



## Investigation of real-life drug intake behaviour in older adults and geriatric patients in Northern Germany – A biopharmaceutical perspective

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### ABSTRACT

Dosing conditions (type and amount of accompanying fluid, the type of food, the time of administration, and dosage form modifications such as crushing tablets) are critical and affect the performance of oral dosage forms in the gastrointestinal tract and thus bioavailability. Because older adults are the primary users of medications and are more susceptible to adverse effects, it is important to understand how they take their medications in order to reduce risks and increase benefits of the pharmacotherapy. The aim of the study was to investigate the real-life drug intake behaviour in geriatric patients and older adults and discuss their influence on drug absorption after oral administration. The data from two settings home vs. hospital and genders women vs. men were presented. A questionnaire study was performed among people aged at least 65 years from two settings (hospital vs. home), recruited mostly from community pharmacies and a regional hospital in Mecklenburg – Western Pomerania. The obtained data demonstrates that older adults and geriatric patients take their medications in the same way regardless of the setting and gender. There were no significant differences. Interviewed participants were mostly adherent to the doctor's recommendations and mostly took their medications in the same way every day. Medications are most commonly taken with a small (100 mL) or large (200 mL) glass of noncarbonated water, after food (during or after breakfast 64 % of intakes in the morning and during or after dinner 81 % of intakes in the evening). Meal usually consisted of bread, either with jam or honey (breakfast), or ham and cheese (dinner). All reported dosage form modifications were made to tablets. In almost all cases it was splitting the tablet, which was performed due to doctor's indication.

### 1. Introduction

In 2022, 19 % of the European population was over 65 years old. That is more than on other continents and worldwide (10 %) (Statista, 2022). The Pew Research Center assumes that the number of people over 65 worldwide will rise from 530.5 million to 1.5 billion by 2050 (Kochhar and Oates, 2014).

People aged 65 and older are a heterogeneous population, it is impossible to differentiate them based only on their chronological age (Stegemann, 2016). Also, the level of independence, frailty, and number of impairments play an important role. All these and several more factors are important in the drug management process. Drug management is defined as the usage of medications in a safe, appropriate and effective

way which includes purchase of the medications, storage of medications at home, preparation of the medication for dosing and administration, and proper drug intake (Hummler, Sarwinska et al., 2023).

The ageing process is not only a change in human appearance but also causes other problems and changes in the entire organism, including the gastrointestinal tract. Older people have also reduced lean body mass, a higher percent of body fat and lower enzymes' activity. The surface area of GIT as well as GIT motility and saliva production are reduced (Bruguerolle, 2008; Geist et al., 2019; Perrie et al., 2012). In our study older adults are considered as individuals aged 65 years old or older and are healthy enough to take care of themselves, geriatric patients however are considered as older adults who due to their health conditions need medical support and receive it in the geriatric wards in

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the hospital (Hummler, Sarwinska, et al., 2023).

Ageing increases the susceptibility to diseases. Many older adults suffer from at least one chronic disease, and often two or even more (multimorbidity) (Johnston et al., 2019). High blood pressure, diabetes, inflammation, cancer, chronic obstructive pulmonary disease and glaucoma are typical diseases in advanced age (Bruguerolle, 2008). In addition, some GIT disorders are more common in people aged 65 and over, e.g. xerostomia, dysgeusia, esophageal peristaltic alterations, dysphagia, Gastroesophageal Reflux Disease (GERD), gastric ulcers, gastritis, peptic ulcer disease, constipation or Irritable Bowel Syndrome (IBS) (Dumic et al., 2019). Due to multimorbidity, patients often take several medications (polypharmacy) (Masnoon et al., 2017). In our study, polypharmacy will be considered as the chronic intake of five or more medications and excessive polypharmacy as the intake of at least ten medications.

Moreover, people aged 60 and older are the main end users of medications, as they use more medications in comparison to younger adults (Che et al., 2014). Although the International Conference on Harmonization (ICH) issued Guideline E7 "Studies in Support of Special Populations: Geriatrics" in 1994 and made recommendations for the participation of older people in clinical trials, people over 65 are still very often excluded from clinical trials (International Conference on Harmonisation, 2006, Hanning et al., 2016). Since most drugs are taken by older adults, even though they have often not been tested on them, the question of the safety and efficacy of drugs in the older population arises.

The conditions under which oral medications are taken, influence their behavior in the gastrointestinal tract (GIT), especially absorption and thus bioavailability. The most important are the type and amount of fluid administered together with a drug, simultaneous food intake and changes in the dosage form. Posture can also play an important role. An example that illustrates the importance of all the above factors is alendronate, which has a low bioavailability after oral administration (Wiesner et al., 2021). Alendronate requires special dosing conditions. Due to the negative food effect, it should be taken in the fasted state and additionally, no food or drinks like coffee or orange juice should be ingested prior to and at least 30 min after intake. Also, it is recommended that alendronate has to be taken in the upright position and patients should stay in this position at least 30 min after intake to avoid esophageal irritations and ulcers (Wiesner et al., 2021). Moreover, alendronate tablets cannot be divided or crushed. In the presented study, all these factors were taken into consideration and older adults were asked about them.

Another important examples from the literature that demonstrate the importance of dosing conditions are danazol and atazanavir. The bioavailability of danazol was increased by the co-administration of medication with a lipid-rich food (Sunesen et al., 2005). In case of atazanavir, medication was administered orally together with water, Coca-Cola® or water with Proton Pump Inhibitor (PPI) (Hens et al., 2020). The pH of the fluid influenced the duodenal drug concentration and the systemic action of the medication.

The first aim of the presented study was to investigate how older adults and geriatric patients take medications in a real-life setting (food, drink, body position and manipulations of drug form). These real-life data can be used for general risk assessment and optimization in terms of clinical pharmacy or in biopharmaceutical insight for simulation or prediction of how these factors influence drug absorption. The second aim was to compare the drug intake behaviour among older adults from two settings: hospital and home setting. A comparison between women and men was also performed. To our knowledge, this is the first study to examine the real-life intake behavior of older adults and geriatric patients, considering the biopharmaceutical aspects.

## 2. Materials and methods

The main tool of the study was a questionnaire. The questionnaire

can be found in the Supplementary data 2 (Questionnaire). The questionnaire was developed and focused on the drug intake process among older adults and geriatric patients regarding mostly food and drink intake. The questionnaire from the main study consisted of 6 parts: General Information (demographic data: age, BMI, place of living, level of independence in drug management); Medication Intake (amount of medications); Medication Intake with Food; Fluids, Vehicles and Way of Taking Medications; Modifications of Drug Forms and Final Questions. The questionnaire was available in German in both paper and digital versions. For the digital Version, the web tool SoSci Survey was used (<https://www.sosicisurvey.de/>, Version 3.5.00, SoSci Survey GmbH, Germany). First, a pilot study was performed on a group of 36 people, in order to assess the feasibility of the tool. The pilot study was performed in hospital and home settings. After evaluation, the questionnaire was reviewed and adjusted to the main study. The study was in the form of an interview, and patients were asked by a member of the study team. No medical intervention was performed.

### 2.1. Study population

Study participants were recruited between the end of August 2022 and the beginning of January 2023 from two settings: hospital (Altermedizinischen Zentrum des Kreiskrankenhauses Wolgast gGmbH – two geriatric wards) and home setting (the daily care ward of the hospital in Wolgast, pharmacies in Greifswald and Wolgast particularly St. Jacobi Apotheke, Stadt Apotheke, Ahorn Apotheke, Elisen Park Apotheke and Anselmino Apotheke, VITALplus Physiotherapie Greifswald, AktivZentrum Boddenhus Greifswald and among the family members of the co-workers of the Biopharmaceutics and Pharmaceutical Technology Department of the University of Greifswald). Informed consent was obtained from all subjects involved in the study. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the ethical review board at the University Medicine of Greifswald, Germany (ethical protocol no. BB 095/22, 21.06.2022).

Participants were recruited based on the inclusion criteria of age 65 years or older, male or female gender, use of at least one oral medication, and ability to give informed consent (no cognitive problems, no dementia/delirium). The mental and cognitive state of the study subjects in the hospital setting was assessed by the hospital personal (physicians, psychologists, and a speech therapist). In the home setting, the cognitive condition of patients was assessed based on the knowledge of pharmacists about patients, the course of the interview and the consistency of given answers. No special examination was performed to keep time expenditure as short as possible for the aged volunteers.

### 2.2. Sample size considerations

Assuming a population of 416 162 people (2020) of 65 years or older in Mecklenburg-Western Pomerania, a sample size of 164 subjects was estimated representative for this population considering a confidence level of 80 % and a margin of error of 5 % (Statista.Com, 2021) (SurveyMonkey <https://www.surveymonkey.com/mp/sample-size-calculator/>, Version: August 16, 2021, SurveyMonkey Europe UC, Shelbourne Road, Dublin, Ireland). The confidence level and a margin of error was chosen as common boundaries for the studies, also chosen previously in other studies. Due to scarce similar studies available in the literature, key estimates were difficult to assess, therefore the practical approach was chosen to focus on the local population. It is a homogenous population; however, the data cannot be generalized for the whole German population.

### 2.3. Data evaluation and statistical analysis

The data was evaluated by means of descriptive analysis. The results were presented as a group of older adults, as well as in subgroups: home and hospital setting, women and men. The acquired data were mostly

**Table 1**

Demographic data - summary.

	Females	Males	All study participants
<b>Hospital</b>	23 (52 %)	21 (48 %)	44 (100 %)
<b>Home</b>	70 (57 %)	53 (43 %)	123 (100 %)
<b>Total:</b>	93 (56 %)	74 (44 %)	167 (100 %)

qualitative; therefore, no statistical tests were performed in these cases. The statistical comparison was performed between subgroups home and hospital and women and men regarding the fluid volume co-administered with medications. Data was tested for normal distribution by Kolmogorov – Smirnov and Shapiro-Wilk test. According to the non-gaussian distribution, statistical comparison between subgroups was performed by Mann-Whitney test. Data were regarded significant if  $p$  value amounted  $p < 0.05$ .

Odds ratio (OR) within certain subgroup and between subgroups for proportion water/fluids other than water co-administered with medications were performed. Odds ratio  $> 1$  means that water is more often chosen than fluids other than water within a subgroup (Eq. (1)) or between subgroups: in hospital setting (Eq. (2)) or in women (Eq. (3)). Tap water, mineral water and carbonated water were considered as “water”.

$$OR_{\text{within a subgroup}} = \frac{\text{number of answer "water"}}{\text{number of answers "fluids other than water"}} \quad (1)$$

$$OR_{\text{between settings}} = \frac{\text{number of answer "water"/number of answers "fluids other than water"}}{\text{number of participants in hospital/number of participants at home}} \quad (2)$$

$$OR_{\text{between sexes}} = \frac{\text{number of answer "water"/number of answers "fluids other than water"}}{\text{number of women/number of men}} \quad (3)$$

BMI values were adjusted for older adults based on the study of Winter et al. (Winter et al., 2014). The normal weight was considered by BMI value 23 – 30, underweight BMI smaller than 23 and overweight higher than 31.

Based on the caloric calculator ([www.myfitnesspal.com/](http://www.myfitnesspal.com/), last accessed on 06.12.2023) the caloric value of breakfast and dinner was calculated. The caloric values for the most commonly chosen variants for breakfast and dinner are presented in Supplementary data 1 (caloric tables).

For the data analysis and presentation, MS Excel (Version 2019, Microsoft Corporation, USA) and Graph Pad Prism 9 (Version 9.5.1 (733)) were used.

### 3. Results

#### 3.1. Demographic - study population

The final number of study participants was 167, of which 123 were from the home and 44 from the hospital. Characteristics of the study population are summarized in Tables 1 and 2. Two patients were

**Table 2**

Demographic data – age and BMI.

	Hospital	Home	All study participants
<b>Age</b> (range, mean $\pm$ SD, years)	65–89, (79 $\pm$ 6.61)	65–96 (78 $\pm$ 7.19)	65–96 (78 $\pm$ 7.05)
<b>BMI*</b> (range, mean $\pm$ SD, kg/m <sup>2</sup> )	20–42 (28 $\pm$ 6.93) *43 participants	17–42 (27 $\pm$ 4.38) *122 participants	17–42 (27 $\pm$ 4.72) *165 participants

excluded for BMI calculations, because they did not know their body weight, however all other answers were full and consistent.

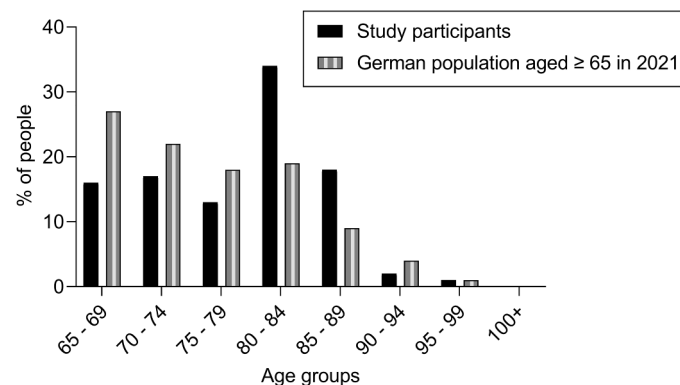
Most of the study subjects – 162 (97 %) lived in the Mecklenburg-Western Pomerania, and only 5 (3 %) participants were from Lower Saxony.

The age of all study participants is presented in the subgroups (every 5 years) in comparison to the older German population in 2021 (Populatinpyramid.com, 2021) (Fig. 1) and regarding setting and gender in the Figure S1 in Supplementary data 3 (tables). All study participants were at least 65 years old. The oldest participant was 96 years old. The largest subgroup was made up of people aged 80 to 84 (34 %). The oldest subgroups 90–94 (2 %), 95–99 (1 %) and 100+ (0 %) were the least numerous.

In total, 93 female and 74 male participants took part in the study. Of these, 23 women and 21 men were in hospital and 70 women and 53 men were at home.

Most of the patients had normal weight (65 %), 15 % were underweight and 21 % were overweight. Consistently, patients with normal BMI values were the most prevalent (63 and 70 % for home and hospital setting, 55 and 77 % for women and men, respectively). Underweighted subjects constituted 17 and 7 % of the participants from the home and hospital setting, respectively, 19 and 9 % of women and men, respectively. On the other hand, overweighed participants constituted 20 and 23 % of the participants from the home and hospital setting, respectively, 26 and 14 % of women and men, respectively. The BMI values of

the study population presented home vs. hospital and women vs. men are presented in Supplementary data 3 (tables).



**Fig. 1.** Comparison of the percent of study participants with the percent of the certain older age groups from German population aged 65 and older in 2021 (Populatinpyramid.com, 2021).

### 3.2. Medications

46 % of participants were taking between 5 and 9 medications per day, 29 % were taking 2 to 4 medications and 23 % were taking 10 or more. Only 2 % of the participants were chronically taking 1 medication.

For both settings, the most common answer was 5 to 9 medications (57 % and 41 %, in hospital and home setting, respectively). However, in the hospital, people took more medications. 39 % of participants were taking 10 or more medications, compared to 18 % in the home setting. In-home setting, the intake of 2 to 4 medications was more common (37% vs. 5 % in the hospital). In both settings, only one medication was the least frequently chosen option (3 % and 0 % in the home and hospital settings respectively). Polypharmacy (defined as intake of five or more medications chronically) appeared more often in the hospital setting than at home (96% vs. 59 %). Considering the gender of study participants, for both genders the answer 5 to 9 medications was also the most commonly chosen (49% vs. 40 %), then 2 to 4 (28% vs. 30 %) and then 10 or more (22% vs. 26 %). However, among women only 5 to 9 was more often than by men. Men, on the other hand, chose more often 2 to 4, 10 and more and 1 (1% vs 4 %). Polypharmacy regarding the gender of study participants was at similar level for men and women (66% vs. 71 %). The data on the amount of medication taken by the study participants is presented in Figs. 2A (amount of medications taken by the whole study population), 2B (home setting vs. hospital setting) and Figure S3 in Supplementary data 3 (tables).

### 3.3. Way of taking medications

54 % of participants took all their medications at once. 27 % separately, one after another. 17 % of the participants took medications differently, which means that they divided the number of medications that they took simultaneously (e.g. 2–4 medications together, 5 medications together and if more than separately, large tablets separately and small together), or they took medications with a vehicle (medium to administer medication e.g. fluid with a higher viscosity to ease

**Table 4**

Different ways of taking medications ( $n = 28$ ).

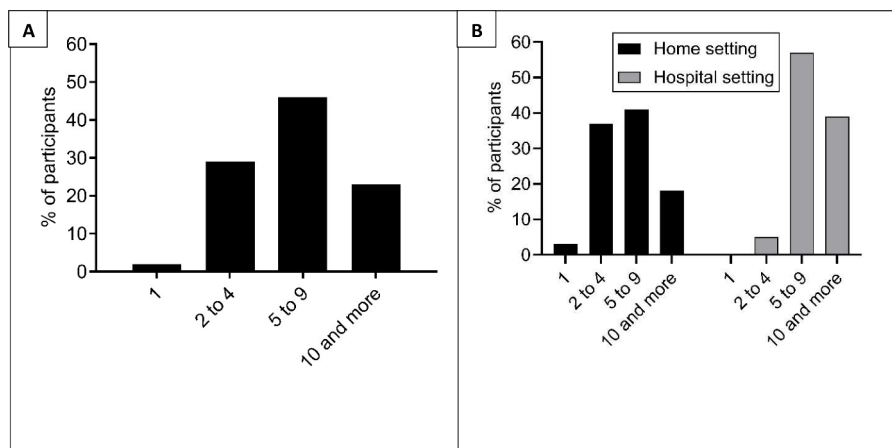
Different	%
When many medications, then 2 to 4 taken together	61
Big tablets separately, smaller together	14
Variable (not always the same)	11
5 together, if more than 5 then separately	7
With vehicle	7

swallowing), or it is variable – not consistent for different medications or times of the day. Table 3 summarizes the way of taking medications in comparison to the total amount of medications taken and Table 4 summarizes the different ways of taking medications. Within subgroups the most often people took all their medications together, 49 % women vs. 59 % men, 54 % home vs. 55 % hospital. For all subgroups, except hospital, the second option was separately. In hospital, however, people more frequently took their medications different. The Figures with way of medications intake in subgroups are available in Supplementary data 3 (tables), file S4.

Study participants from a home setting were also asked if they manage their medications on their own, or if they receive any help. 12 % of the study subjects received help from either family members (daughter, son, wife, stepson) or the healthcare providers (day care unit, care service, or still from the hospital after discharge).

### 3.4. Dosage form modifications

71 % of study participants reported taking medications as they are, so without any modification, 29 % reported performing modifications. All the reported modifications (51) were performed on tablets, mostly dividing tablets in two parts and sometimes in four parts (43), then chewing tablets (3) and keeping tablets in the mouth until they dissolve and then swallowing (3). 92 % of participants who performed modifications were doing so due to doctor's indication. In most cases, they divided the tablets and took only one of the parts (e.g. bisoprolol,



**Fig. 2.** Amount of chronically taken medications A among all study participants ( $n = 167$ ) and B regarding the settings (at home  $n = 123$ , in hospital  $n = 44$ ).

**Table 3**

Way of taking medications in comparison to the total amount of medications taken ( $n = 167$ ).

Amount of taken medications	Way of taking medications			
	Only 1 medication	All together	Separately	Different
0 or 1	4	–	–	–
2 to 4	0	21	23	4
5 to 9	0	48	14	14
10 and more	0	21	8	10
Total (100 %)	4 (2 %)	90 (54 %)	45 (27 %)	28 (17 %)

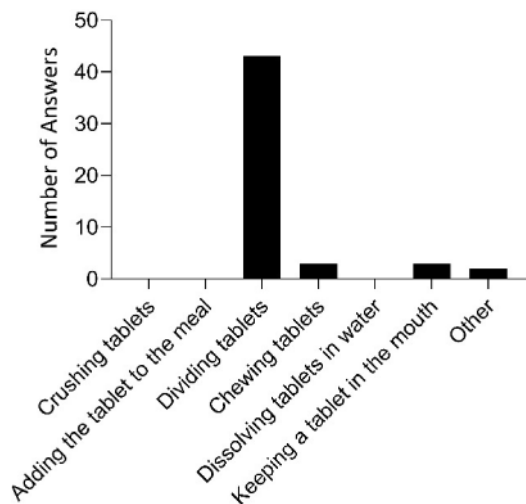


Fig. 3. Changes to the solid dosage form made by study participants (n = 48), multiple choice question, (n = 51 answers in total).

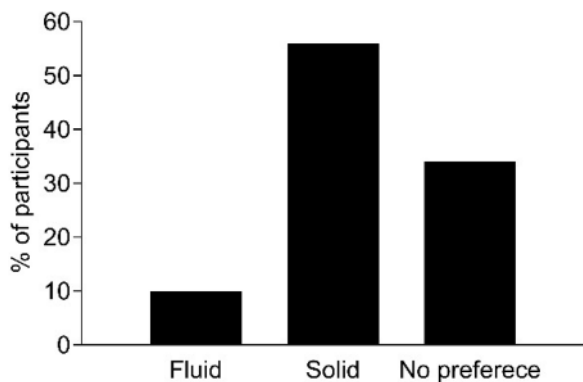


Fig. 4. Preferred oral dosage form for all study participants n = 167.

metoprolol). 2 % performed modifications to achieve faster action, 4 % due to problems with swallowing (dividing in two parts and swallowing two parts, one after another) and one participant gave several reasons for modifications for different medications (first to not get addicted to medication (taking only half of the tablet), second to ease the swallowing (dividing in two parts and swallowing two, one after another), and third to obtain the faster action (keeping the tablet in the mouth to dissolve)). There were no modifications reported on capsules (e.g.

opening) or fluid medications. Dosage forms' modifications are summarized in Fig. 3. Splitting the tablets was mostly performed under the medical control, as a recommendation to receive the appropriate dose.

### 3.5. Oral dosage form preference

In terms of preference for oral dosage forms, most participants preferred solid dosage forms (56 %), followed by no preference (34 %). Only 10 % of participants preferred fluid forms. The general preference of the study participants for oral drugs is shown in Fig. 4. Detailed information on the preference between home and inpatient settings and between women and men is given in the Supplementary data 3 (tables), Figure S6.

In the home environment, the response 'no preference' was more common than in the hospital (38 % compared to 18 %), where respondents similarly chose fluid and no preference (18 % and 20 % respectively).

Regarding gender of study participants, for women the most preferred oral dosage forms were solid forms (59 %), then no preference (30 %) and then fluid (11 %). For men, the same trend was observed, 53 %, 38 % and 9 %, respectively. Comparing preference of both subgroups, men answered more often no preference than women.

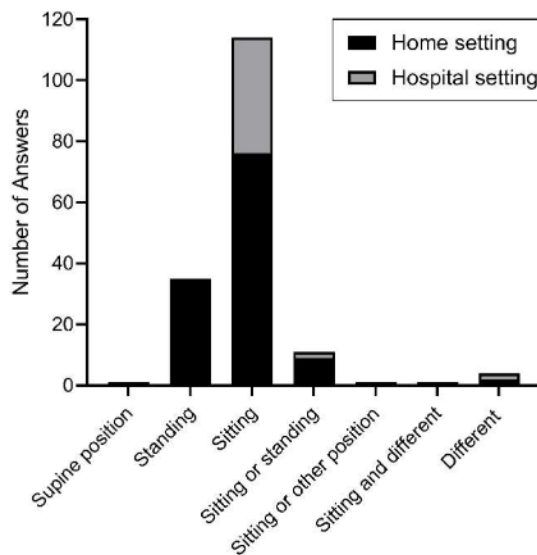


Fig. 6. Body position while taking medication for all study participants (n = 167), at home (n = 123) and in hospital (n = 44), multiple choice question, (n = 189 answers in total).

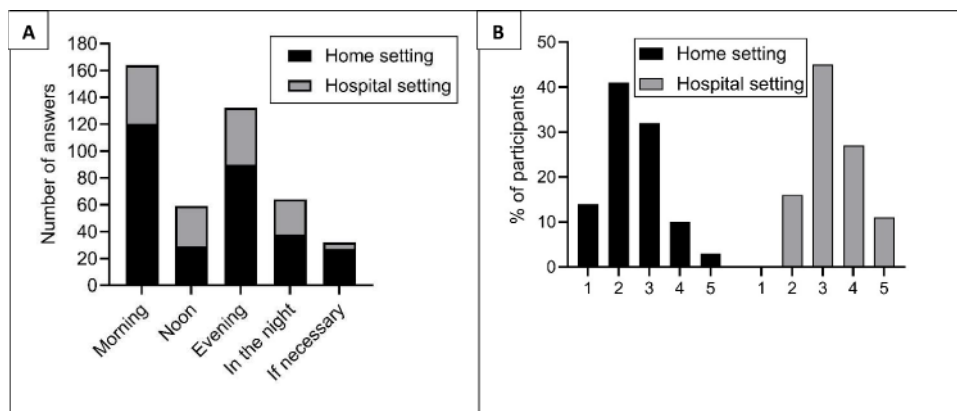


Fig. 5. A: Time of medication intake among all study participants (n = 167), at home (n = 123) and in the hospital (n = 44). B: Amount of daily drug administrations regarding the setting: home n = 123, hospital n = 44, (n = 450 answers in total).

### 3.6. Time of dosing – time of the day

164 participants reported taking their medications in the morning, 59 at lunchtime, 130 in the evening, 64 at night and 32 when needed (Fig. 5A).

Some patients in our study took medications only once a day - only in the morning (14 out of 167 participants) or only evening (2 out of 167). The most common combination was dosing twice a day - morning and evening (43 out of 167), three times a day – morning, noon and evening (24 out of 167) or even four times a day – morning, noon, evening, and night (22 out of 167). 9 participants took the medication at all times of the day: morning, noon, evening, night and when needed. Drug intake “if needed” was reported 32 times and mostly regarded intake of analgesics.

In terms of the setting, people at home usually took medications in the morning and evening. In the hospital, however, “at lunchtime and in the evening” was also a common answer.

Regarding the amount of daily drug administrations, the most common administration plan was three times a day. It was also the most common for the participants from hospital setting. For the participants from home setting the most common was intake twice a day (Fig. 5B).

### 3.7. Body position

Most patients took their medications while sitting (114), standing (35) and sitting or standing (11), i.e. in an upright position. Only one person from the hospital setting took their medications in supine position. Also, one person from the hospital took medications either sitting or in different position – half-laying. 5 participants reported taking medications differently e.g. for different medications or for different times of the day (Fig. 6).

Sitting was the most commonly chosen option in hospital (38) and at home (76). Standing was not chosen in the hospital, and at home was a common option (35) and the supine position was not chosen at home and in hospital was chosen only once.

### 3.8. Drug intake regarding meals

The selection of products for a certain meal performed by study participants was inclusive. A meal could consist of all of the selectable options. Drink were considered as a part of the meal.

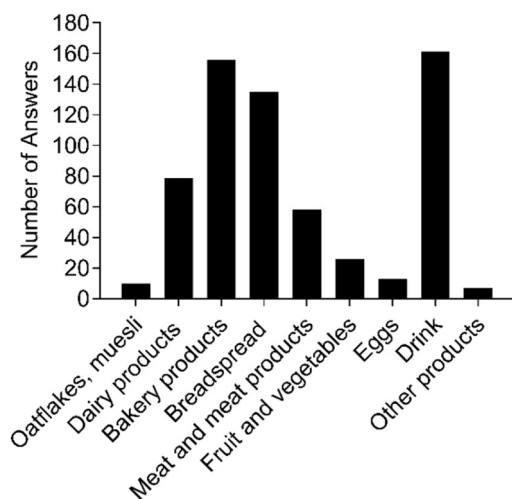


Fig. 7. Typical breakfast of the study participants, who take their medications at breakfast time ( $n = 164$ ), multiple choice question, ( $n = 645$  answers in total).

#### 3.8.1. Breakfast

The most commonly consumed breakfast items are shown in Fig. 7 and were bakery products (156), bread spread (135) and a drink (161). More specifically, breakfast was generally sweet and consisted of a bread roll (55) or one (46) or two (40) slices of bread with jam (115), less often honey (48) and/or butter. The preferred drink was a cup of coffee (59).

Typically, drug intake took place directly after breakfast (77) (Fig. 8A). Participants also mentioned intake up to 30 min before breakfast (39) (mostly in the case of l-Thyroxine or proton pump inhibitors (PPIs)).

#### 3.8.2. Lunch

Due to the great variability of the responses, it was not possible to assess the typical lunch. It can be stated that the respondents eat typical German dishes (consisting of meat, potatoes and some vegetables/salad), pasta dishes or stew. Medication was usually taken directly after food intake (29 out of 59). During lunch, respondents most often drank water (26).

Most hospitalized patients took their medication at lunchtime (24 % at home (29 out of 123) compared to 64 % in hospital (30 out of 44)). In this case, the patients ate what they had been given in the hospital.

#### 3.8.3. Dinner

The most commonly consumed products for dinner are shown in Fig. 9 and were bakery products (120), meat and meat products (100), dairy products (86) and drinks (125). More specifically, dinner was generally savoury and consisted of a slice of bread (68) with sausage/ham (84) and/or cheese (76). Tea (88) (mostly herbal tea (29), peppermint tea (22), fruit tea (18)) was preferred to water (32), which is still the usual choice. As a rule, drugs were taken directly after dinner (69) (Fig. 8B).

Taking all meals together, drug intake was mostly after food intake. Of the participants who took their medications during breakfast time, 41 % took them before breakfast and 61 % after breakfast. In the case of lunch, 22 % took their medications before lunch and 59 % after lunch. In the case of dinner, 18 % of participants took their medications before dinner and 74 % after dinner. Some participants also had to take medications before and after food within one meal, e.g. l-thyroxine or PPI before breakfast and diuretics and antihypertensives after.

#### 3.8.4. Caloric value

Based on the online calorie calculator, the caloric values of a real-life breakfast and dinner were calculated. These two meals were the most common for medication intake and the most homogeneous among all study participants. Lunch was highly variable, and it was difficult to find a typical meal. In addition, medication was generally not taken during lunchtime. The tables with the caloric values of the different breakfast and dinner variants can be found in the Supplementary data 1 (caloric tables).

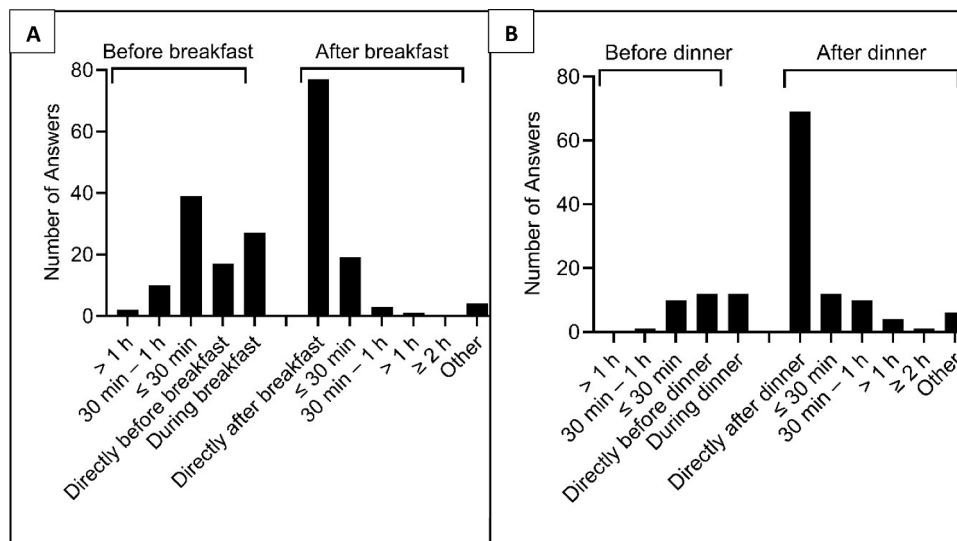
The estimated calorie value for several breakfast variants was 107 - 286 kcal and for dinner 137 - 366 kcal.

#### 3.8.5. Gastric emptying from the fed stomach

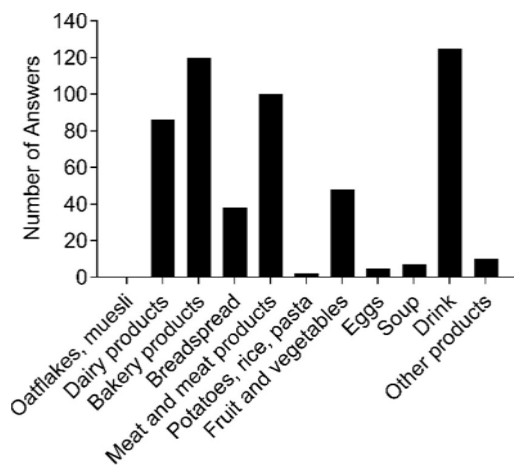
Depending on the type of food, the gastric emptying rate in the fed stomach is 2 - 4 kcal per minute (Kong and Singh, 2008). Estimating that FDA breakfast contains 800 - 1000 kcal, one can count that gastric emptying would last between 200 and 500 min (3 h 20 min - 8 h 20 min).

Data from the presented study estimated the caloric value for breakfast between 107 and 286 kcal. In this case, gastric emptying would be between 27 min and 143 min (27 min - 2 h 23 min).

For dinner, the estimated caloric value was 137 - 366 kcal, and the calculated gastric emptying time was between 34 min and 183 min (34 min - 3 h 3 min).



**Fig. 8.** Timing of medication intake in relation to food intake in study participants who take their medication A at breakfast time ( $n = 164$ ), ( $n = 198$  answers in total).and at B dinner time ( $n = 130$ ), multiple choice question ( $n = 133$  answers in total).



**Fig. 9.** Typical dinner of study participants who take their medications during dinner ( $n = 130$ ), multiple choice question, ( $n = 541$  answers in total).

### 3.8.6. Food vehicles

The usage of food vehicles was not frequently reported. It was only mentioned by 6 participants (4 from the hospital and 2 from the home setting).

The usage of vehicles was more common in the hospital. Four female participants aged 75–87 reported using vehicles such as last bites of food (e.g. bread), soup, fruit pulps (e.g. apple) or vegetable puree (e.g. carrot, potato), sauce, broth, apple juice, compote and yoghurt.

In the home setting, only 2 people reported taking medications with the last bite because they felt the medication was stuck in their throat (male and female, 68 and 77 years old, respectively).

## 3.9. Fluids co-administered with medication

### 3.9.1. Type of fluid

The most commonly chosen fluids for medication intake were non-carbonated water – tap water (71) and/or mineral (still) water (69), then tea (32) and carbonated water (24). Other fluids were mostly mixtures of water with juice or other caloric beverages (Fig. 10).

In order to compare the subgroups, odds ratio analysis was performed. The analysis compared the usage of any type of water (mineral,

tap, carbonated) to fluids other than water within a subgroup and in subgroups home vs. hospital and women vs. men.

In hospital setting, people chose water 2.71 times more often than fluids other than water (Eq. (1)) and in the home setting 2.19 times more often (Eq. (1)). In hospital setting water was chosen 1.24 times more often than at home (Eq. (2)).

Women chose water 2.61 times more often than other fluids (Eq. (1)), men 2 times more often (Eq. (1)). Women chose water 1.31 times more often than men (Eq. (3)).

### 3.9.2. Amount of fluid

The study participants mostly took their medication with a small glass/cup of 100 mL (32 % of cases) and a large glass/mug of 200 mL (30 % of cases). Nevertheless, a relevant number of participants also took their medication with few sips of the fluid (21 % of cases) (Fig. 11).

Regarding the setting, the most numerous answers were 200 mL for home setting (33 % of cases) and 100 mL (33 % of cases) for hospital setting. Among women, 100 and 200 mL was equally chosen (31 % of cases). Among men, 100 mL was more frequent (33 % of cases). The data from the subgroups are available in the supplementary data – tables, Figure S7.

The difference between mean fluid volumes in the subgroup setting: home - hospital was 21.1 mL and in subgroup gender: women - men was 3.1 mL. The results from Mann-Whitney test for home vs. hospital was  $p = 0.07$  and for women vs. men  $p = 0.8671$ . In both cases, the difference was not significant. The graphs with all volumes are available in the Supplementary data 3 (tables), Figure S8.

Most participants always use the same fluid and the same amount of fluid to administer their medication (75 % and 89 % respectively). The same percentage was reported for the home and hospital settings. For women, it was 76 % for always using the same fluid and 95 % for always using the same amount of fluid, for men 73 % and 81 % respectively.

## 4. Discussion

The main aim of this study was to find out how older adults and geriatric patients take their medication. The data were collected by conducting a questionnaire study among people aged 65 and older from two settings: at home and in the hospital. The data on medication intake is important because the way how the medication is taken (in particular the type and amount of fluid administered with the medication, food intake, changes to the dosage form) directly influences the behavior of

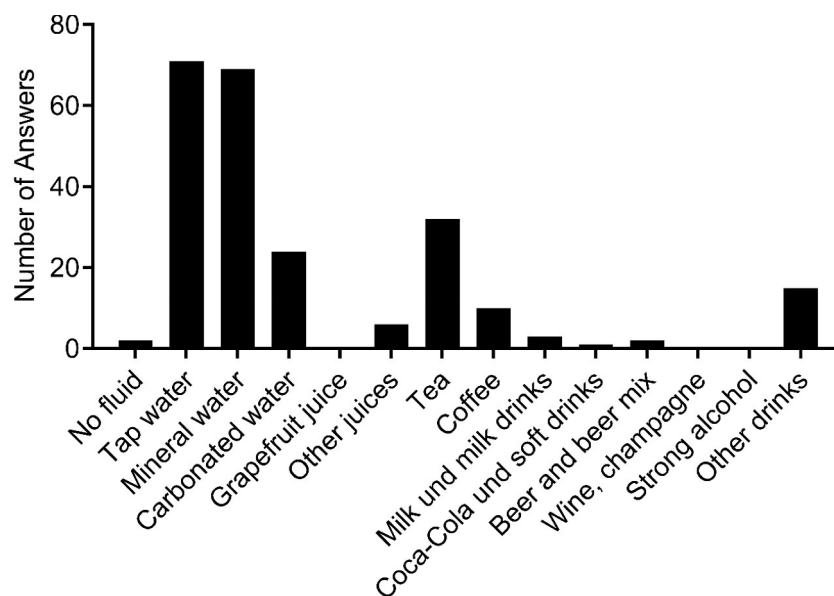


Fig. 10. Type of fluid co-administered with medications by study participants ( $n = 167$ ), multiple choice question ( $n = 235$  answers in total).

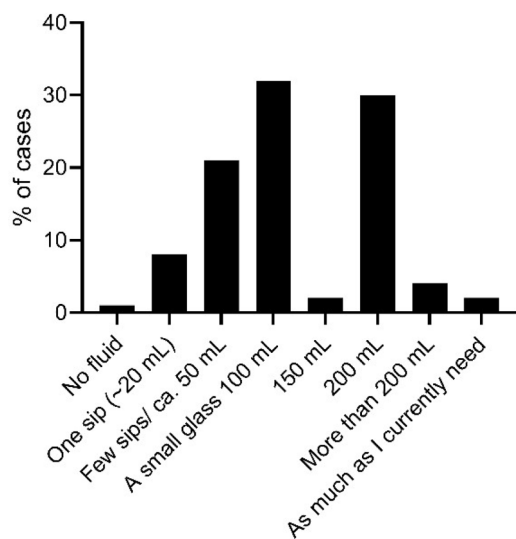


Fig. 11. Amount of fluid co-administered with medications by the whole study population  $n = 167$ ,  $n = 169$  answers in total. Data are presented as a percentage of cases/answers.

the oral dosage form in the gastrointestinal tract. Our results for certain subgroups are comparable in relation to the hospital and home environment and for men and women. There were only minor differences between the subgroups. This shows that the surveyed population was homogeneous in terms of drug intake behaviour.

#### 4.1. Demographic data

The BMI values were demonstrated according to the values for the older population based on the study by Winter et al. (Winter et al., 2014). Most of the study participants had normal BMI (65%). However, 21% of the whole study population were overweight. In the literature there are limited data about the influence of obesity on the drug absorption process, some data demonstrated no influence. However, obesity can influence the distribution, metabolism and elimination processes, due to among others different body composition (higher fat level – distribution of lipophilic medications) (Blouin and Warren,

1999). In obesity also, gastric emptying rate is increased (Smit et al., 2018).

On the contrary, 15% of study population was underweight. Literature data demonstrated the higher mortality risk for underweight people. However, low body mass is often related to the severe disease, which can cause death. Moreover, changed BMI values (underweight or overweight) also affects the drug pharmacodynamic e.g. the effective dose of the medication (Blouin and Warren, 1999). Medications for children are often dosed based on the body mass of a child. Similar approach could be also favorable for older population to individualize the pharmacotherapy to the certain patient and achieve effective and safe pharmacotherapy.

#### 4.2. Medications

As it was expected, polypharmacy was common among study participants. Polypharmacy, defined as taking at least 5 different medications, occurred in 69% of participants (including excessive polypharmacy - patients taking 10 or more medications) (Masnoon et al., 2017). As expected, people in the hospital were taking more medication and their general health was worse than that of older adults living in the community. Polypharmacy in hospital setting was almost 100%. Polypharmacy in home setting was lower (59%) than in the hospital setting in our study and one reported in the study by Schneider et al. of out-patients with chronic pain in Berlin (89.5%) (Schneider et al., 2021). Moreover, the literature data about the polypharmacy in older German adults aged 65 years or more demonstrated the polypharmacy approximately 42% and the trend to increase (Moßhammer et al., 2016).

The study by Junius-Walker et al. performed among the German population at least 70 years old, reported the prescribed polypharmacy and polypharmacy including OTC drugs, which was 26.7% and 53.6%, respectively (Junius-Walker et al., 2007). In our study, however, we cannot distinguish if reported polypharmacy includes OTC medications or not. Nevertheless, the results are closer to the option including OTC medications (59% vs. 53.6%).

In general, the more medication patients take, the greater the risk of interactions and adverse effects. In the study of Karas et al. the potential of interactions escalated from 5.6% while using two drugs up to 100% for eight drugs (Karas, 1981). 23% of our study participants take at least 10 different medications, thus interactions between them are unavoidable. In case of polypharmacy patients, the interactions should be

investigated individually for each patient to assess their clinical importance. Many older adults, however, take the same combinations of medications, therefore investigating the most commonly prescribed medications combinations can help discovering interactions that are a common problem for many people.

#### 4.3. Way of taking medications

Most of the interviewed patients, as a whole population and within subgroups, took all their medication at once. This may indicate that the patients do not suffer from swallowing problems, as they are able to swallow several medications at the same time. On the contrary, the intake of medications separately may indicate that people may use more fluid. For example, if one sip is taken after 5 tablets at the same time and one sip is taken after each of the 5 tablets, the final volume of water available for the dissolution of the active pharmaceutical ingredient (API) will be different.

Taking all medications at the same time was common in the hospital. Patients were often given all their medications in a small cup (e.g. all their morning medications) and took them all at once as if they were drinking a shot from a glass. It was common for them to not even see which or how many medications they were receiving. The second common answer in the hospital was different. It demonstrates that drug intake process in the hospital is quite variable.

Taking all medication at the same time can also be a strategy to avoid manual handling of tablets since patients do not have to handle them separately, only take them all together. Older adults often suffer from limited dexterity or arthritis. Both make it difficult to grasp small objects with the fingers (in this case tablets).

#### 4.4. Dosage forms modifications

All reported changes in dosage form were made to tablets, where the tablets were most often split, chewed and swallowed or held in the mouth until they dissolved and then swallowed.

However, in the case of chewing tablets 2 out of 3 patients did so because of the particular dosage form, so this was in line with the summary of product characteristics (chewable tablets). Only one participant stated that they were doing so because this accelerated the effect of the drug. The same situation appeared among people who reported keeping the tablets in the mouth. 2 out of 3 of them, reported using tablets rapidly dissolving in the mouth. One person out of these 3 also was dissolving tablets in the mouth to accelerate the action. In these two cases, these changes were not under the control of medical staff and were not in line with the summary of product characteristics. This is especially true for one participant who always chewed the analgesic. This can lead to the health implications described in the literature e.g. the irritation of the gastrointestinal tract, including drug-induced esophageal disorder (Jaspersen, 2000). Nonetheless, this modification was only reported once from all 167 subjects.

Dividing tablets was the most common modification performed by approx. 25 % of patients and it is an easy way to adjust the dose to specific needs, especially in special populations such as children or geriatric patients. Sometimes it could be performed for ease of swallowing.

Splitting the tablets was mostly performed under the medical control. Mostly participants were performing modifications due to the doctor's indication and the reason for dividing tablets was economical. Doctors often prescribe patients higher doses of the medication and advise patients to take only half of the tablet. This situation is due to the same or comparable price of the medication in two different doses. At the same price, a patient will be able to use medication for a longer time, which is, in fact, favourable for the patient as well as for the health care system (Fawell et al., 1999). However, patients have to be sure that it is possible to divide certain medications. Moreover, related to their age they need to be physically able to perform this splitting accordingly.

To avoid performing dosage form modifications by patients, solid dosage forms can be adjusted to the special needs of patients, taking into consideration among others the size and the shape of tablets which directly influence the swallowability and handling (Hummler et al., 2023; Hummler et al., 2023c).

#### 4.5. Oral dosage form preference

The study by Witticke et al. the preference of patients about dosing regimens and medications were investigated (Witticke et al., 2012). In the study there is no data about the age of the participants, however they have been taking their medications already for at least six years or even more than 10. Regarding solid oral dosage form preferences, tablets were the most commonly taken and preferred by patients. Capsules had also high preference (54.2 %) however they were used only by 21.8 %. On the contrary fluid dosage forms, syrups had 100 % preference, however were taken only by 0.9 % of participants and oral drops were the least preferred, but the prevalence in using was also low. In our study, most of the participants preferred solid dosage forms, as a general population and regardless of the setting and sex. Fluid medications were more commonly preferred in the hospital. At home, dealing with fluid medications is not convenient, especially for older adults. People often have problems with dosing appropriate amounts of medication or pouring the fluid on or onto the dosing tool (a spoon, or a small cup). Moreover, the taste or the smell of the fluid medications is also important factor for patients. Several patients also stated that fluid medications are easier to swallow. In the hospital, nurses provide patients with medications, so patients do not have to worry about preparation and just have to take the medication, which is convenient in case of fluid medications. Solid dosage forms are convenient to administer and for most of the people easy to swallow. Participants also often mentioned that they receive only solid dosage forms from the doctor.

Taking into consideration special needs and preferences of the individual patient is also a good approach to increase the adherence of the patient (Witticke et al., 2012). Often there are several options to change the dosage form from the solid to fluid (or the opposite) or to find the same medication but in different shape or size of tablet. When patients took medications in the way, the most convenient for them, it would be easier to be adherent and achieve successful and safe pharmacotherapy.

#### 4.6. Dosing conditions

Patients are often informed about special dosing regimens e.g. intake of l-Thyroxine or PPIs 30 minutes before breakfast. Many study participants mentioned it, were aware of it, and were adherent to this recommendation. Mentioned medications demonstrate negative food effect and therefore have to be taken before food.

Moreover, in the case of medications for osteoporosis people often mentioned special dosing conditions e.g. intake of more water, standing body position or intake on an empty stomach.

#### 4.7. Time of the day

During the day, the most common times for medication intake were morning and evening. 98 out of 167 participants took their medications at least at both given times. Data from the literature demonstrates that patients preferred once daily dosing schedule (79.2 %). The more daily application patients had, the less patients liked it (Witticke et al., 2012). Regarding time of the day, morning and evening were prevalent times for drug intake (94.5 vs. 66.4 %). Morning drug intake was, however, more accepted (~50 % vs. 25 %). The most preferred time of the day for the drug administration was at night (62.5 %), however this option was the least prevalent (7.3 %) (Witticke et al., 2012). The time for the drug intake with the lowest preference was at the noon (11.8 %), however, it was quite common (30.9 %) (Witticke et al., 2012). In our study, night drug intake was a bit more prevalent than noon (65 vs. 59 out of 167

participants). Both times were not common.

In our study, participants most often took their medications three times and then two times a day. Drug intake once a day was common only in-home setting and mostly regarded drug intake in the morning. There is no collected data about the preference of daily drug administrations of our study participants.

#### 4.8. Body position

In general, people mostly take their medications while sitting (the whole study population, as well as home and hospital setting). Generally, at home, people tend to be fitter and more likely to move. They are independent and able to take care of themselves. In the hospital, people stay in their beds for a long time, mostly in the supine position. They have a lower ability to move. In the hospital in Wolgast, people normally are admitted for at least two weeks. Very often, however, they have to stay there longer. During hospital stay the daily routine and drug intake process of patients are adjusted to the hospital rules.

The variability in reported body position while taking medications was not great. Most of participants took their medication constantly in the same position (150). Only 5 mentioned that it is different for different medications or times of the day.

As different medications, medication for osteoporosis was mentioned (patient normally took medications while sitting however on Fridays the intake of medications for osteoporosis was while standing). In demonstrates that the patient behaves accordingly to intake conditions for the special medication.

As different times of the day people mentioned e.g. they took medications in the position in which they currently were, or normally sitting but evening in supine position, or mornings sitting and evening staying, or for sleep medications supine or sitting and morning sitting.

It is generally recommended to swallow medications in an upright position (Osmanoglou et al., 2004). Firstly, the upright position ensures the good flow of the bolus. It is important to reduce the risk of drug-induced esophageal disorders. Drug-induced esophageal disorders appear when the drug sticks in the esophagus and can cause several problems e.g. an erosion in the esophagus, perforation or even drug-induced deaths (Jaspersen, 2000; Rose and Tobin, 1980). Drugs which are considered to cause esophageal disorder are antibiotics (e.g. doxycycline, tetracycline, clindamycin); NSAIDs (aspirin, diclofenac, ibuprofen) or other (potassium chloride, alendronate, nifedipine, warfarin) (Jaspersen, 2000). Many of these medications are commonly and chronically used by the older population. It is crucial to make patients aware of the risk and how to minimize it.

Furthermore, the study of Osmanoglou et al. indicated that the body position influences the esophageal retention of capsules. In the upright position, the transit of a capsule was shorter than in the supine position. In the supine position, especially gelatin capsules may stick to the esophagus (Osmanoglou et al., 2004).

Body position influences the pharmacokinetics of orally administered medications. There are several mechanisms which influence pharmacokinetics (Queckenberg and Fuhr, 2009). The study of Renwick et al. demonstrates that positions, such as sitting, standing or lying on the right side, are the positions that promote fast gastric emptying and thus drug absorption of an exemplary BCS class II compound. However, the effect was stronger in the fasted state and with non-nutrient fluid (Renwick et al., 1992).

On the contrary, the study of Steingoetter et al. demonstrated that even radical alterations in body position during intake of non-nutrient fluid do not influence gastric emptying relevantly (Steingoetter et al., 2006).

There are contradictory data in the literature about the influence of body position on the medication or gastric emptying, nevertheless, in all cases, it is safer for patients to take medications in the upright position and our study participants mostly behaved accordingly.

#### 4.9. Drug intake regarding meals

##### 4.9.1. Time of dosing regarding meal intake

Drug intake of study participants tended to be organized around mealtime and food intake. In the study of Sanders et al. up to 71 % of participants (aged at least 50 years old) took their medications during mealtime. Taking medications directly after food intake causes better adherence to doctor's recommendations and decreases the risk of forgetting about drug intake (Sanders and Van Oss, 2013).

In the study by Witticke et al. 56.6 % of people preferred to take medications after meal, it was prevalent in 48.2 %. On the contrary, up to 75 % of patients preferred taking medications independently of food intake (prevalence 32.7 %). What is interesting, the lowest preference was given to intake 30 min before meal intake 17.8 % and was quite prevalent (40.9 %). Likewise, in our study, drug intake 30 min before food ingestion was prevalent as well as directly after food intake (Witticke et al., 2012). For many patients, drug intake 30 min before the breakfast (PPIs or l-thyroxine) is advised by the doctor, so people were adherent to this recommendation. However, it may be uncomfortable, since people have to wait with food intake. Drug intake after the meal is often the matter of the routine.

Drug intake combined with food ingestion was quite common, however, patients also should be aware of possible interactions between drugs and specific food.

##### 4.9.2. Biopharmaceutical relevance of time of medication intake regarding meal ingestion

Based on Fig. 8, in the presented study, terms directly after or directly before food intake are considered as within 5–10 min. Drug intake during food ingestion is considered as starting to consume the meal, then taking the drug and continuing food ingestion.

From the biopharmaceutical point of view, the time of dosing the medication with food may have some implications.

Medication intake before food ingestion is considered as fasted state condition, regardless of the time gap. In the fasted state, the stomach functions according to MMC (Migrating Motor Complex). It is the specific pattern of motility in the distal stomach, which consists of four phases with different contraction patterns (Koziolek et al., 2019; Takahashi, 2013). The complex starts with less frequent contractions, which gradually increase in strength and frequency. Depending on the phase, which the stomach currently performs, the drug can reach a duodenum at different times. By only performing an interview, we cannot, however, predict what phase was ongoing when patients were taking their medications.

A dosage form taken during the food ingestion will be placed in the food mixture. It can be trapped in the chyme and will need more time to reach the duodenum.

On the other hand, a medication taken directly after food ingestion may be placed on the surface of the food mixture. In this case, medication will need even more time to reach a duodenum. However, there is a Magenstraße phenomenon, when a medication is administered in the fed state together with water, it is taken together with the fluid along the stomach wall and reaches the duodenum faster, allowing obtaining fasted-state-like conditions in the postprandial state (Grimm et al., 2017; Schick et al., 2020). From the biopharmaceutical point of view, both drug intake during as well as after food ingestion would be considered as fed-state conditions.

##### 4.9.3. Standardized clinical study meal versus real-life breakfast

As expected, real-life breakfast considerably differs from the FDA breakfast from food effect studies (FDA, 2002). FDA breakfast is a worst-case scenario, and its role is to cause the biggest physiological response of the organism (Koziolek et al., 2015). The FDA breakfast consists of eggs, bacon, toasts with butter, hash brown potatoes and milk, and has approximately 800 – 1000 kcal (FDA, 2002).

Clinical studies with the participation of older adults aged at least 65

years could be difficult and/or dangerous for them. The ingestion of the high caloric and high fat FDA breakfast may harm them since often they suffer from diseases which require the specific diet. Moreover, the size of the meal to ingest is big, evidently bigger than an investigated real-life breakfast. Therefore, it might be reasonable to investigate the typical breakfast eaten by this special population and standardize it as an alternative for the studies for the special population.

In the literature, there are also examples of fed-state studies performed with different meals than FDA breakfast. These options include: bread, egg omelette and water (~ 382 kcal); continental breakfast (2 bread rolls, butter, low-fat cheese, slice of ham, jam, coffee, tea or non-sparkling water ~ 707 kcal); 4 slices of bread, cheese, butter, milk and orange juice (~1000 kcal); bread, rise, fried egg, fried fish, cereal, cake, chocolate, yogurt, tea, coffee, milk (no data about caloric values); rice, bean paste soup, pickles, milk (700 kcal) or bread with margarine, boiled egg, milk (500 kcal); white bread, butter, jam, rose hip tea (no data about calories value) (Madsen and Graff, 2004; Huppertz et al., 2021; Sunesen et al., 2005; Sugita et al., 2019; Oguma et al., 1991; Ledergerber et al., 1985).

Real-life breakfast from the presented study consists of a bread roll or bread with jam and a coffee, the estimated caloric value might be 100 – 300 kcal depending on the products. The results of our study demonstrated that older people ate rather light breakfast, similar by constituents to the example of the continental breakfast from the literature mentioned before. However, the examples from the literature have higher caloric content than real-life meals from our study. Generally, choosing bakery products such as bread or bread roll together with butter, cheese, ham, eggs or sweet bread spread like jam or honey seems reasonable to be a standard breakfast.

#### 4.9.4. Dietary habits of the older population

The study by Heuer et al. demonstrated that older adults in Germany (65–80 years old) consume the most of sweet spreads and herbal/fruit tea in comparison to the younger population (Heuer et al., 2015). In our study, these two products were also commonly used by the older population. Sweet spread (jam, honey) were typically eaten for the breakfast. Fruit and herbal teas were preferred as a drink for dinner.

Another point is the dietary habits of older adults. Older adults were ingesting mostly carbohydrates and their diet was poor in protein. Protein is especially important due to its influence on muscles. With increasing age, the recommended protein intake per kilogram of body weight increases from 0.8 g in adults to 1 – 1.2 g in older adults (Dodd, 2020). In the aged population, protein intake is of particular importance due to among others loss of muscle mass and strength (sarcopenia) and frailty.

Moreover, the recorded caloric intake for breakfast and dinner of our study population seemed to be low. It was not a goal of the presented study to investigate the nutrition of older adults, however collected data may demonstrate some issues in this matter, which may be worth investigating.

The exemplary breakfast recommended by the German Nutrition Society (Deutsche Gesellschaft für Ernährung DGE) for the older adults aged at least 65 years old consists of two slices of wholemeal toast (60 g), margarine (12 g), strawberry jam (30 g), some quark (20 g), one cup of coffee with milk (150 mL) and one glass of vegetable juice (200 mL) and contains approx. 372 kcal. (Deutsche Gesellschaft für Ernährung, 2012). The exemplary dinner consists of cucumber salad: - cucumber (150 g) - herb vinegar (½ tsp) - rapeseed oil (5 mL), two slices of mixed wheat bread (90 g), margarine (12 g), one slice of three-quarter fat cheese (30 g), some cream cheese (7 g) and 2 cups of herbal tea (300 mL) and contains approx. 447 kcal (Deutsche Gesellschaft für Ernährung, 2012). The tables with nutrition values for DGE recommendations are available in Supplementary data 1 (caloric tables). Generally, the typical food eaten by participant in our study is similar to the recommendations from DGE. In all cases, the base for the breakfast and dinner is bread. In our study however, there is no collected data about the type of bread.

Breakfast is generally sweet and dinner savory. Moreover, drinks from our results were also in agreement with these exemplary meals.

#### 4.9.5. Influence of food on the conditions in GIT available for dissolution

Ingested food changes the conditions in GIT. Directly after food ingestion, the stomach is full of content, which results in elevated gastric pH, increased volumes of the gastric content and also constitutes the physical barrier for a drug (Stillhart et al., 2020). It influences gastric emptying and drug PK, especially absorption. However, in the case of the breakfast and dinner of study participants in our study, the meal was not big, it was not a high-fat and high-caloric meal, so the food effect may be smaller than in the case of FDA breakfast. Anyway, specific interactions with certain food components and specific drugs cannot be precluded and need to be considered individually.

Specific food ingredients make specific conditions, e.g. the presence of glucose reduces the amount of small intestinal fluid, however grapefruit juice as well as fructose-containing beverages increases it (Grimm et al., 2018).

Fat, due to the highest caloric value among other ingredients (9 kcal/g, carbohydrates 4 kcal/g and proteins) will cause slower gastric emptying in the fed state (Kong and Singh, 2008).

In the presented study, older participants eat sweet breakfast, which consists mostly of carbohydrates. As we can see in the results section, bread is the main constituent of the breakfast as well as dinner of German older adults. The study of Marciani et al. demonstrated that whole-meal bread decreases the speed of stomach emptying and reduces the content of free mobile water in the small intestine (Marciani et al., 2013). The free fluid in the intestine is a medium for the dosage form and drug to dissolve. Therefore, the intake of medications directly after bread ingestion may influence drug absorption. Similar findings were reported by Oguma et al. The ingestion of the bread or rise meals affected the absorption of cefaclor, by reducing the maximum concentration of the drug in the serum, moreover the time to maximum concentration was increased (Oguma et al., 1991). In the same study, also the size of the ingested meal affected the results. The bigger the meal, the bigger the influence on the maximum concentration and time to maximum concentration (Oguma et al., 1991).

Generally, carbohydrates are a group of several compounds (monosaccharides, oligosaccharides and polysaccharides), therefore the effect of the carbohydrates on drug absorption may be variable and difficult to predict (Deng et al., 2017). Carbohydrates-rich diet also delays gastric emptying (Deng et al., 2017).

#### 4.9.6. Food vehicles

In the home setting, only two patients reported usage of food vehicles, which were the last bites of food. In the hospital setting, people use more and different vehicles. Not only do they take their medications with the last bite, but also mix them with soup, fruit pulps (e.g. apple) or vegetable puree (e.g. carrot, potato), sauce, broth, apple juice, compote or yoghurt.

Choosing the proper vehicle to administer medications is crucial to ensure safe and effective pharmacotherapy. Not only the taste preferences of patients should be taken into consideration, but also the physicochemical properties of the vehicle (e.g. pH, buffer capacity, viscosity) and drug substance (e.g. solubility). The estimated pH values of the vehicles commonly used by study participants found in the literature are presented in Supplementary data 3 (tables) (Table S1). The vehicles have certain pH levels and may affect medications differently.

The literature demonstrates that the influence of certain vehicles is drug-dependent e.g. yoghurt did not change the dissolution of crushed atenolol, however, it slowed the dissolution of amlodipine and warfarin (Manrique et al., 2014). Also, in the case of crushed carbamazepine, yoghurt reduced the dissolution and made it look similar like a dissolution of the whole tablet. In another study, the effect of different vehicles on montelukast granules was investigated. In this study, the highest dissolution was obtained when montelukast was mixed with

plain yoghurt and the lowest with applesauce (Martir et al., 2020).

#### 4.10. Fluids co-administered with medications

##### 4.10.1. Type of fluid

It is generally recommended to take medications together with a whole glass of neutral fluid, the best option is non-carbonated water. Patients from the presented study reported co-administration of non-carbonated water with a medication which is in allowance with the recommendations. Hens et al. reported that in their study the most commonly used fluid to administer medications by adults in Belgium was also water (Hens et al., 2017).

Water was commonly chosen among all study participants as well as in subgroups. Based on the odds ratio, within subgroups, women and study participants from the hospital setting tended to use water more often than fluids other than water. Water was more commonly chosen in hospital than at home and among women than in men. In both cases, however, the differences were not significant and they are not relevant. Nevertheless, the results demonstrated that in most of cases participants use water and that is the positive outcome in accordance with the recommendations.

In our study, patients also often used tea to swallow their medications. They often drank herbal teas during the day and with meals, especially dinner. The most commonly used herbal teas, which were mentioned specifically were: peppermint, fennel, anise, chamomile, sage, nettle and different herbal mixes (including tea mixes for sleep or digestion). Other mentioned teas were green, ginger, black and rose.

Tea infusions contain many compounds that may influence drug absorption, e.g. mint tea contains i.e. essential oils, fatty acids, polyphenols (McKay and Blumberg, 2006). Due to the variety of the constituents, it also influences the organism, especially the gastrointestinal tract.

In the case of the tea (or a soup mentioned before as a food vehicle), a question about the temperature arises. The temperature of the fluid or vehicle may be an important factor that influences the stability of the hard gelatin capsules (HGC). HGCs are sensitive to temperature and their solubility depends on the temperature (Majee et al., 2017). HGC dissolve faster in higher temperatures (Al-Tabakha et al., 2015). Administering a gelatin capsule with a warm drink could be a way to accelerate the capsule rupture (Chiwele et al., 2000). Different temperatures may also influence the gastric emptying rate. The study by Sun et al. shows that warm (50 °C) and cold (5 °C) fluid in comparison to the drink at 37 °C slowed down the initial rate of gastric emptying, however only cold was statistically significant (Sun et al., 1988).

Drug intake with carbonated water was also common among participants. Patients used carbonated water as well as medium carbonated. The study of Van Den Abeele et al. demonstrated the influence of carbonated water on the pharmacokinetics of paracetamol from tablets, which was reported to be faster and less variable than when taken with tap water (Van Den Abeele et al., 2017). In the study of Kelly et al., the dissolution of paracetamol tablets in carbonated and non-carbonated water was assessed (Kelly et al., 2003). The results demonstrate that the dissolution rate in carbonated water was faster than in degassed water and 0.05 M HCl.

The fluid co-administered with a medication influences the pH in the GIT, it has a crucial role when it comes to solubility and thus bioavailability (Koziolek et al., 2019).

Thus, it is a good outcome that in 70 % (164 out of 235 answers) of the recorded drug intake cases, the aged patients reported taking any kind of water (non-carbonated and/or carbonated) with their medication.

##### 4.10.2. Influence of fluid volume on drug absorption

The amount of fluid co-administered with a drug is crucial for the drugs' solubility, especially in case of the poorly soluble compounds.

A small glass of 100 mL was the most common amount of water used

by participants. A big glass of 200 mL was also often chosen. Based on the results from the Mann-Whitney test, it can be seen that there were no significant differences between the volume of fluid used by study participants in subgroups home vs. hospital and women vs. men. The difference between home and hospital is about one sip and between women and men even smaller. Such small differences are clinically irrelevant and do not make difference from biopharmaceutical point of view.

The answer 200 mL is close to EMA's (European Medicines Agency) recommendation to use at least 150 mL of water to administer medications (EMA, 2010). Either way, both results do not fulfil the recommendations of the FDA for food studies (intake of 240 mL) (FDA, 2002).

In the study of Hens et al., real-life dosing conditions among children and adults aged at least 16 years old were investigated (Hens et al., 2017). In the above-mentioned study, a glass of a volume of 240 mL was used. Adults ( $n = 895$ ) mostly administered medications with half of the glass, which is in agreement with the results from the presented study (100 mL). However, the answer one sip was not so common among the older population as among adults from the mentioned study from Belgium.

The results of our study are also in accordance with the study of Fuchs et al., who investigated the volume of fluid used by people to swallow medications (Fuchs, 2009). The group of people 60 years and over was using on average 113 mL of water ( $n = 67$ ).

The amount of water co-administered with a drug may influence the drug behaviour in the gastrointestinal tract. For example, reduced absorption of cefteram-pivoxil 30 mL versus 150 mL of water was observed (Matsumoto et al., 2001). Moreover, a lower variability in  $C_{max}$  of nifedipine was achieved when given with 250 mL versus 50 mL (Nader et al., 2016). This is well in line with recent data on gastric emptying of lower fluid volumes which show an increased variability in gastric emptying rate, which is most often a prerequisite for absorption (Grimm, Aude, et al., 2023, 2023).

#### 4.11. Limitations

The presented work has several limitations. The first one is that the study was in the form of an interview. In this study, patients self-reported their answers. It may result in a bias or be influenced by the patients' experiences and honesty in their responses. Moreover, only motivated people participated in the study, and it can be assumed that they are mostly adherent to the recommendations due to a more positive attitude toward pharmacotherapy in general.

Secondly, no data about exact medication plan (names of medications, ways of taking medications – prescription or preference), or diseases from which patients suffered were collected. These pieces of information may also add value to the interpretation of the results.

Additionally, surveying in geriatric wards in the hospital was hindered due to the general bad condition of patients and still ongoing COVID-19 pandemic. Patients in the hospital were examined for cognitive impairments by the specialists during the hospital admission. Many of them suffered from dementia or delirium, which excluded them from participating in the study and thus limited the sample size of the study. Moreover, many of the patients in the hospital were not able to answer all the questions, because they did not know the answers. The recruitment of the in-patients was more challenging than the out-patients.

In the study, the sample was restricted to North Germany, mostly the Mecklenburg-Western Pomerania region; thus, the results may not reflect a national trend. In order to confirm whether this data set represents a national trend, it would be useful to examine the older population from other parts of Germany. Additionally, it would be interesting to investigate and compare the drug intake behaviour of older Germans with that of older citizens from other European or even world countries.

## 5. Summary

In the present study, the dosing behavior of patients aged 65 years and older was investigated. Data on real-life dosing conditions in older adults and geriatric patients provide a general overview of how this special population take their medication. The data provide novel insights into factors that may influence drug absorption. The main findings of the study in terms of pharmacokinetics are as follows. First, patients aged 65 years and over most frequently use non-carbonated water for drug intake. Secondly, the most commonly used amount of water is the small glass (about 100 mL). In addition, many people also use a large glass (approx. 200 mL). Thirdly, the most common food eaten by older adults in Northern Germany (Mecklenburg - Western Pomerania) in temporal connection with drug intake is bread. The study participants eat bread for both breakfast and dinner, each with jam or honey and ham and/or cheese. Fourthly, medication intake is linked to food intake. The participants usually take their medication directly after food ingestion (breakfast and/or dinner). Fifthly, the participants in the study stated that they only performed modifications for tablets. The most common modification in dosage form was splitting tablets. Study population in our study was highly homogenous. There were no significant differences between subgroups (home vs. hospital, women vs. men). The general results were the same for all subgroups and whole population. Since the mode of drug intake has a direct impact on the process of drug absorption from the GIT (gastrointestinal tract), our data can help to understand the process of drug absorption and modifying factors in older adults, considering the special needs of this specific population. Furthermore, the above data can be further utilized in vitro and/or *in silico* simulations to evaluate how these conditions and factors (particularly the amount and type of fluid and food intake) affect the dosage form or the behaviour of specific drugs.

## CRedit authorship contribution statement

**Dorota Sarwinska:** Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Michael Grimm:** Writing – review & editing, Visualization, Methodology, Conceptualization. **Julius Krause:** Writing – review & editing, Visualization, Resources, Methodology, Conceptualization. **Philipp Schick:** Writing – review & editing, Visualization, Methodology, Conceptualization. **Maik Gollasch:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Marwan Manna:** Writing – review & editing, Resources. **Christoph A. Ritter:** Writing – review & editing, Methodology, Conceptualization. **Werner Weitschies:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

## Conflicts of interests

The authors declare no conflict of interest.

## Data availability

Data will be made available on request.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ejps.2024.106814](https://doi.org/10.1016/j.ejps.2024.106814).

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