

Knowledge, Attitudes, and Practices of Pharmacists Toward Splitting or Crushing Oral Solid Dosage Forms in Palestine: Safety and Therapeutic Implications

Abdel Naser Zaid¹, Yaser Abdallah², Sa'ed H. Zyoud^{2,3,*}

¹Pharmaceutical Chemistry and Technology Department, College of Medicine and Health Sciences, An-Najah National University, Nablus 44839, Palestine. ²Department of Clinical and Community Pharmacy, College of Medicine and Health Sciences, An-Najah National University, Nablus 44839, Palestine. ³Poison Control and Drug Information Center (PCDIC), College of Medicine and Health Sciences, An-Najah National University, Nablus 44839, Palestine.

*Corresponding author: saedyoud@najah.edu

Received: (28/3/2018), Accepted: (1/2/2019)

ABSTRACT

Tablet splitting and crushing is a widespread practice among health-care providers and patients for increasing dose flexibility, or making tablet parts easier to swallow, or allowing cost savings for medications. However, this practice may be dangerous because some formulations and classes of drugs are unsuitable for crushing or splitting and may cause significant problems, especially in drugs with low therapeutic indices. This study was conducted to examine the knowledge, attitudes and practice of pharmacists toward splitting or crushing oral solid dosage forms (OSDFs) in Palestine. This is a self-administered cross-sectional questionnaire survey involving 300 pharmacists who work at community pharmacists and hospitals in the West Bank area of Palestine and was conducted during the period May 2013 to August 2013. Data were collected using a pretested questionnaire consisting of four sections and analyzed using descriptive statistics and correlation. A total of 325 questionnaires were distributed and 300 were completed. About 67.3% of the pharmacists had good knowledge. Nearly 69% of the pharmacists had a good attitude. There was a positive correlation ($p=0.002$, $r=0.18$) between knowledge and attitude scores among pharmacists. Approximately 83.7% of the pharmacists had good practices. There was a significant difference between practice and non-practice respondents regarding knowledge score ($p=0.037$). This study has identified knowledge, attitude and practice gaps among health-care practitioners, especially among pharmacists. Therefore, improving appropriate knowledge regarding splitting and crushing OSDFs is required by planning and developing programs for local health education purposes.

KEYWORDS: Splitting tablets; Pharmacists; Oral Solid Dosage Forms; Crushed drugs.

BACKGROUND

One of the significant current discussions from a medical and legal point of view is splitting or crushing oral solid dosage forms (OSDFs). Splitting OSDFs refers to the practice of dividing a tablet to provide a lower dose of the active ingredient or to obtain multiple smaller doses for many purposes. While crushing tablet refers to the process of converting tablets into powder by using suitable pharmacy tools such as mortar and pestle. These may provide several advantages. Patients usually split tablets for various reasons, such as: (i) providing the patient with the desired dose when the product is not available at the required strength, e.g. hydrochlorothiazide: the available dose is 25mg and the drug is commonly used in doses of 12.5mg, thus the patient needs to split the tablet to receive the smaller dose. Another example is converting atenolol tab-

lets into capsules with the desired filling weight [1]. This practice is useful for children or older persons; (ii) slowing the titration of the medication to start therapy with the lowest possible doses and then starting to increase the dose until reaching the desired dose to enable toleration of the drug and reduce the incidence of side effects of certain drugs, e.g. with beta-blockers such as metoprolol used post myocardial infarction, patients cannot tolerate full doses of 50mg and instead are given 12.5mg, then the dose will be increased. The lowest dose available is 50mg, which necessitates the tablet being split into quarters to give the wanted dose [2]. Another example of the benefit of splitting a tablet in slow titration is patients who are taking anticoagulation therapy with warfarin: patients require frequent dose changes to stay at an appropriate level of anticoagulation. Instead of purchasing more than one strength, patients resort to purchasing one

strength and splitting the tablets to adjust the dose as required [2]; other reasons include (iii) reducing medication costs; (iv) making the swallowing of large tablets easier [3-5]; and (v) providing medication dose flexibility [6, 7]. Regarding crushing tablets, it is an acceptable method of medication administration for patients with swallowing problems due to the large size of the capsules or due to a bad taste or the number of tablets to be administered, and crushing tablets and mixing them with food is considered a convenient method of administration to individuals with memory loss or confusion [8].

It is important to realize the possible effects of tampering with drugs. Altering the design of dosage forms may cause a change in the pharmacokinetic and pharmacological effect of drugs [9]. There are some problems associated with splitting or crushing OSDFs. It creates hazards for pharmacists: splitting or crushing teratogenic drugs or carcinogenic drugs such as valganciclovir or methotrexate expose pharmacists to risks via the aerosolization of powder, in a similar way to some hormones, corticosteroids, mycophenolate and many other drugs [9]. In fact, powder dust is one of the major factors that must be controlled during the manufacturing of OSDFs, since this factor is responsible of cross contamination and may cause serious hazards to operators. Splitting or crushing OSDFs may have a negative effect on drug stability; an example of that is nifedipine-coated tablets, as this drug is very light-sensitive when it has been crushed [9]. Proton-pump inhibitors such as omeprazole and pantoprazole are enteric coated. This coat protects them from acidic environment of the stomach. This permits them to reach unchanged the site of absorption. The effect of the drug coating will be removed by crushing it and this will lead to decreasing the effect of the drug in the small intestine [10]. Changes in bioavailability are another problem associated with crushing OSDFs [9]. These changes may be very significant for drugs with a narrow therapeutic window such as carbamazepine or digoxin [9]. In fact, one of the major disadvantages of sustained release tablets is due to the rupture of this design (coat or matrix) which cause the release of the con-

tent in the gastrointestinal tract (GIT) causing toxic levels of the active pharmaceutical ingredients.

For drugs that have a problem with their taste such as ciprofloxacin, clarithromycin and sertraline, coating is utilized to hide their unpleasant bitter or anaesthetic taste [9]. Sugar coating, which contains a hard thick layer, may be used for coating drugs such as ibuprofen [9]. Film coating, which contains a thinner layer than sugar, is also used for coating many drugs such as ciprofloxacin, pseudoephedrine and cefuroxime axetil [9]. So crushing drugs that have a bitter taste may lead patients to reject taking drugs unless they are mixed with suitable food or drink [9]. In fact, clarithromycin is one of the worst bitter tasting drugs, this drug reaches the salivary gland after being absorbed and distributed. This will result in a strong bitter after taste that may decrease patient compliance.

Previous research in the world has produced few studies about this issue [11-13]. In fact, this study is considered to be the first in Palestine to measure the knowledge, attitudes and practices of health-care practitioners regarding crushing and/or splitting OSDFs. This study may increase the awareness of health-care practitioners toward splitting or crushing OSDFs, the appropriate decision and the best way to consider crushing or splitting tablets.

METHODS

Study design and study area

This is a questionnaire-based cross-sectional analytical study; it is designed to measure the attitudes, knowledge and practices of pharmacists toward crushing or splitting OSDFs. Palestine consists of two zones separated geographically: the West Bank and the Gaza strip, with a total population of about three million inhabitants. Nearly 62% live in the West Bank and 39% live in the Gaza Strip. The West Bank is divided into three regions and 11 governorates. The north area comprises: Jenin, Tulkarm, Nablus, Qalqilya, Tubas and Salfit; the middle area comprises: Jerusalem, Ramallah and Jericho; the south area comprises: Bethlehem and Hebron [14].

This study was conducted in the West Bank of Palestine from May 2013 until August 2013. The authors acquired a list of the names of hospitals and their addresses from the Ministry of Health, and obtained a list of names of all community pharmacies and their addresses from the Palestinian Pharmaceutical Association. Based on the list, the authors visited the following governorates in the West Bank: Nablus, Jenin, Tulkarm, Qalqilya, Tubas, Ramallah, Bethlehem and Hebron [14].

Population of the study

The population of the study was pharmacists who work in community pharmacies and hospitals in the West Bank. Community pharmacists comprise one of the most important sectors of health-care professionals; in addition to their role in providing drugs, they are also considered a source of information about health and drugs. The West Bank, which is located west of the River Jordan, has a total population of three million and is divided into three regions – north, south and middle – in 11 governorates. There are 3217 registered pharmacists in the West Bank and the majority of them work in the private sector [15]. Others work in hospitals, clinics, and pharmaceutical industries and companies.

Sample size calculation and sampling procedure

In this study the convenience samples of pharmacists from hospitals and community pharmacies were taken from the visited governorates in the West Bank. Community pharmacies that were closed or in which the pharmacist in charge was not present at the time of the visit were excluded from the study. Hospitals in which the pharmacist in charge was not present at the time of the visit were excluded from the study.

The expected number of pharmacists who were licensed by the Palestinian Pharmaceutical Association and working within their field and connected with splitting or crushing OSDFs was around 1200. Based on this, Raosoft software (<http://www.raosoft.com/samplesize.html>) was used to calculate a suitable sample size

and this was 292 for pharmacists. In order to minimize erroneous results and increase the study reliability, the target sample size included 300 samples for pharmacists.

DATA COLLECTION INSTRUMENT

The questions used in the tool had been developed based on previously published studies in other countries [7-11, 13, 16-24]. The tool was piloted and tested before the study was officially carried out. The questionnaire used in the tool consists of four sections: 1. demographic data (gender, age, workplace, education, place and year of graduation), 2. practice in splitting/crushing tablets (5 questions), 3. attitudes (9 questions answered as yes/no/don't know), and 4. knowledge (1 on source of information and 14 on specific examples). Attitude was scored from 0 to 9 points with 'good attitude' denoted as a score from 6 to 9 points and 'poor attitude' from 0 to 5 points. The Knowledge score was based on the 14 examples and a score of 8 to 14 was considered 'good knowledge' and 0 to 7 as 'poor knowledge'.

The internal consistency and validity of the questionnaire were ensured for the instruments used in our study, namely the attitude scale (nine items, Cronbach's alpha =0.76) and the knowledge scale (14 items, Cronbach's alpha =0.73). The tool used in this study had been constructed by the authors and was reviewed and corrected by three PhD holders in clinical and pharmaceutical sciences that had at least four years of pharmacy practice to ensure face and content validity.

Ethical approval

All aspects of the study protocol were obtained from the Institutional Review Board (IRB) at An-Najah National University and the required permission from the Palestinian Ministry of Health. The authors obtained verbal consent from the community pharmacists who participated in the study.

Statistical analysis and scoring

Statistical analyses were performed by using the Statistical Package for the Social Sciences (SPSS version 16.0). Mean and standard deviation was computed for contin-

uous data. Frequencies and percentages were calculated for categorical variables. Data that were not normally distributed were expressed as a median with a range of values (lower-upper quartiles). Data that were not normally distributed were analyzed by the Kruskal-Wallis or Mann-Whitney U test. Variables were tested for normality using the Kolmogorov-Smirnov test. Spearman's correlation coefficient was used to assess whether there was a correlation between variables. Categorical variables were compared using Chi-squared and Fisher's exact tests, as applicable. A p-value of less than 0.05 was considered to be statistically significant for all analyses. Internal consistency was assessed using Cronbach's alpha.

RESULTS

Table (1): Demographic characteristic of pharmacists

Variable	Pharmacists N=300 Frequency (%)
Graduation institute	
Local institute	237 (79)
Arab institute	43 (14.3)
Others	20 (6.7)
Gender	
Male	87 (29)
Female	213 (71)
Place of work	
Hospital	90 (30)
Primary care	22 (7.33)
Community pharmacy	188 (62.6)
Age category years	
20-29	169(56.14)
30-39	89(29.5)
40-49	19(6.31)
50-59	17(5.64)
≥60	7(2.32)
Educational level	
Bachelor of Science	261 (87)
Master of Science	39 (13)
Age	
Mean ±SD	32±9.6
Experience years	
Mean ±SD	8.4±9

Knowledge of the respondents about crushing or splitting OSDFs

The level of knowledge about crushing or splitting OSDFs, its safety and therapeutic implications were evaluated using statements

Demographic characteristics

A total of 325 questionnaires were distributed to the hospitals, community pharmacies and primary health-care centers in Palestine. Twenty-five of the questionnaires were found to be incomplete and were therefore excluded from the analysis. As shown in the summary of demographic characteristics in Table 1, the vast majority of the respondents were females (71%) and 29% were males. More than half of the respondents (62.6%) were working in community pharmacies. The average age of the participants was 32±9.6 years and the average number of years of experience was 8.4±9. Majority of the pharmacists (87%) had a bachelor degree. The majority of the participants (79%) studied at and graduated from local universities.

shown in Table 2. When the participants were asked whether extended-release (ER) solid products should not be split or crushed because they are planned for drug release in the intestine not in the stomach, only 29.3%

correctly answered no. Among the 300 respondents, 94.6% of the pharmacists knew that ER formulation consisted of layers or micro grains with progressive dissolution time. Respondents were less knowledgeable about whether Tegretol 400 mg CR® divitabs can be split or not; only 25.7% of the pharmacists agreed with this statement. Only 25% of the pharmacists knew that combination products in the same tablet will not affect the appropriateness for splitting or crushing OSDFs. In fact, 79.3% of the pharmacists correctly disagreed that Tegretol 400 mg CR® divitabs can be crushed. About 87% of the pharmacists knew that baby aspirin cardio cannot be split because it is enteric coated. In particular, 11.8% of the pharmacists did not know that Lescol XL® (fluvastatin) should not be crushed or split because it is extended release, 63.3% of the pharmacists agreed that omeprazole enteric-coated granules should not be crushed because this will inactivate

the active ingredients. About 62.6% of the pharmacists knew that the administration of crushed nifedipine XL® resulted in increased toxicity. 60.7% of the pharmacists correctly agreed that pancreatin tablet should not be crushed because this will inactivate the active ingredients. About 29% of the pharmacists did not know that antineoplastic drugs should not be split or crushed because this will expose pharmacists to health risks. Respondents were less knowledgeable about whether nifedipine-coated tablets should not be crushed because the drug is highly light-sensitive; only 27% of the pharmacists agreed with this statement. Nearly 80% of the pharmacists knew that the administration of crushed enteric-coated sulfasalazine tablets led to the release of the drug too early. Finally, majority (74.2%) of the pharmacists correctly answered that the administration of crushed alendronate may cause oesophageal irritation.

Table (2): Responses to questions regarding knowledge of pharmacists toward crushing or splitting oral solid dosage forms (OSDFs).

Variable	Response Frequency (%) N=300
K1: Most extended release formulation must not be split or crushed because it is planned for passing the stomach intact and beginning drug release in the intestine: Yes No I do not know	212 (70.7) 88 (29.3)* 0 (0)
K2: Most extended release formulation must not be split or crushed because it is consisting of layers or micro grains with progressive dissolution time: Yes No I don't know	284(94.6)* 8 (2.7) 8 (2.7)
K3: Tegretol 400 mg CR® (carbamazepine, Novartis company) Divitabs can be split? Yes No I do not know	77 (25.7)* 197 (65.7) 26 (8.7)
K4: If tablet contains a combination product; this will not affect the appropriateness or recommending for splitting or crushing or not? Yes No I don't know	75 (25)* 190(63.3) 35 (11.7)
K5: Tegretol 400 mg CR® (carbamazepine, Novartis company) Divitabs can be crushed? Yes No I don't know	14 (4.7) 238(79.3)* 48 (16)

Variable	Response Frequency (%) N=300
K6: Baby Aspirin cardio® (acetyl salicylic acid, Bayer company) cannot be split or crushed because it is Enteric coated Extended release I don't know	261(87)* 17 (5.7) 22 (7.3)
K7: Lescol XL® (fluvastatin, Novartis company) should not be split or crushed because it is Enteric coated Extended release I don't know	25 (4.5) 210(38.2)* 65 (11.8)
K8: Omeprazole enteric coated granule should not be crushed or split because this will: Increase Toxicity Inactivate active ingredient I don't know	75 (25) 190(63.3)* 35 (11.7)
K9: The administration of a crushed nifedipine XL tablet resulted in Increase Toxicity Inactivate active ingredient I don't know	188(62.6)* 49 (16.3) 63 (21)
K10: Pancreatin tablet should not be split or crushed because this will Increase Toxicity Inactivate active ingredient I don't know	46 (15.3) 182(60.7)* 72 (24)
K11: Antineoplastic agent should not be split or crushed because: This will inactivate active ingredient These agents may expose careers or health care professionals to health risks I don't know	46 (15.4) 166(55.5)* 87 (29)
K12: Nifedipine coated tablet should not be crushed because The drug is highly light sensitive Increase conc. and toxicity I don't know	81 (27)* 133 (44.5) 85 (28.4%)
K13: The administration of a split or crushed enteric coated sulphasalazine tablet resulted in Increase the serum concentration and lead to toxicity The drug is being release too early I don't know	20 (6.7) 241(80.3)* 39 (13)
K14: Alendronate drug should not be crushed because This will inactivate active ingredient Due to risk of esophageal irritation I don't know	32 (10.7) 221(74.2)* 45 (15.1)

*was used for correct answer

Attitudes of the respondents toward crushing or splitting OSDFs

Data on respondents' attitude toward crushing or splitting OSDFs are found in Table 3. In general, 28.3% of the pharmacists thought that splitting tablets is a useful way to reduce medication costs. In response to the question of whether physicians should prescribe split tablets as often as possible to reduce medication costs, the viewpoint of al-

most 90.7% of the pharmacists disagreed with this idea. Most (95.6%) of the pharmacists agreed that sometimes it is difficult to break tablets because they are small or hard. A93.7 positive response was reported by the pharmacists when they were asked whether sometimes even scored tablets cannot be divided into equal parts. Only 3.5% of the pharmacists supported the idea that all tablets can be split or crushed if required. Nearly

61% of the pharmacists agreed that sometimes they are not sure whether tablets are indeed suitable for splitting or crushing. With regard to the information about splitting or crushing OSDFs, 44% of the pharmacists expect to find information about this in the **Table (3)** Responses to questions regarding attitudes of pharmacists toward crushing or splitting oral solid dosage forms (OSDFs).

package leaflets. Thirty-three percent of pharmacists in this study didn't ask experts about how to split tablets best. Finally, over 57.6% of the pharmacists thought that splitting or crushing OSDFs is part of the doctor's role or responsibility.

Variable	Response Frequency (%)N=300
A1: Tablet splitting is a useful way to reduce medication costs Yes No I don't know	85 (28.3) 203 (67.7)® 12 (4)
A2: To reduce medication costs physician should prescribe split tablets as often as possible. Yes No I don't know	15 (5) 272 (90.7)® 13 (4.3)
A3: Sometimes it is difficult to break tablets (e.g. because they are very small or hard) Yes No I don't know	286 (95.6)+ 4 (1.3) 9 (3.1)
A4: Sometimes even scored tablets cannot be divided into equal part Yes No I don't know	281 (93.7)+ 16 (5.3) 3 (1)
A5: If required, all tablets may be split or crushed Yes No I don't know	19 (6.3) 266 (88.7)® 15 (5)
A6: Sometimes I am not sure whether tablets are indeed suitable for splitting or crushing. Yes No I don't know	183 (61.2) 101(33.8)® 15 (5)
A7: If tablets are not suitable for splitting or crushing, I expect to find this information in the package leaflet. Yes No I don't know	132 (44)+ 158 (52.7) 10 (3.3)
A8: I have ever been asked expert on how to split tablets best Yes No I don't know	172 (57.3) 99 (33)® 29 (9.7)
A9: I think that modifying the dosage form is part of the doctor's role or responsibility Yes No I don't know	173 (57.6)+ 107 (35.6) 20 (6.7)

® was used for correct negative answer

+ was used for correct positive answer

Practices of the respondents toward crushing or splitting OSDFs

Data on respondents’ practice toward crushing or splitting OSDFs are found in Table 4. In general, around 15% of the pharmacists in the study had split or crushed enteric-coated or sustained-release OSDFs such as baby aspirin cardio, Tegretol CR®, Pentasa® etc. Around 95% of the pharmacists didn’t receive training in drug stability after splitting or crushing OSDFs. As far as encourag-

ing pill splitting as a way to help patients save money is concerned, 14.7% of the pharmacists agreed with this statement. When the pharmacists were asked how often they split tablets as a way to obtain the desired dose, only 7.7% of them answered daily, 26% weekly, 39.3% monthly and 27% didn’t split tablets. Finally, when the pharmacists were asked how often they crushed tablets, only 3.6% of them answered daily, 4.3% weekly, 22.3% monthly and 69.6% didn’t crush tablets.

Table (4) Responses to questions regarding practices of pharmacists toward crushing or splitting oral solid dosage forms (OSDFs).

Variable	Response Frequency (%N=300)
P1: Have you encourage pill splitting as a way to help patient save money Yes No	44 (14.7) 256 (85.3)
P2: Have you split or crush enteric coated tablet like Baby aspirin or sustained release like (TegretolCR; AdizemCD; Osmo-Adalat; Pentasa) ®? Yes No	48 (15) 252 (85)
P3: Have you received training in drug stability after splitting or crushing OSDFs? Yes No	14 (4.7%) 286 (95.3%)
P4: How often have you split tablets as a way to reach the desired dose? Daily Weekly Monthly Non	23 (7.7) 78 (26) 118 (39.3) 81 (27)
P5: How often have you done tablet crushing? Daily Weekly Monthly Non	11 (3.6) 13 (4.3) 67 (22.3) 209 (69.6)

Knowledge, attitude and practice scores among pharmacists

The reported knowledge score as measured by mean scores value and attitude score were 8.7 ± 2.7 and 6.4 ± 1.4 , respectively. There was a significant modest positive correlation ($r=0.18$, $p=0.002$) between the attitude and knowledge scores. The reported attitude score as measured by mean score value for practice respondents (i.e. who crushed or split OSDFs) was 6.3 ± 1.4 vs. 6.3 ± 1.4 for

non-practice. There was no significant difference between practice and non-practice respondents regarding attitude score (p -value 0.67). The reported knowledge score as measured by mean score value for practice respondents was 9.4 ± 2.9 vs. 8.6 ± 2.6 for non-practice. There was a significant difference between practice and non-practice respondents regarding knowledge score ($p=0.037$).

Knowledge score among pharmacists

The median knowledge score among pharmacists was 9 (interquartile range: 7–11). Nearly two-thirds of respondents (67.3%) had a good level of knowledge (a total knowledge score 8–14) and 32.7% of respondents had a poor level of knowledge. As shown in Table 5, a significant difference in the knowledge of pharmacists toward crushing or splitting OSDFs was found among participant groups according to age

Table (5): Association of socio-demographic with pharmacists' knowledge score.

Variable	Pharmacists Frequency (%) N=300	Knowledge score Median (interquartile range)	p- value
Graduation institute			
Local institute	237 (79)	10(7-11)	0.096 ^a
Arab institute	43 (14.3)	8(7-10)	
Others	20 (6.7)	9(6-10)	
Gender			
Male	87 (29)	10(7-11)	0.441 ^b
female	213 (71)	9(7-11)	
Place of work			
Hospital	90 (30)	10(6-11)	0.382 ^a
Primary care	22 (7.33)	8(7-10)	
General pharmacy	188 (62.6)	9(7-11)	
Age category Years			
20-29	169(56.14)	10(7-11)	0.048 ^a
30-39	89(29.5)	9(7-10)	
40-49	19(6.31)	10(6-10)	
50-59	17(5.64)	8(5-9)	
≥60	7(2.32)	11(6-11)	
Educational level			
Bachelor of Science	261 (87)	9(7-11)	0.551 ^b
Master of Science	39 (13)	10(7-11)	
Specialty			
General pharmacy	281 (93.7)	9(7-11)	0.468 ^a
Clinical pharmacy	15 (5)	10(9-11)	
Pharmaceutics	4 (1.3)	10(7.75-11.5)	

^a Statistical significance of differences calculated using the Kruskal-Wallis test

^b Statistical significance of differences calculated using the Mann-Whitney U test

Attitude scores among pharmacists

The median attitude score among pharmacists was 6 (interquartile range: 5–7). More than two-thirds of pharmacists (69%) had a good attitude (a total score of 6–9 points) and 31% of pharmacists had a poor attitude (a total score of 0–5). As shown in Table 6, a significant difference in the attitudes of pharmacists toward crushing or splitting OSDFs was found among participant groups according to specialty only (Kruskal-

Wallis test; $p < 0.05$). There was no significant association between the five demographic variables of gender, education level (Mann-Whitney test, $p > 0.05$), graduation institute, place of work, specialty (Kruskal-Wallis test; $p > 0.05$) and the knowledge of pharmacists about crushing or splitting OSDFs. Pharmacists aged more than 60 years old were associated with a high median score of knowledge.

Wallis test; $p < 0.05$) There was no significant association between the five demographic variables (gender, education level (Mann-Whitney test, $p > 0.05$), graduation institute, age and place of work (Kruskal-Wallis test; $p > 0.05$) and the attitudes of pharmacists toward crushing or splitting OSDFs. Pharmaceutics specialist pharmacists were associated with a higher median score of attitude than general and clinical pharmacists.

Table (6): Association of socio-demographic with pharmacists' attitudes score.

Variable	Pharmacists Frequency(%) N=300	Attitudes score Median (interquartile range)	P value
Graduation institute			
Local institute	237 (79)	6(5-7)	0.149 ^a
Arab institute	43 (14.3)	7(6-8)	
Others	20 (6.7)	6(5-8)	
Gender			
Male	87 (29)	6(5-8)	0.931 ^b
Female	213 (71%)	6(5-7)	
Place of work			
Hospital	90 (30)	6(5-8)	0.807 ^a
Primary care	22 (7.33)	6(5-7)	
General pharmacy	188 (62.6)	6(5-7)	
Age category			
20-29	169(56.14)	6(5-7)	0.165 ^a
30-39	89(29.5)	7(5-8)	
40-49	19(6.31)	7(5-7)	
50-59	17(5.64)	6(5-8)	
≥60	7(2.32)	6(5-7)	
Educational level			
Bachelor of Science	261 (87)	6(5-7)	0.281 ^b
Master of Science	39 (13)	6(5-8)	
Specialty			
General pharmacy	281 (93.7)	6(5-7)	0.004 ^a
Clinical pharmacy	15 (5)	5(5-6)	
Pharmaceutics	4 (1.3)	8(7.25-8.75)	

^a Statistical significance of differences calculated using the Kruskal-Wallis test

^b Statistical significance of differences calculated using the Mann-Whitney U test

Practices among pharmacists

The number of pharmacists with good practice who didn't crush or split enteric-coated or sustained-release OSDFs was 251 (83.7%). As shown in Table 7, a significant difference in the practice of pharmacists toward crushing or splitting enteric-coated or sustained-release OSDFs was found among participant groups according to age only ($p < 0.05$). There was no significant associa-

tion between the five demographic variables (gender, education level, graduation institute, specialty and place of work ($p > 0.05$)) and the practice of pharmacists toward crushing or splitting enteric-coated or sustained-release OSDFs. The study found that the age category from 20 to 29 years was associated with the highest frequency of good practice value among pharmacists.

Table (7): Association of socio-demographic with pharmacists' practice frequency total scores.

Variable	Total Pharmacy Frequency N=300(%)	Yes Frequency(%)	No Frequency(%)	P value
Graduation institute				
Local institute	237 (79)	42(85.7)	184(77.6)	0.076
Arab institute	43 (14.3)	7(14.3)	34(14.3)	
Others	20 (6.7)	0(0)	19(8)	
Gender				
Male	87(29)	15(30.6)	72(28.7)	0.786
female	213(71)	34(69.4%)	179(71.3)	
Place of work				
Hospital	91(30.3)	14(28.6)	77(30.7)	0.773
Primary care	22(7.3)	7(14.3)	15(6)	
General pharmacy	187(62.3)	28(57.1)	159(63.3)	

Variable	Total Pharmacy Frequency N=300(%)	Yes Frequency(%)	No Frequency(%)	P value
Age category				
20-29	168(56)	34(69.4)	134(53.4)	0.03
30-39	89(29.7)	15(30.6)	74(29.5)	
40-49	19(6.3)	0(0)	19(7.6)	
50-59	17(5.7)	0(0)	17(6.8)	
≥60	7(2.3)	0(0)	7(2.8)	
Educational level				
Bachelor of Science	261(87)	45(91.8)	216(86.1)	0.272
Master of Science	39(13)	4(8.2)	35(13.9)	
Specialty				
General pharmacy	281(93.7)	47(95.5)	234(93.2)	0.903
Clinical pharmacy	15(5)	0(0)	15(6)	
Pharmaceutics	4(1.3)	2(4.1)	2(0.8)	

DISCUSSION

This study identifies the current knowledge, attitudes and practice of health-care practitioners regarding splitting or crushing OSDFs and awareness about its safety and therapeutic implications. It also identifies the demographic characteristics associated with particular knowledge, attitudes and practices and highlights the gaps in public knowledge about this subject. In relation to this issue, pharmacists are often the first point of contact for patients in the community. Pharmacists have a huge role to play in giving information to the public about how best to split or crush OSDFs. To fulfill this aim they should have excellent medication knowledge in all aspects of this subject. However, there is little research on pharmacists' experiences, and knowledge about oral dosage forms [24-27]. No research has directly focused on attitudes, knowledge and practice of pharmacists toward splitting or crushing OSDFs.

Previous related studies on the same subject in the region were not available or found. In fact, to our knowledge this study is the first one to be conducted in our region. This study was conducted among 300 pharmacists to investigate their knowledge, attitudes and practices regarding splitting or crushing OSDFs. The study results revealed that the vast majority of the respondents were females. This is compatible with the statistics of the Palestinian Ministry of Health (2008), which estimated that most of the pharmacists

in the West Bank were females. Nearly two-thirds of pharmacists had a good level of knowledge. This result can be justified since the curriculum of pharmacy includes courses that focus on pharmaceutical technology which deals with modified release dosage forms. We didn't find any study similar to ours regarding the knowledge of pharmacists, thus we are unable to discuss this in the light of other results. However, studies performed among different subjects, such as a study in the UK that was conducted to investigate the knowledge of UK hospital pharmacists regarding adverse drug reaction reporting, showed that pharmacists have a reasonable knowledge about spontaneous adverse drug reaction reporting schemes [28]. Australian study aimed to observe medication solid dosage form modification in aged care facilities (ACFs), and assess staff levels of self-perceived knowledge of medication modification and the types of resources available to them. Authors found that improved staff training is needed to reduce the observed high incidence of inappropriate medication crushing[13].

The absence of ongoing pharmacy education creates negativity regarding their role in educating the public. Many studies show that the public trusts information provided by pharmacists. A study carried out in the West Bank found that the public has a good perception of community pharmacists [29]. Another study conducted in the West Bank showed that 30% of pregnant women take over-the-counter (OTC) drugs from commu-

nity pharmacies and 45% use herbal medications during pregnancy [11, 30].

In 2003, a cross-sectional study was carried out by Jaradat and Sweileh to describe community pharmacy practice in Palestine. They found that OTC sales of many prescription medications were common and unregulated. It also shows that the substitution of prescribed medications was widespread [31]. Another study was conducted by the same authors to determine the sources and needs of drug information for community pharmacies in Palestine. The authors concluded that few information sources were available for community pharmacies, and this was not sufficient for pharmacists to provide patients with appropriate drug information [31]. Australian study aimed to observe medication solid dosage form modification in aged care facilities, and assess staff levels of self-perceived knowledge of medication modification and the types of resources available to them. Authors found that improved staff training is needed to reduce the observed high incidence of inappropriate medication crushing [13].

Out of 300 pharmacists, around one third of the respondents could differentiate between extended-release and enteric-coated preparations. However, a study conducted by Mafiana et al. [21] found that only 38% of nurses could correctly indicate how they would recognize sustained formulations. This showed that there is a shortage of ongoing education after graduation. On the other hand, the respondents were not well informed about the effect of more than one active ingredient in the same tablet on splitting OSDFs: only 25% of the participants knew that combination products in the same tablet will not affect the appropriateness for splitting or crushing OSDFs. Respondents were less knowledgeable about whether nifedipine-coated tablets should not be crushed because the drug is highly light-sensitive, which may have a negative impact on drug stability. This is very dangerous because most pharmacists are not aware of this problem. Among health-care practitioners, most pharmacists were not knowledgeable about the changes that happen when crushing or splitting Tegretol® 400 mg GR, and Lescol

XL®. This is a cause for concern because many studies have shown that adverse reactions and death have occurred due to changes in the physical characteristics of some of these drugs. Schier et al. [17] gave an example of a case of the death of a patient due to the administration of crushed controlled-release nifedipine with labetalol. The administration of crushed controlled-release nifedipine resulted in severe patient hypotension, and the concurrent administration of labetalol prevented a compensatory heart rate increase and this led to death [17]. Furthermore, a study by Cornish reported on death as a result of respiratory depression in a patient due to the administration of crushed sustained-release codeine in addition to the loss of efficacy of crushed enteric-coated omeprazole [19]. According to our study, in addition to these findings from literature there is a need for the scope in teaching to improve pharmacists' knowledge in this respect.

Tablet splitting and crushing is one of many ways used by health practitioners to offer medications in the wanted dose. Recently, researchers have been showing increased interest in this field, especially the administration of crushed drugs for patients with swallowing difficulties [11, 18, 22, 32-35]. Patients who are unable to swallow, because of debilitating problems, need a feeding tube for nutrition or the administration of drugs. There is little information about this issue, and it is associated with a risk of toxicity, occlusion and decreased efficacy. Accordingly, the health practitioner must find the best way in order to administer drugs to patients through a feeding tube.

In 2003, the British Association for Parenteral and Enteral Nutrition (BAPEN) published guidelines on how to administer drugs via a feeding tube, which include: (i) try to use an alternative route instead of an oral route such as injection or discontinue the administration of the drug temporarily or switch to another drug that has the same effect and is available through another oral dosage form [11]; (ii) when no alternative route or drug is available, use liquid or dispersible tablets, and when the formulation has to be changed, the dose equivalencies

must be taken into consideration; (iii) if tablets or capsules must be used, the properties of the formulation must be taken into consideration [11]; (iv) to avoid drug/food interaction, the medicine must be administered between eating; and (v) flushing techniques must be correct to avoid tube closure.

Issues related to swallowing difficulties would be mentioned; if there is no alternative route for administration, the solid dosage form is considered [32]. Sometimes unlicensed drug use occurs. Crushed tablets may cause closure of the feeding tube, which may result in death or trauma to the patient. When OSDFs are crushed it must be taken in to consideration that some formulations should not be crushed or opened such as unscored tablets, some film- and sugar-coated tablets, enteric- or protective-coated tablets, sustained-release preparations, sustained-release granules, some microencapsulated drugs, buccal and bitter-tasting tablets.

Our study illustrated that two-thirds of pharmacists agreed that tablet splitting was not a useful way to reduce medication costs, didn't believe that physicians should prescribe split tablets as often as possible to reduce medication costs, believed that sometimes it is difficult to break tablets because they are small or hard, and that sometimes even scored tablets cannot be split into two equal parts, and don't think that all tablets can be split if required. A study conducted by Quinzler et al. [20] showed that splitting tablets in primary care centers is a frequent event due to economic considerations. In the same study nearly 1% of all tablets that were divided could not be fragmented or disintegrated.

Nearly half of the participants agreed that they are not sure whether tablets are indeed suitable for splitting or crushing, that they have never asked an expert how to split tablets best, and that they expect to find information in the package leaflet if tablets are not suitable for splitting or crushing. A study conducted by Al-Ramahi et al. [36] to explore the attitude of the Palestinian public and health-care professionals towards patient package inserts (PPIs) found that a high per-

centage of consumers always read the PPIs. Authors also found that 74.0% of consumers and 83.7% of health-care professionals said that the information in the PPIs needs to be improved. It is clear that drug companies should improve the pharmacological and pharmaceutical contents in PPIs [36]. In fact, these recommendations may be useful in this regard, since it may be helpful for patients and healthcare providers about right way to conduct this practice.

In general, around 15% of the pharmacists have split or crushed enteric-coated or sustained-release OSDFs, which means that part of pharmacists used this wrong practice, and this may be the result of the lack of knowledge among pharmacists or as a result of physician orders. We didn't find any study similar to ours among pharmacists, thus we are unable to discuss this in the light of other results. A retrospective cohort study by Chia-yu et al. [23] found that there were 1252 incidents of inappropriate pill splitting by doctors (1%) among 124,300 prescriptions with special oral formulations. A study conducted by Hanssens et al. [16] in Qatar found that the proportion of nurses knowing about OSDFs that should not be crushed after two days' training has increased from 0% to 30%. This indicates without doubt the importance of training for pharmacists in addition to launch clinical pharmacy counseling to reduce inappropriate pill splitting and crushing, which would contribute to positive patient outcomes [37, 38]. This may raise the question about the need of a multidiscipline course with aim to teach and train students in pharmacy, nursing and medicine about common health care practices.

Nearly 73% of pharmacists split tablets, while 30.2% of pharmacists crushed tablets. More than two-thirds didn't encourage pill splitting to save money. Similar to what has been found in literature, crushing or splitting OSDFs was a common practice. A study by Nissen et al. [39] found that among nurses who administered medication in a hospital in Australia, 75% crushed tablets.

Strengths and limitations of the study

This study is considered the first in Palestine to measure the knowledge, attitudes and practices of health-care practitioners regarding crushing and/or splitting OSDFs. Previous research across the world produced a few studies concerning some parts of this issue. The main limitation of this study is that pharmacists were drawn from a convenience sample therefore; our findings cannot be generalised. Finally, this cross-sectional study was only designed to identify associated risk factors; it cannot assess causality.

CONCLUSIONS

In conclusion, the study found that pharmacists had good knowledge about splitting or crushing OSDFs, although this practice is common among pharmacists. The study provided information about special formulations and classes of drugs that must not be split or crushed. Pharmacists must cooperate with a view to improve pharmaceutical information about these practices. This study raises the requirement of continuing education programs for pharmacists about this important subject. Moreover, the obtained results indicate the importance of including a course for pharmacy students with the aim of improving their knowledge in many pharmaceutical, clinical and toxicological health care disciplines in order to minimize potential medication or practice errors during their future careers. Additionally, preparing an information system compiled using up to-date dedicated lists that contain information on crushing, splitting and suspending medicines.

FUNDING: None.

COMPETING INTERESTS

The authors declare that they have no competing interests.

Authors' contributions

YA collected the data and wrote the first draft of the manuscript, SZ contributed to the study design, data analysis, interpretation, data analysis, writing and revision. AZ contributed to study design and to the final draft

of the paper. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

The research team would like to thank all pharmacists who agreed to complete the survey. Furthermore, the authors would like to express many thanks and gratitude to An-Najah National University and the Palestinian Ministry of Health for their help and ethical approval to conduct this study.

REFERENCES

- 1) Zaid AN, Al-Ramahi R, Shahed Q, Saleh B, Elaraj J. Determinants and frequency of pharmaceutical compounding in pharmacy practice in Palestine. *Int J Pharm Pract.* 2012;20(1):9-14.
- 2) Bachynsky J, Wiens C, Melnychuk K. The practice of splitting tablets: cost and therapeutic aspects. *Pharmacoeconomics.* 2002;20(5):339-46.
- 3) Green G, Berg C, Polli J, Berends DM. Pharmacopeial standards for the subdivision characteristics of scored tablets. *Pharmacopeial Forum.* 2009;35:1598-603.
- 4) Fawell NG, Cookson TL, Scranton SS. Relationship between tablet splitting and compliance, drug acquisition cost, and patient acceptance. *Am J Health Syst Pharm.* 1999;56(24):2542-5.
- 5) Duncan MC, Castle SS, Streetman DS. Effect of tablet splitting on serum cholesterol concentrations. *Ann Pharmacother.* 2002;36(2):205-9.
- 6) Cohen JS. Ways to minimize adverse drug reactions. Individualized doses and common sense are key. *Postgrad Med.* 1999;106(3):163-8, 71-2.
- 7) van Santen E, Barends DM, Frijlink HW. Breaking of scored tablets: a review. *Eur J Pharm Biopharm.* 2002;53(2):139-45.
- 8) Gill D, Spain M, Edlund BJ. Crushing or splitting medications: unrecognized hazards. *J Gerontol Nurs.* 2012;38(1):8-12.

- 9) Root T, Tomlin S, D. E. Pharmaceutical Issues when crushing, opening or splitting oral dosage forms. Royal pharmaceutical society. 2011. http://www.medicinesmanagementstoke.nhs.uk/documents/RPS_Pharmaceutical_Issues_when_Crushing_Opening_Splittin_g_sdosageforms_june_2011.pdf. Accessed July 23 2013.
- 10) Mitchell JF. Oral dosage forms that should not be crushed. Institut for safe medication and practice. 2013. <http://www.ismp.org/tools/donotcrush.pdf>. Accessed August 18 2013.
- 11) Bowman C. Administration of drugs to patients with swallowing difficulties. J Malta College Pharm Pract. 2007(12):42-5.
- 12) Akram G, Mullen AB. Paediatric nurses' knowledge and practice of mixing medication into foodstuff. Int J Pharm Pract. 2012;20(3):191-8.
- 13) Mercovich N, Kyle GJ, Naunton M. Safe to crush? A pilot study into solid dosage form modification in aged care. Australas J Ageing. 2014;33(3):180-4.
- 14) Ministry of Health, Palestinian Health Information Center. Health Report Mid Year 2013. 2013. <http://www.moh.ps/attach/546.pdf>. Accessed September 16 2014.
- 15) Sweileh WM, Zyoud SeH, Al-Haddad MS. Pharmacy Practice in Palestine. In: Fathelrahman AI, Ibrahim MIM, Wertheimer AI, editors. Pharmacy Practice in Developing Countries. Boston: Academic Press; 2016. p. 253-66.
- 16) Hanssens Y, Woods D, Alsulaiti A, Adheir F, Al-Meer N, Obaidan N. Improving oral medicine administration in patients with swallowing problems and feeding tubes. Ann Pharmacother. 2006;40(12):2142-7.
- 17) Schier JG, Howland MA, Hoffman RS, Nelson LS. Fatality from administration of labetalol and crushed extended-release nifedipine. Ann Pharmacother. 2003;37(10):1420-3.
- 18) Quinzler R, Schmitt SP, Pritsch M, Kaltschmidt J, Haefeli WE. Substantial reduction of inappropriate tablet splitting with computerised decision support: a prospective intervention study assessing potential benefit and harm. BMC Med Inform Decis Mak. 2009;9:30.
- 19) Cornish P. "Avoid the crush": hazards of medication administration in patients with dysphagia or a feeding tube. CMAJ. 2005;172(7):871-2.
- 20) Quinzler R, Gasse C, Schneider A, Kaufmann-Kolle P, Szecsenyi J, Haefeli WE. The frequency of inappropriate tablet splitting in primary care. Eur J Clin Pharmacol. 2006;62(12):1065-73.
- 21) Mafiana RN, Tagi A, Al-Zakwani I. Evaluation of nurses' knowledge of oral solid dosage forms that should not be crushed at a university hospital in Oman. J Pharmaceutical Health Services Res. 2013;5(1):49-53.
- 22) Morris H. Administering drugs to patients with swallowing difficulties. Nurs Times. 2005;101(39):28-30.
- 23) Chia-yu C, Chia-chen H, Shu-chiung c, Chin-chin H, Chia-lin C, Min-shan W et al. Association between Physician Specialty and Risk of Prescribing Inappropriate Pill Splitting. PloS one. 2013;8(7):70-113.
- 24) Zaid AN. Attitude and perception of patients and health care practitioners toward oral sustained release dosage forms in Palestine. Saudi Pharm J. 2010;18(4):251-6.
- 25) Nguyen T-M-U, Lau ET, Steadman KJ, Cichero JA, Dingle K, Nissen L. Pharmacist, general practitioner, and nurse perceptions, experiences, and knowledge of medication dosage form modification. Integ Pharm Res Pract. 2014;3:1-9.
- 26) Lau ET, Steadman KJ, Mak M, Cichero JA, Nissen LM. Prevalence of swallowing difficulties and medication

- modification in customers of community pharmacists. *J Pharm Pract Res* 2015;45(1):18-23.
- 27) Abbott R, Edwards S, Whelan M, Edwards J, Dranitsaris G. Are community pharmacists equipped to ensure the safe use of oral anticancer therapy in the community setting? Results of a cross-country survey of community pharmacists in Canada. *J Oncol Pharm Pract*. 2014;20(1):29-39.
- 28) Green CF, Mottram DR, Rowe PH, Pirmohamed M. Attitudes and knowledge of hospital pharmacists to adverse drug reaction reporting. *Br J Clin Pharmacol*. 2008;51(1):81-6.
- 29) Khdour MR, Hallak HO. Societal perspectives on community pharmacy services in West Bank - Palestine. *Pharm Pract (Granada)*. 2012;10(1):17-24.
- 30) Sawalha AF. Consumption of prescription and non-prescription medications by pregnant women. *Islamic Univ J*. 2007;2(15):41-57.
- 31) Jaradat N, Sweileh W. A descriptive study of community pharmacy practice in Palestine: Analysis and future look. *An-Najah Univ J Res (N Sc)*. 2003;17(2):287-300.
- 32) Hansen DL, Tulinius D, Hansen EH. Adolescents' struggles with swallowing tablets: barriers, strategies and learning. *Pharm World Sci*. 2008;30(1):65-9.
- 33) Kelly J, D'Cruz G, Wright D. Patients with dysphagia: experiences of taking medication. *J Adv Nurs*. 2010;66(1):82-91.
- 34) Stegemann S, Gosch M, Breitzkreutz J. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. *Int J Pharm*. 2012;430(1-2):197-206.
- 35) Lohmann K, Freigofas J, Leichsenring J, Wallenwein CM, Haefeli WE, Seidling HM. Development and evaluation of an algorithm to facilitate drug prescription for inpatients with feeding tubes. *Eur J Clin Pharmacol*. 2015;71(4):489-97.
- 36) Al-Ramahi R, Zaid AN, Kettana N, Sweileh W, Al-Jabi D. Attitudes of consumers and healthcare professionals towards the patient package inserts - a study in Palestine. *Pharm Pract (Granada)*. 2012;10(1):57-63.
- 37) Marquis J, Schneider MP, Payot V, Cordonier AC, Bugnon O, Hersberger KE et al. Swallowing difficulties with oral drugs among polypharmacy patients attending community pharmacies. *Int J Clin Pharm*. 2013;35(6):1130-6.
- 38) Raimbault-Chupin M, Spiesser-Robelet L, Guir V, Annweiler C, Beauchet O, Clerc MA et al. Drug related problems and pharmacist interventions in a geriatric unit employing electronic prescribing. *Int J Clin Pharm*. 2013;35(5):847-53.
- 39) Nissen L, Haywood A, Steadman K. Solid medication dosage form modification at the bedside and in the pharmacy of queensland hospitals. *J Pharm Pract Res* 2009;39(2):129-34.