Artiz	Tabuk	KSA
Amoxillin and cluvanic acid	Amoclan	Hikma Pharma	Jordan
Ibuprofen	Sapofen	Spimaco	KSA
Chlorzoxazone and Paracetamol	Relaxon	Jamjoom pharma	KSA
Metronidazole	Riazole	Riyadh pharma	KSA
Azithromycin	Azionce	Jamjoom pharma	KSA
Ranitidine hydrochloride	Ranid	Tabuk	KSA
Amoxicillin	Moxal	Julphar	UAE
Acetylsalicylic acid	Disprin	Riyadh pharma	KSA
Paracetamol	Fevadol	SPimaco	KSA
Lansoprazole	Takepron 15	The Arab Pharmaceutical Manufacturing Company (APM)	Jordan
Loratadine	Lorine	Spimaco	KSA
Domperidone	Dompy	Jamjoom pharma	KSA
Metronidazole	flazol	Tabuk pharmaceuticals	KSA
Glyburide and Metformin Hydrochloride	Glucovance	Riyadh pharma	KSA
Ibuprofen	Profinal	Julphar	UAE

Table 2. Characteristics of the participants.

Characteristics	
Gender	
Male	51 (20.5%)
Female	197 (79.5%)
Age groups (years)	
18–30	149 (60.1%)
31–41	56 (22.6%)
42-51	25 (10.1%)
52 and above	18 (7.3%)
Educational level	
Less than high school	8 (3.2%)
High school or diploma	53 (24.1%)
Bachelor	169 (68.1%)
Postgraduate (MS, and PhD)	18 (7.3%)

the volunteer sample believed that the water amount taken with an OSDF did not impact the administered drug, and 33% were uncertain.

The participants' positions while taking OSDF medication are presented in Figure 3.

Only 11% of the participants were transforming OSDF medications before administration by crushing tablets or opening capsules. However, 20% believed that crushing ODSF or opening capsules had no effect on drug safety or efficacy, and 37% were not sure if this practice would have any impact on the drug.

Approximately 30% of the sample changed the original primary package of the OSDF medication before the ad-

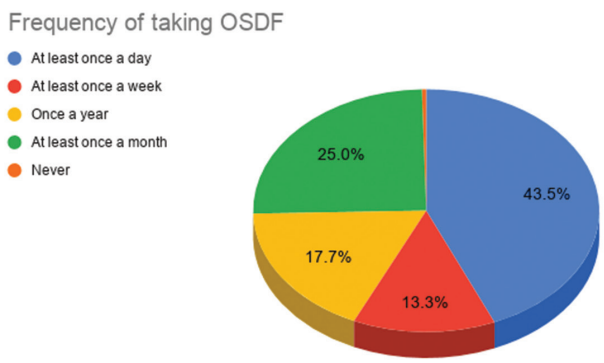

Figure 1. Frequency of OSDF medication administration among the participants.

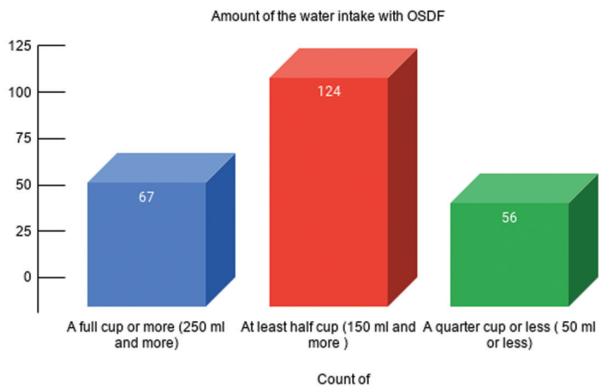

Figure 2. Amount of concomitant water intake with OSDF medications.

ministration by, for example, keeping them in a piece of tissue. However, 17% of the sample believed that changing the original packaging of OSDF had no impact on drug efficacy or safety.

In terms of OSDF preferences, 79% of our sample preferred tablets over capsules. The open-ended question showed that the most common reason, according to 60% of the participants, was that they believed that tablets are easier to swallow compared to capsules. Other reasons for tablet preferences were given, such as the feeling that capsules can be trapped and adhere to the esophagus, causing dysphagia, in addition to the bad taste of the capsule shell. Eighty-two percent of the participants preferred tablets (Immediate release (IM) or prolonged-release (PR)), 12% preferred effervescent tablets, and only 5% preferred chewable tablets. The most preferred shape of OSDF by our sample was round (Figure 4), and the most common reason was that the round shape requires less effort in swallowing.

Most of the participants preferred the white color, as presented in Figure 5. The most common reason was that there was a sense of no additives in white color tablets, which made them feel a white color is the safest. Another given reason was the common use of a white color for OSDF.

The leaflet scanning of OSDF administration criteria in the sample of 32 OSDF drugs is summarized in Table 3.

Discussion

Optimizing OSDF medication administration is necessary to provide the best possible outcomes. OSDF swallowing difficulties, which differ from dysphagia, can be induced by emotional and psychological causes, and they can negatively affect medication adherence (Forough et al. 2018). Studies have reported that OSDF swallowing difficulties impact approximately 10–40% of the healthy adult population (Forough et al. 2018). In concordance with these studies, approximately 30% of our sample indicated that they have some swallowing difficulties while taking OSDF medications. Although swallowing difficulties with OSDF are common and their potential clinical risks are high, studies provide little information about this issue, especially on outcomes and patient practices to overcome their swallowing difficulties (Marquis et al. 2013). Different factors, such as the patient position at swallowing, pill shape and dimensions, and the amount of water intake with ODSF can help relieve unpleasant swallowing experiences. To minimize esophageal irritation and facilitate swallowing ability, patients tend to crush tablets or open capsule contents. Some patients also try to mask any unpalatable taste of OSDF drugs by taking sweet drinks or mixing the crushed pills with soft food such as yogurt, jam, juices, and milk (Forough et al. 2018).

These coping strategies were addressed not only by patients but also by some caregivers and healthcare practitioners, especially in nursing home care (Caussin et al. 2012; Schiele et al. 2013; Manrique et al. 2014; Almukainzi

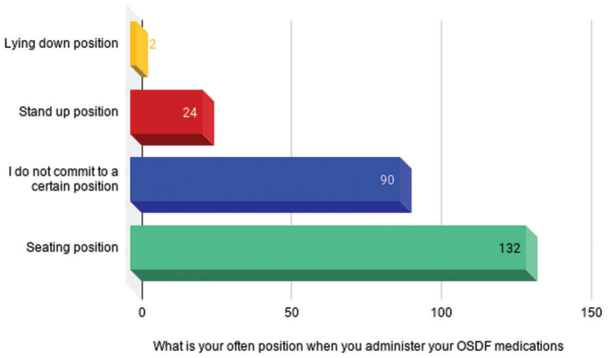

Figure 3. The participants' positions while taking OSDF medications.

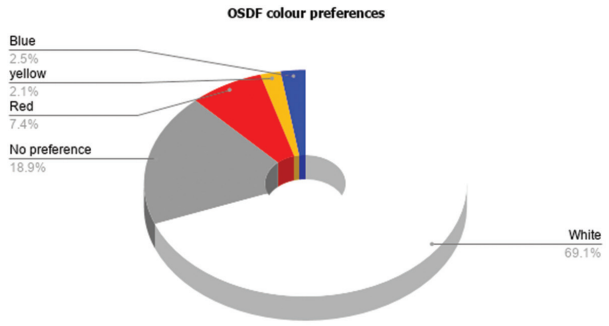

Figure 4. The participants' preferences for OSDF color.

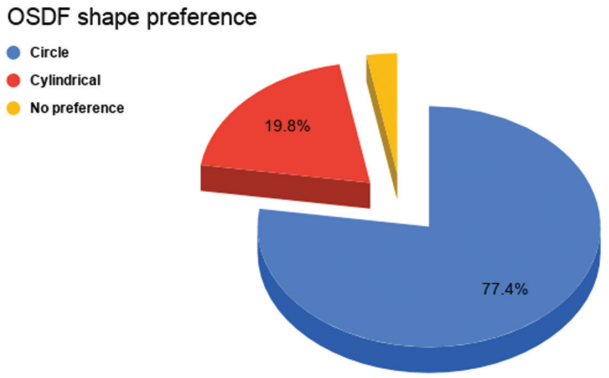

Figure 5. The participants' preferences for OSDF shape.

Table 3. Administration criteria of OSDFs stated in the most common local drug leaflets

Criteria	N=32
Specified water as the liquid to be administered with OSDFs	46.875%
Identify the amount of intake water	37.5%
Determine if ODSF can be manipulated*	53.125%
Storing in original package till the using time	21.875%
Pinpoint the position while taking OSDFs	0%
Storage temperature	96.875%

* Determine whether OSDF should be administered as whole and not to be broken, opened or crushed before administration or can be scored.

et al. 2020; Sefidani Forough et al. 2020). Although only a few of the participants admitted that they modified OSDF medication before its administration by crushing or chewing OSDF, many of them believed these practices do not affect the drug's efficacy or safety. Unless otherwise suggested, OSDF medications should be taken intact.

Modifying OSDF medications before administration by crushing tablets or opening capsules may lead to toxicity by inducing dose dumping as in PR form or alterations in the drug taste as in sugar-coated tablets (Stubbs et al. 2008; Forough et al. 2018). Moreover, IR OSDF medicines are designed to disintegrate and dissolve in the gastrointestinal tract (GIT), so crushing these tablets or opening the capsule may result in an alteration of the rate of absorption (Manrique et al. 2014). These practices can also cause a loss of part of the dose during crushing and administration to the patient (Sefidani Forough et al. 2020; Shane et al. 2017). Other concerns related to OSDF modification are the risk of occupational and caregiver exposure (Caussin et al. 2012; Forough et al. 2018; Forough et al. 2020). Implementing training interventions regarding the best and safest medication administration has shown positive outcomes in nurses' practices and is recommended to be integrated as a part of professional development training (Stuijt et al. 2013).

Studies have shown that the retention rate of ODSF in the digestive tract decreases significantly with increasing volumes of intake water (Osmanoglou et al. 2004). A quantity of at least 250 ml of intake water with OSDF is essential to ensure a rapid transfer of OSDF through the esophagus, thus decreasing swallowing difficulties. A study conducted in Germany aimed to investigate the volume of water used by patients when administering their medications, where every patient who bought tablets or capsules from a participating pharmacy and wanted to take their medicine immediately received a glass of water (Fuchs 2009). The volume of water consumed by the 136 participants was measured after taking their medication. The results showed that the water intake with OSDF in 15.4% was only 60 ml (Fuchs 2009). Likewise, most of the participants in our study admitted that they took less than 250 ml of water with their ODSF medications (Figure 2), and many of them assumed that the amount of water had no impact on the absorption. A statement about the amount of water that should be consumed with OSDF was missing from most of the scanned sample drug leaflets, as presented in Table 3. This can explain the poor compliance with the recommendation of 250 ml intake water for OSDF administration.

OSDF disintegration, dissolution, absorption and bioavailability depend on the physicochemical properties of the drug and the patients' physiological conditions; therefore, alterations in these factors may affect drug absorption (Jaruratanasirikul and Kleepkaew 1997; Almukainzi et al. 2014a, b; Almukainzi et al. 2016; Bolger et al. 2019). In this study, many participants were taking beverages other than water with their medications. Taking acidic beverages such as coffee, teas, juices or even dairy drinks such as milk with medications can potentially alter drug bioavailability and consequently increase or decrease drug therapeutic outcomes (Forough et al. 2018). The effect of concomitant beverages with OSDF may not be limited to an interaction with the drugs but may also affect their physical properties such as solubility and pH. Studies have investigated the *in vitro* and *in vivo* impact of concomitant beverage intake on drug disintegration, dissolution and bioavailability (Odou et al. 2001 ; Zuo et al. 2013; Manrique et al. 2014 ; van Leeuwen et al. 2016; Nomani et al. 2019). Carbonated drinks such as Cola are among the most widely consumed beverages worldwide; Coca-Cola significantly impacts the *in vivo* bioavailability of some OSDF drugs, such as ibuprofen and erlotinib, when consumed with drugs (Kondal and Garg 2003; van Leeuwen et al. 2016; Nomani et al. 2019). Milk another common example of a beverage that significantly decreases drug bioavailability by delaying the drug disintegration time, which may be a reflection of its high viscosity and low surface tension (Odou et al. 2001; Chuong et al. 2010; Zuo et al. 2013; Garin et al. 2014). As the ability of the patient to use OSDF as intended is significant, the presence of these recommendations in drug leaflets is extremely important (Liu et al. 2014). As shown, in our results, many of our participants were not aware of the impact of concomitant beverages. One of the most common reasons could be related to the absence of this information, as found in our sample drug leaflets (Table 3).

Therefore, it is important that every inserted leaflet in the OSDF package contains all OSDF drug administration recommendations.

Regulatory agencies recognize the need for the presence of the OSDF administration criteria on patient information leaflets (PIL). For example, the United States food and drug administration (US-FDA), the European Medicines Agency (EMA), the South African Health Products Regulatory Authority (SAHPRA), and the Saudi FDA guide sponsors/applicants regarding the required labeling information (European Commission 2009; Executive Board of the Health Ministers' Council for GCC States 2011; Fda et al. 2014; SAHPRA 2019; SFDA 2019). However, these documents are viewed as recommendations and do not establish legally enforceable responsibilities. The finding of this study showed the importance of implementing stricter legislation with drug manufacturers concerning the presence of the OSDF medicine administration criteria on PIL to enhance drug safety and efficacy.

In addition to the above-discussed factors that affect drug absorption in the GIT, the characteristics of drug formulations might have an impact on patient acceptability and hence ensure adherence and therapeutic outcomes (Liu et al. 2014, 2016). Previous studies found that gelatin capsules were preferred over tablets (Overgaard et al. 2001). On the other hand, the participants in this study

preferred tablets over capsules. The discrepancies in these results can be explained by the age of the participants, as the esophageal transit time of tablets was significantly longer in the elderly due to the physiological changes associated with age (Hey et al. 1982).

Fast melting tablets are OSDFs that are designed to be easier to swallow than conventional tablets (Almukainzi et al. 2019). However, limited evidence exists regarding the acceptability and preference of these solid dosages over conventional tables (Liu et al. 2014, 2015). Our results emphasized this finding, as most of our sample preferred conventional tables.

The size, shape and color of OSDF depend on many factors such as active ingredient and excipients amount and color, stability, the necessity of coating, and type of coating. Color and shape are also important factors that impact patients' psychological responses. The findings of this study, allied with previous studies (Overgaard et al. 2001; Hasamnis et al. 2011), showed that the most preferred shape is round for the ease of swallowing. In alignment with the results of a previous study conducted by Overgaard et al. (Overgaard et al. 2001), this study showed that a white color was the preferred color of OSDF. One of the most common explanations for the preference of a white color, as found in this study, is the sense that a white OSDF has no additives added.

According to the results of our study, the ideal OSDF is small in size, white in colour and circular in shape. Consumer preferences need to be considered by pharmaceutical firms when developing a generic drug or managing the life cycle of a drug (Ibrahim et al. 2010, 2012; Shariff et al. 2020). This finding can also service pharmacists to provide personalized pharmaceutical care, particularly in the presence of drug brand alternatives. This can be especially crucial to consider for over-the-counter drugs (OTCs). OTC usage saves health care systems up to $100 billion per year, as in the US, by promoting self-administration and reducing doctors' visits (BoozCo 2012).

Conclusion

Non-adherence to proper usage of OSDF can lead to poor disease management and increase side effects. This study showed inadequate compliance with the OSDF medicine administration criteria. Moreover, an absence of the main recommendations of OSDF drug administration in most of the investigated OSDF drug leaflets was found. In this study, white, round tablets are the most preferred formulation of OSDF drugs. Enhancing patient compliance and awareness about the importance of OSDF administration criteria is essential for safe and effective drug administration. Optimizing the administration manner of OSDF medications, bearing in mind patients palatability, is a demanding factor to be considered by pharmaceutical manufacturers, regulatory agencies and clinical practitioners.

Acknowledgments

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