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Identification of different shapes, colors and sizes of standard oral dosage forms in diabetes type 2 patients—A pilot study

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ABSTRACT

The clear identification of drug products by the patients is essential for a safe and effective medication management. In order to understand the impact of shape, size and color on medication identification a study was performed in subjects with type 2 diabetes mellitus (T2D). Ten model drugs differentiated by shape, size and color were evaluated using a mixed method of medication schedule preparation by the participants followed by a semi-structured interview. Detection times were fastest for the large round tablet shape and the bi-chromatic forms. Larger size was easier to identify than the smaller sizes except for the bi-chromatic forms. The shape was the major source of errors, followed by the size and the color dimension. The results from this study suggests that color as a single dimension are perceived more effectively by subjects with T2D compared to shape and size, which requires a more demanding processing of three dimension and is dependent on the perspective.

1. Introduction

The prescription of oral drug products to patients is the most common intervention in the treatment of acute and chronic diseases. The drug products are dispensed by pharmacists to the patient for independent use at home or by caregivers in hospitals or nursing homes directly to the patients on a daily basis. The increasing prevalence of multimorbidity leads to polypharmacy and complex medication schedules (Qato et al., 2016; Charlesworth et al., 2015). Non-adherence to medication is considered to be responsible for 30%–60% of the preventable drug related hospital admissions in the USA (Howard et al., 2003; Marcum et al., 2012). Unintentional overdose has been identified as responsible for two thirds of drug related admissions and mainly concerns warfarin, insulin, oral antiplatelet drugs and oral hypoglycamic agents (Budnitz et al., 2011). A recent study further provided evidence that only every second patient of 75 years and older is able to manage polypharmacy (≥5 medications) independently at home (Sino et al., 2014). Managing drug therapy and medicinal products requires sufficient cognitive, motoric and sensory capacity to identify the drug products, reading and understanding the instructions and administering the drug as intended (Stegemann et al., 2010). Forty percent of patients 75 years and older were not able to read leaflet instructions due to poor visual performance (Moisan et al., 2002). Diabetic retinopathy, a microvascular damage caused by diabetes type 1 and type 2, is a major root cause for severe visual impairments affecting up to 50% of patients after 10 years (ACCORD Study Group, 2010).

Medication errors have been identified as a major health burden and risk for patients, which has led to the development of safety considerations for minimizing medication errors through drug product design during the drug product development by the EMA (EMA, 2015) and the FDA (FDA, 2016). One consideration in this guidance is the differentiation between different dose strengths for solid oral dosage forms by means of size, shape and color. Early work in four different patient populations (demented, depressed and normal old with an mean age of 75 years and in young volunteers with a mean age of 22 years) investigating sorting times for colors and forms showed faster identification of the color compared to the form dimension (Grewal et al., 1985). Similar results were obtained when comparing color spot detection, which was detected 5–9 times better than the luminance spot (Chaparro et al., 1993). Much less is known about the impact of shapes and sizes on human detection and recognition. The perception of shape involves different dimensions of depth, horizontal binocular disparity and

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perspective to recognize a 3D structure (Van Damme and van de Grind, 1993; Welchman et al., 2005).

The aim of this pilot study was to investigate the impact of shape, size and color on the identification of solid oral dosage forms in T2D patients receiving polypharmacy under simulated home conditions. Another aim was to collect patient responses to the different product design features in terms of their subjective perception and the objective performance.

2. Material and methods

2.1. Study design

The study received approval of the ethical committee at the Medical University of Graz (No. 28-035 ex 15/16) and was conducted at the Medical University of Graz between May 18 and June 30, 2016. The study consisted of an observational task performance by using a uniform crossover design followed by a semi-structured interview.

2.2. Study population

Twenty-two subjects with T2D provided written consent to participate to the study. Participants were included when they had T2D, lived independently, were aged 55 years or older and received polypharmacy (≥5 different medications). Additional patient data were collected from the health records and included age, sex, duration of T2D, presence of retinopathy or polyneuropathy and the number of prescribed oral medication. The participants used vision aids according to their personal mode of behavior to reflect the typical medication preparation situation. From the 22 participants, one patient was excluded due to inability to finish the tasks. The data of 21 participants were analyzed.

2.3. Model drug product design

The study medication (SM) samples consisted of 10 model oral drug products, which were composed of 5 designs with different shapes and colors. Each of the 5 design concepts was presented as a small and a large version whereby the size dimensions were comparable between the design concepts. The design concepts of the SM generated from existing, marketed drug products and included round, oblong, diamond and a capsule shapes (Fig. 1). For the evaluation of the color, the oblong form was presented in white and yellow color and the capsules shared either yellow (large capsule-oblong form) or blue (large – small capsule). The round, oblong and diamond shaped design concepts were prepared by 3D printing (Colorcon, Idstein, Germany), the capsule shaped design concepts were generated from hard capsules (Capsugel, Bornem, Belgium).

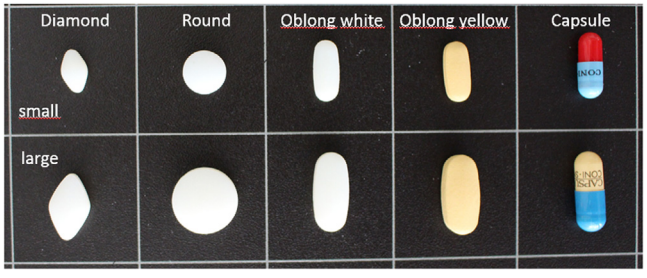

Fig. 1. Model oral drug products investigated in the study.

2.4. Observational task performance

The objective of the task was to evaluate the identification and selection of the different drug product designs under polypharmacy conditions. Seven units of each drug product design were collected in a white bowl (70 units in total). All participants were used to medication schedules and prepared a medication schedule composed of all model drug products to familiarize with the SM. Each patient had to prepare four different medication schedules, whereby each medication schedule focused on two specific design features (1. color – large size, 2. color – small size, 3. shape – color and 4. shape – size). The products were named according to their specific design features (e.g. small round, large round etc.). In each medication schedule 7 items of the SM had to be identified and filled into a dosing aid with four compartments in accordance with the medication schedules into morning, noon, evening and night doses. The participants performed the task in a quiet room sitting in front of a white table with good lightening. The bowl with the SM was placed on the right side and the medication schedules on the left side and the dosing aid in front of them.

Before starting the four medication schedules, the SM and the task was explained to the participants and a generic medication schedule was filled which included all 10 different drug product designs. After assuring that the participants understood the task, each patient filled the four medication schedules in randomly allocated sequence such that each schedule occurs only once within each sequence and once within each period (1-2-3-4; 2-3-4-1; 3-4-1-2 or 4-1-2-3). Participants were videotaped during the task performance until the end of the semi-structured interview. The task performance was analyzed by determining the time required to determine the relevant item (identification time, in seconds) and by the number of incorrect item selections (errors). The time was measured from the moment when the participant directed attention to the bowl and started searching for the item until the item was touched with the hand. The time required to take hold of the item and transfer it to the dosing aid was not measured. Participants were neither interrupted nor corrected during their preparation of the four medication schedules. The verbal feedback of the participants during the task performance was recorded but not commented.

2.5. Narratives and semi-structured interview

During the task performance the verbal and narrative feedback of the participants was collected and analyzed in the context of the task. After performing the medication schedule tasks, participants were interviewed in a semi-structured manner with open ended questions to collect direct feedback on the experience and their subjective perception. The second part of the semi-structured interview was the collection of feedback on the own medication and personally important issues and strategies related to preparation and management at home. During the interview, the participants were not interrupted and the interviewer only asked clarifying questions in order to obtain additional details or further pursue a participant's narrative descriptions.

2.6. Statistical evaluation

For statistical analysis, SPSS Version 24 (IBM Corp, Armonk, NY, USA) was used. All outcome parameters are summarized descriptively. Continuous variables are presented as mean ± standard deviation (SD) or median (med), minimum (min) and maximum (max), categorical data as frequencies and percentages.

The mean identification time per item in a schedule (in total 7 drugs) was calculated in order to evaluate the impact of the four different medication schedules and the four periods on

identification time for each participant. The mean identification time per drug design was calculated to evaluate the impact of the ten different oral drug products for each person. E.g. over all four medication schedules each participant had to identify the drug design diamond small three times. As the outcome of this the mean value of the three measurements was calculated for each participant. Errors are presented as the number of participants with at least one incorrect item selection within the different periods, medication schedules and oral drug products. Additionally, the total number of errors in relation to the total number of drugs is given.

3. Results

3.1. Patient population

The 21 participants with T2D participating in the study had a mean age of 67.3 ± 7.1 years with a median T2D duration of 13 years (range 2–25 years) and lived independently and in their own homes. Eight of the participants were female (38.1%) and 13 were male. A median of 7 medications was prescribed ranging from 5 to 20 medicines to be managed. Retinopathy was diagnosed in 4 (21%) and polyneuropathy in 10 (56%) participants. Insulin was prescribed to about half of the participants (Table 1).

3.2. Task performance

The 21 participants performed a total of 588 identification points of the SM. Each participant identified 28 items of the study medication, 2 times diamond large, oblong yellow small, oblong yellow large, capsule small, 3 times diamond small, round small, round large, oblong white small, and 4 times oblong white large and capsule large. Overall, the mean identification time for one item of the SM was 3.0 ± 1.1 s and in total 30 errors were made by 13 (62%) participants and of these one error was made by 5, two errors by 4, 3 errors by 3 and 8 errors by one participant.

The mean identification times were similar across the periods and varied between 3.1 s for the first and third task and 2.9 s for the second and forth task with standard deviations between 1.0–1.2 s. The period had a slight impact on the error rate with 6 (29%), 4 (19%), 7 (33%) and 8 (38%) participants making at least one error in the 1st, 2nd, 3rd and 4th medication schedule task respectively (Supplemental Table 1).

The mean time to identify the SM was longer for the small sizes except with the bi-chromatic design. For the large sizes, round shape and bi-chromatic design were identified fastest, followed by oblong shape (white or yellow) and diamond shape. Only one error was made for round shapes and most errors occurred with white color and oblong shapes (Table 2).

A comparison of the four different medication schedules revealed mean identification times of 2.8 ± 0.9 s, 3.2 ± 1.1 s, 2.4 ± 0.8 s and 3.5 ± 1.1 s (Fig. 2) with 6 (29%), 5 (24%), 7 (33%) and 7 (33%) participants making at least one error for schedules 1–4 respectively (Supplemental Table 2).

A total of 30 errors were observed across the 588 medication selection tasks during the medication schedule preparations. As depicted in Table 3a, 13 of the 21 participants (62%) made at least one error, whereby the lowest error rate was observed with the first medication schedule being prepared (6/147 errors) and the highest error rate with the last medication schedule (10/147 errors) as shown in Table 3b.

The study medication investigated four different shapes (diamond, round, oblong and capsule shape), two different sizes (large and small) and four different colors (white, yellow, yellow-red and yellow-blue). From the 30 errors occurred across all the dimensions, the errors were caused by shape detection errors (16 cases; e.g. selection of round instead of diamond or oblong), size errors (9 cases; e.g. oblong large instead of oblong small) and color related errors (5 cases; e.g. oblong small white instead of oblong small yellow) as depicted in Table 4. No color error was observed between monochromatic (white or yellow) and bi-chromatic forms sharing one color (light blue/yellow and light blue/red).

3.3. Narratives and semi-structured interview

Each of the participants prepared the medication schedules in a very focused and systematic manner. They went either from left to right (filling in all diamond small into the dosing aid etc.) or from top down (filling in all morning medications etc.). During the search for the model drug product from the vessel, participants used the verbal representation of the search item (e.g. round large). While the word “round” was consistently used for the round shape, participants developed proprietary word for the diamond (e.g. “ . . . this funny guy.”) and the oblong form (e.g. “ . . . the grand slim”). The capsule was often expressed by their color (e.g. “ . . . the red-blue one.”). The verbal backing of the search showed that for the diamond, oblong white and oblong yellow forms participants prioritized shape first and size (large-small) second, sometimes with the reassurance of a second look at the medication schedule. The participants who made 8 errors commented that the preparation task was very stressful.

Following the performance of the tasks, participants were asked about their experience with preparing the medication schedules and preferences for one or the other form (What did you find most difficult? What did you find easiest to identify?). There was no difference between preference for shape or color. In the case of the easiest detectable dimension, about half of the patients (11) perceived the shape as the easier dimension for differentiation even though the detection times for the color dimension (except for the large round shape) was faster than for the shape dimension in all patients. Three participants reported issues with the large diamond shape, referring to perceived swallowing issues. The large round and oblong shapes, however, were mentioned as the easiest to identify by 7 participants with reference being made to their experience with metformin and metformin fixed dose combination products.

In the semi-structured interview 20 of the 21 participants reported that they use some kind of dosing aid (between 2 and 4 compartments) and prepare the medications in advance. Of these 20 participants, one participant did it on a daily base, the other 19 participants on a weekly or even bi-weekly base. When asked what problems they experience with their own medication at home, all answered spontaneously that they have no problems since they have already been using the medication for a long time. When asked more precisely regarding issues in differentiating the medicines or handling the drug products, one third of the participants continued to report no issues. Another third reported issues in a third person language (“ . . . when I see others of my age

Tables 1
Demographics and characteristics of the study participants.

	N total	N (%), mean ± SD or med (min–max)
Female	21	8 (38.1%)
Age (yrs)	21	67.3 ± 7.1
Diabetes duration (yrs)	16	13 (2–25)
Number of medicines prescribed	18	7 (5–20)
Retinopathy	19	4 (21%)
Polyneuropathy	18	10 (56%)
Insulin treatment	19	10 (53%)

Table 2
Mean identification times, Standard deviation, minimum and maximum times in seconds as also the error rate of the different product design concepts.

	identification time				persons with error			error total		
	Mean	Standard Deviation	Minimum	Maximum	N patients total	N	%	N drugs total	N	%
Diamond small	4.71	1.44	2.33	8.67	21	2	9.5	63	2	3.2
Diamond large	3.64	1.46	1.50	6.00	21	3	14.3	42	4	9.5
Round small	3.48	1.42	2.33	8.67	21	0	0	63	0	0.0
Round large	1.65	0.81	1.00	3.67	21	1	4.8	63	1	1.6
Oblong small white	4.19	1.82	2.33	10.00	21	5	23.8	63	5	7.9
Oblong large white	2.73	1.01	1.50	5.00	21	8	38.1	84	9	10.7
Oblong small yellow	3.81	1.74	2.00	9.50	21	2	9.5	42	2	4.8
Oblong large yellow	2.69	1.37	1.00	6.00	21	3	14.3	42	3	7.1
Capsule small	1.67	0.78	1.00	4.50	21	2	9.5	42	2	4.8
Capsule large	1.63	0.52	1.00	2.50	21	2	9.5	84	2	2.4

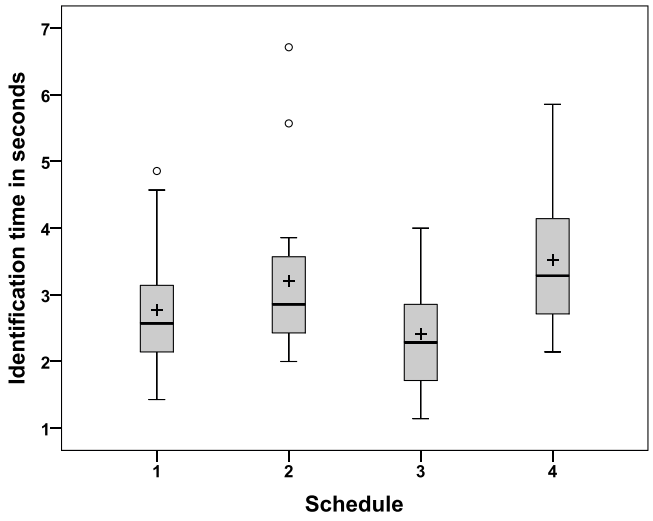

Fig. 2. Box-and-whisker plot for the mean identification time per item in schedule 1–4, representing the evaluation of color – large size (schedule 1), color – small size (schedule 2), shape – color (schedule 3) and shape – size (schedule 4).

or even younger than me . . . " and the last third explained their personal strategies for circumventing a problem (e.g. "· · ·I take my finger nail, which I don't cut (show her thumb) . . . and just pierce the foil with it . . . ").

The interviews revealed that all of the T2D participants had already been taking their medications for a long time and had developed their own strategies for the preparation of the medication in the course of this. Only two participants acknowledged that they sometimes did not follow their medications as prescribed, but consider this as forgivable. Seven participants mentioned a big size (round or oblong) as the easiest to differentiate within their own medication schedule as this product is substantially bigger that the other medicines. The majority of participants had at least two drug products prescribed that were very similar in size and shape (e.g. tablets of furosemide and L-thyroxine). To manage identification and determination of these similar products, participants fill the drug products from the packaging directly into the dosing aids without any reexamination at the dosing moment. Participants were searching for differentiation features on the micro level (special surface shine, break score design) in case of an accidental mix up. Tablet splitters were frequently used due to the frequent prescription of half tablets. Differentiation of halved tablets was reported to be even more difficult as it affects shape and size perception. One participant used tablet thickness comparison to differentiate between the two halved tablets. Three participants mentioned issues with drug product identification following generic substitution (e.g. generic substitute of simvastatin was equal to the gliclazide tablet).

4. Discussion

The eyes are the most important sensory organ of human beings and the visual processing of information is a major guiding principle through everyday life course. Humans visually perceive objects by encoding of three-dimensional imaging, color discrimination and processing through working memory (Woodman et al., 2001). With

Table 3a
The number of error per person, per medication schedule.

error/person	1st schedule task	2nd schedule task	3rd schedule task	4th schedule task	Total
Schedule 1	1/6	0/4	1/5	4/6	6/21
Schedule 2	2/6	1/6	0/4	2/5	5/21
Schedule 3	2/5	2/6	2/6	1/4	7/21
Schedule 4	1/4	1/5	4/6	1/6	7/21
Total	**6/21**	**4/21**	**7/21**	**8/21**	**13/21**

Table 3b
The number of errors per model drug, per medication schedule.

error/model drug	1st schedule task	2nd schedule task	3rd schedule task	4th schedule task	Total
Schedule 1	1/42	0/28	1/35	5/42	7/147
Schedule 2	2/42	1/42	0/28	3/35	6/147
Schedule 3	2/35	5/42	2/42	1/28	10/147
Schedule 4	1/28	1/35	4/42	1/42	7/147
Total	**6/147**	**7/147**	**7/147**	**10/147**	**30/588**

Table 4
Root cause of the errors per medication schedule.

	Schedule 1	Schedule 3	Schedule 3	Schedule 4	Total
Shape errors	3	4	5	4	**16**
Size errors	2	1	4	2	**9**
Color errors	2	1	1	1	**5**

intensive drug therapy and polypharmacy becoming an integral part of treatment for multimorbid and older patients, the identification of and differentiation between different solid oral dosage forms is becoming an important safety consideration for patients as well as caregivers (Ward et al., 2010; Iyasere et al., 2014). We performed a pilot study in T2D patients, 55 years of age or older and polypharmacy (≥5 medicines prescribed) to investigate the identification and differentiation of ten model drug products with different shape, size and color properties. We used a top-down, goal-directed visual search task methodology in which the single model drugs were both, a relevant or irrelevant search target. Dependent on the special search target from the medication schedule, a model drug had to be identified within the other model drugs based on the specific design features, whereby the model compounds with other design features act as distractors to this specific task. This set-up reflects the typical medication preparation scenario at home, after the drug products have been released from the primary packaging. With this semi-structured interview additional information was captured, such as the participant experience and perception of own therapy.

Participants identified the large white round tablet shape and the two bi-chromatic capsules almost immediately, followed by the oblong shape and the diamond shape with the longest detection times. As confirmed through the semi-structured interviews, participants reported that their own medications include several white round shaped tablets, which suggests that the white round tablet shape is stored in their visual working memory and guides selective attention and recognition (Downings and Dodds, 2004). In contrast to this, the small white round tablet due to its noticeably smaller size does not automatically capture the attention and requires a controlled attention mode to differentiate from the other distracting small shape form. According to the perceptual load theory, this identification of small round shape is a high perceptual load process in order to reject irrelevant and interfering search targets (Lavie, 2010). The high perceptual load process for determining the small round shape is also supported by the findings that no errors were made with the small round shape, while one error was observed with the large round shape as a low perceptual load process (Lavie et al., 2004).

Larger sizes were generally detected earlier than the small sizes, except for the bi-chromatic forms, for which the visual detection times were comparable (1.67s versus 1.63s for the small and large size respectively). The large shapes oblong and diamond tend to have a higher error rate compared to the small versions of the same shape, which is in accordance with the findings for the round shape. The errors were either shape errors in which the round shape was selected instead of the targeted oblong and diamond shape or size errors where the right shape was selected, but in the wrong size. The longer detection times and higher error rate for the shape and size errors could be explained by a cognitive low demanding preservation of a singleton search mode by the patients (Bacon and Egeth, 1994). Thus participants were either focusing on the shape or the size instead of capturing the 3D structure of the tablet in a feature search mode (Folk et al., 1992). Interestingly, the oblong mono-chromatic yellow small and large size had less errors than their white counterparts whereby the errors were based on size (small instead of large and vice versa) or color (selected the white counterpart), but not on shape. This suggests that the different mono-chromatic color either supported shape perception or captured attention in the visual search in a way superior to the shape factor.

The search task performed by the participants was accompanied by a narrative transcript of the relevant search target. In contrast to the round shape and the capsule shapes, for the diamond and oblong shapes the participants used different expressions and some had no clear verbal representation for the shape. Cognitive science has provided evidence of the visual and semantic representations of object categories in the human brain to support complex visual task performance (Huth et al., 2012; Van Gulick and Gauthier, 2014). The mediation effect of semantic representations on visual attention might have been involved in the high error rate with the oblong and diamond shaped forms (Shen et al., 2016).

Despite the large differences in the size and the comparative set up of the identification task (side-by-side in the bowl), we observed a considerable error rate related to the size. These results suggest that the error rate will increase with a decreasing size difference that can be found in real medication conditions, especially when certain size dimensions (e.g. radius) are equal and the only differentiator is for example, the tablet height. The ease of size differentiation also depends on comparison (Rey et al., 2014). It should also be noticed that the use of size for the sake of differentiation might lead to unnecessary large tablet sizes that raise swallowability issues and hence an inappropriate medication alteration (Stegemann et al., 2012; Van Riet-Nales et al., 2016).

Color is a single dimension that does not require the higher cognitively demanding process as that for the 3D structure of the object (Welchman et al., 2005). Previous work confirmed the color singleton captured attention automatically without requiring attention (Theeuwes, 1994; Yantis 1993). Color detection is relatively unaffected by age, visual and even cognitive impairments (Stegemann, 2005). These findings were confirmed by the consistently fast detection times of the bi-chromatic forms included in this study. The four errors observed were solely based on the confusion between the small size (blue/red) and the large size (blue/yellow). One of the reasons for this could be that the colors were not part of the semantic presentation within the medication schedules (capsule small, capsule large) as was the case for the shape dimension (diamond small, diamond large etc.). Searching for capsules blue/yellow or capsules blue/red would have been the semantic representation of the search target. The synergistic effects of visual and semantic representations might be explained by faster orientation of attention to the target, a reduction of visual similarity and confusability by the semantic information and a different encoding mechanism, which is implicit for the visual and explicit for the semantic context (Brockmole et al., 2008). Another contributing factor might have been that the bi-chromatic forms shared one color (blue) and the large capsule also shared the yellow color with the oblong yellow tablets that might have drawn the attention to the blue as the differentiating color.

Another observation from the study was that the preparation of the medication schedules could cause substantial stress to the participants that could in turn lead to errors (Annac et al., 2013). For example, the patient who made the 8 errors felt very stressed and made issues by capturing only one dimension, either the right shape but wrong size or the right size but the wrong shape. In order to manage their own medication schedules all the participants were using some kind of dosing aid to prepare their daily schedules. The participants directly or indirectly confirmed the visual similarities between different medicines and the related issues with identification of their own schedules. The participants

have developed their own strategies to deal with the issues in preparing their medications. This might explain why the subjective feedback of the participants ("Different shapes are much easier to identify than colors") and the objectively measured times do not correspond.

In the pilot study we did not observe a learning effect across the four medication scheduling tasks; on the contrary, we observed a slight increase in the error rate with more medication schedule task finished. This might be caused by the fact that medication preparation is a cognitively demanding task and we could observe fatigue and declining concentration with each medication schedule. A larger number of patients would be required, however, to confirm this observation.

This pilot study has some important limitations. The study includes only 21 participants, which makes a detailed interpretation of the results difficult. Nevertheless, the results from the task performance and the semi-structured interviews are very consistent between the participants and are in accordance to previous studies (Carlson et al., 2005; Windham et al., 2005; Wijk and Sivik, 1995; Wijk et al., 2002). The pilot study was also restricted to a limited number of shapes and colors and two markedly different sizes. The limitations of the SM should facilitate product differentiation and it can be postulated that more shapes, sizes and colors will rather increase than decrease the risk for identification errors. The pilot study only included two bi-chromatic forms, which shared colors with each other and with the mono-chromatic forms, with the result that the colors were not included in verbal form. This might have limited their impact on preventing errors in the top-down and feature search mode applied in this study mimicking the typical medication preparation (Eimer and Kiss, 2010; Harris et al., 2015).

The pilot study only included the familiarization with the SM by a generic medication schedule followed by the four medication schedule tasks. This set-up did not allow for contextual cueing effects through implicit learning and implementation into visual context memory, which could support spatial attention and object identification (Chun and Jiang, 1998).

5. Conclusion

Independent preparation of medical schedules by the participants at home is a complex and error sensitive task. Safe and adherent drug use requires visual attention to the medication, which is derived from a stimulus that is automatically selected and captured to perform the task of drug administration (Olivers et al., 2006). The highest errors rate was found for the different shape except the round shape, which is categorized and preserved in the working memory as medicine. As we used a feature search based study task, the participants used the verbal representation of the objects during the search to facilitate the specific item identification. With the exception of the round shape, there was no commonly used verbal representation for the oblong and diamond shape, which had the highest error rate. This suggests that the use of shape as a differentiator for oral dosage forms is relatively limited due to suitable and commonly recognizable shapes. Identification by size seems to be the least suitable differentiating feature. Despite the noticeable variances in the size differences between the same shapes tested and their direct comparison in the study set up, size errors were very common. Colors represent a single dimension and are captured automatically compared to the 3D structure recognition involved in shape determination. The size dimension has been found to be the least differentiating dimension. Subjects with T2D included in this trial had long experience with their own medication schedules and used dosing aids for complexity management. Over time, they had developed proprietary strategies to differentiate between the drug products, but reported difficulties, when medicines have a very similar appearance or when tablets were split in two halves. The study confirmed the importance of better understanding the identification and differentiation of medicines in medication management by the patients under polypharmacy conditions together with the impact and rational use of product features and design elements to prevent unintended medication errors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijpharm.2016.11.066.

References

ACCORD Study Group, 2010. Effects of medical therapies on retinopathy progression in type 2 diabetes. N. Engl. J. Med. 363 (3), 233–244.
Annac, E., Manginelli, A.A., Pollmann, S., Shi, Z., Müller, H.J., Geyer, T., 2013. Memory under pressure: secondary-task effects on contextual cueing of visual search. J. Vis. 13 (13), 6 (1–15).
Brockmole, J.R., Hambrick, D.Z., Windisch, D.J., Henderson, J.M., 2008. The role of meaning in contextual cueing: evidence from chess expertise. Q. J. Exp. Psychol. 61 (12), 1886–1896.
Budnitz, D.S., Lovegrove, M.C., Shehab, N., Richard, C.L., 2011. Emergency hospitalizations for adverse drug events in older Americans. N. Engl. J. Med. 365 (21), 2002–2012.
Carlson, M.C., Fried, L.P., Xue, Q.-L., Tekwe, C., Brandt, J., 2005. Validation of the Hopkins medication schedule to identify difficulties in taking medications. J. Gerontol. Med. Sci. 60A (2), 217–223.
Chaparro, A., Stromeyer, C.F., Huang, E.P., Kronauer, R.E., Eskew, R.T., 1993. Colour is what the eye sees best. Nature 361, 348–350.
Charlesworth, C.J., Smit, E., Lee, D.S.H., Alramadhan, F., Odden, M.C., 2015. Polypharmacy among adults aged 65 years and older in the United States: 1988–2010. J. Gerontol. A Biol. Sci. Med. Sci. 70 (8), 989–995.
Chun, M.M., Jiang, Y., 1998. Contextual cueing: implicit learning and memory of visual context guides spatial attention. Cognitive Psychol. 36, 28–71.
Downings, P.E., Dodds, M.C., 2004. Competition in visual working memory for control of search. Vis. Cognition 11 (6), 689–703.
EMA, 2015. Good Practice Guide on Risk Minimisation and Prevention of Medication Errors. Final. EMA/606103/2014 (18. November 2015).
Eimer, M., Kiss, M., 2010. Top-down search strategies determine attentional capture in visual search: behavioral and electrophysical evidence. Atten. Percept. Psychophys. 72 (4), 951–962.
FDA, 2016. Safety Considerations for Product Design to Minimize Medication Errors. Guidance for Industry. UCM331810 (April 2016).
Folk, C.L., Remington, R.W., Johnston, J.C., 1992. Involuntary covert orienting is contingent on attentional control setting. J. Exp. Psychol. Hum. Percept. Perform. 18, 1030–1044.
Grewal, B.S., Davies, I.R.L., Haward, L.R.C., 1985. Is poor Weigl performance in elderly demented patients due to interference? IRCS Med. Sci. 13, 302–303.
Harris, A.M., Becker, S.I., Remington, R.W., 2015. Capture by color: evidence for dimension-specific singleton capture. Atten. Percept. Psychophys. 77, 2305–2321.
Howard, R.L., Avery, A.J., Howard, P.D., Partridge, M., 2003. Investigation into the reasons for preventable drug related admissions to a medical admissions unit: observational study. Qual. Saf. Health Care 12, 280–285.
Huth, A.G., Nishimoto, S.V., Vu, A.T., Gallant, J.L., 2012. A continuous semantic space describes the representation of thousands of object and action categories across the human brain. Neuron 76, 1210–1224.
Iyasere, C.A., Simmons, L.H., Fintelmann, F.J., Dighe, A.S., 2014. Case 38–2014: an 87-year-old man with sore throat, hoarseness, fatugue, and dyspnea. N. Eng. J. Med. 371 (24), 2321–2327.
Lavie, N., Hirst, A., de Fockert, J.W., Viding, E., 2004. Load theory of selective attention and cognitive control. J. Exp. Psychol. Gen. 33 (3), 339–354.
Lavie, N., 2010. Attention, Distraction, and cognitive control under load. Curr. Dir. Psychol. Sci. 19 (3), 143–148.
Marcum, Z.A., Pugh, M.J.V., Amuan, M.E., Aspinall, S.L., Handler, S.M., Ruby, C.M., Hanlon, J.T., 2012. Prevalence of potentially preventable unplanned

hospitalizatoion caused by therapeutic failures and adverse drug withdrawal events among older veterans. J. Gerontol. A Biol. Sci. Med. Sci. 67 (8), 867–874.
Moisan, J., Gaudet, M., Grégoire, J.-P., Bouchard, R., 2002. Non-compliance with drug treatment and reading difficulties with regard to prescription labelling among seniors. Gerontology 48, 44–51.
Qato, D.M., Wilder, J., Schumm, P., Gillet, V., Alexander, C., 2016. Changes in prescription and Over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. JAMA Intern. Med. 176 (4), 473–482.
Olivers, N.L., Meijer, F., Theeuwes, J., 2006. Feature-based memory-driven attention capture: visual working memory content affects visual attention. J. Exp. Psychol. Hum. Percept. Perform. 32 (5), 1243–1265.
Rey, A.E., Riou, B., Versace, R., 2014. Demonstration of an Ebbinghaus illusion at a memory level. Exp. Psychol. 61 (5), 378–384.
Shen, W., Qu, Q., Li, X., 2016. Semantic information mediates vsiual attention during spoken word recognition in Chinese: evidence from the printed-word version of the visual-world paradigm. Atten. Percept. Psychophys. 78, 1267–1284.
Sino, C.G.M., Sietzema, M., Egberts, T.C.G., Schuurmans, M.j., 2014. Medication management capacity in relation to cognition and self-management skills in older people with polypharmacy. J. Nutr. Health Aging 18 (1), 44–49.
Stegemann, S., Ecker, F., Maio, M., Kraahs, P., Wohlfahrt, R., Breitkreutz, J., Zimmer, A., Bar-Shalom, D., Hettrich, P., Broegman, B., 2010. Geriatric drug therapy: neglecting the inevitable majority. Aging Res. Rev. 9, 384–398.
Stegemann, S., Gosch, M., Breitkreutz, J., 2012. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. Int. J. Pharm. 430, 197–206.
Stegemann, S., 2005. Colored capsules – a contribution to drug safety. Pharm. Ind. 67 (9), 1088–1095.
Theeuwes, J., 1994. Stimulus-driven capture and attentional set, Selective search for colour and visual abrupt onsets. J. Exp. Psychol. Hum. Percept. Perform. 20 (4), 799–806.
Van Damme, W.J., van de Grind, W.A., 1993. Acitive vision and the identification of three-dimensional shape. Vis. Res. 33 (11), 1581–1587.
Van Gulick, A.E., Gauthier, I., 2014. The perceptual effects of learning object categories that üpredict perceptual goals. J. Exp. Psychol. Learn. Memory Cognition 40 (5), 1307–1320.
Van Riet-Nales, D.A., Hussain, N., Sundberg, K.A.E., Eggenschwyler, D., Ferris, C., Robert, J.-L., Cerreta, F., 2016. Regulatory incentives to ensure better medicines for older people: from ICH E7 to the EMA reflection paper on quality aspects. Int. J. Pharm. 512 (2), 343–351. doi:http://dx.doi.org/10.1016/j.ijpharm.2016.05.001.
Ward, J., Buckle, P., Clarkson, P.J., 2010. Designing packaging to support the safe use of medicines at home. Appl. Ergon. 41, 682–694.
Welchman, A.E., Deubelius, A., Conrad, V., Bülthoff, H.H., Kourtzi, Z., 2005. 3D shape perception from combined depth cues in human visual cortex. Nat. Neurosci. 8 (6), 820–827.
Wijk, H., Sivik, L., 1995. Some aspects of color perception among patients with Alzheimer's disease. Scand. J. Caring Sci. 9, 3–9.
Wijk, H., Berg, S., Bergman, B., Börjesson Hanson, A., Sivik, L., Stehen, B., 2002. Colour perception among the very elderly related to visual and cognitive function. Scand. J. Caring Sci. 16, 91–102.
Windham, G.B., Griswold, M.E., Fried, L.P., Rubin, G.S., Xue, Q.-L., Carlson, M.C., 2005. Impaired vision and the ability to take medications. J. Am. Geriatr. Soc. 53, 1179–1190.
Woodman, G.F., Vogel, E.K., Luck, S.J., 2001. Visual search remains efficient when visual working memory is full. Psychol. Sci. 12 (3), 219–224.
Yantis, S., 1993. Stimulus-driven attentional capture and attentional control settings. J. Exp. Psychol. Hum. Percept. Perform. 19 (3), 676–681.