

Stability of medicines after repackaging into multicompartment compliance aids: eight criteria for detection of visual alteration

Valerie Albert¹  · Michael Lanz² · Georgios Imanidis² · Kurt E. Hersberger¹ · Isabelle Arnet¹

© The Author(s) 2017. This article is an open access publication

Abstract

Introduction Multicompartment compliance aids (MCA) are widely used by patients. They support the management of medication and reduce unintentional nonadherence. MCA are filled with medicines unpacked from their original packaging. Swiss pharmacists currently provide MCA for 1–2 weeks, although little and controversial information exists on the stability of repackaged medicines.

Objective We aimed to validate the usefulness of a simple screening method capable of detecting visual stability problems with repackaged medicines.

Methods We selected eight criteria for solid formulations from *The International Pharmacopoeia*: (1) rough surface, (2) chipping, (3) cracking, (4) capping, (5) mottling, (6) discoloration, (7) swelling, and (8) crushing. A selection of 24 critical medicines was repackaged in three different MCA (Pharmis[®], SureMed[™], and self-produced blister) and stored at room

temperature for 4 weeks. Pharmis[®] was additionally stored at accelerated conditions. Appearance was scored weekly.

Results Six alterations (rough surface, cracking, mottling, discoloration, swelling, and crushing) were observed at accelerated conditions. No alteration was observed at room temperature, except for the chipping of tablets that had been stuck to cold seal glue.

Conclusion The eight criteria can detect alterations of the appearance of oral solid medicines repackaged in MCA. In the absence of specific guidelines, they can serve as a simple screening method in community pharmacies for identifying medicines unsuitable for repackaging.

✉ Valerie Albert
valerie.wentzky@unibas.ch

Michael Lanz
michael.lanz@fhnw.ch

Georgios Imanidis
georgios.imanidis@fhnw.ch

Kurt E. Hersberger
kurt.hersberger@unibas.ch

Isabelle Arnet
isabelle.arnet@unibas.ch

¹ Pharmaceutical Care Research Group, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland

² Institute of Pharmaceutical Technology, School of Life Sciences, University of Applied Sciences and Arts Northwestern Switzerland, Mattenstrasse 24a, 4058 Basel, Switzerland

Key Points

After 4 weeks of storage at room temperature, no alteration was revealed for 24 critical medicines repackaged in Pharmis[®] punch cards or self-made triplex-blister.

Eight criteria can detect visual alteration of repackaged medicines.

The criteria can serve as a screening method for pharmacists to detect visual stability problems.

Introduction

A pillbox, multidrug punch card or blister pouch are customized patient medication packages, also called dose administration aids or multicompartment compliance aids (MCA). These containers are filled with solid, oral medicine, which is distributed into the compartments according to an individual intake schedule. MCA are mostly recommended for patients with polypharmacy who benefit from better management of daily medicines, with the aim of

overcoming unintentional nonadherence [1]. MCA are usually prepared by patients themselves, pharmacists, or other caregivers, and are in widespread use [2]. Before the MCA are filled, the medicine is removed from the primary packaging commercialized by the original manufacturer. There is no further manipulation except if splitting is prescribed. However, removal from the original packaging invalidates the expiry date indicated by the manufacturer. According to a recent review, only little information is available about the stability of medicines in MCA [3]. Studies showed that some medicines can be repackaged only if consecutive storage occurs under special conditions, such as exclusion of light [4]. The storage outside the original packaging may lead to product deterioration and degradation of the active ingredient, resulting in a lack of efficacy and probably a lack of safety of the product. Furthermore, the change of appearance can lead a patient to refuse to take the medication, which in turn may have a negative influence on the therapy, even though the chemical and physical stability may be unaffected [5].

In the USA, medicine comes in bulk containers and is repackaged into amber plastic bottles by the pharmacists. It is assumed that the pharmaceutical industry has tested in-use stability to allow repackaging every time a new prescription is filled. Thus, the medicine is exposed to new ambient atmospheric conditions. New expiration dates, so called beyond-use dates, are assigned to nonsterile solid compounds after opening the original container. According to the US Food and Drug Administration (FDA), the use of a repackaging container that allows not more than 0.5 mg of moisture adsorption per day (class A) is sufficient to assign a new expiration date without conducting new stability studies [6]. The US Pharmacopoeia allows a beyond-use date for repackaged medicines in customized patient medication packages of 60 days, or the remaining of the original expiration date, unless the original manufacturer's product labeling indicates otherwise [7].

Factors that may influence the stability of a repackaged solid medicine can be grouped into (1) the formulation itself, for example, effervescent tablets are by definition highly sensitive to moisture; (2) the chemical and physical properties of the ingredients (i.e. pharmaceutical active substances and excipients) together with the manufacturing process—they yield a solid form with a unique pattern of resistance towards external influences; (3) the storage conditions, which include humidity, temperature, light, and oxygen; and (4) the repackaging material (it should protect the solid form from external influences) [8].

Several guidelines for repackaging medicine have been published by pharmaceutical societies in the UK [9], Australia [10], Austria [11], Spain [12], and Germany [13]. However, recommendations on the stability of solid forms, packaging material or storage time and conditions are

mostly required to be “appropriate” without further specifications. The Danish Medicines Agency sets the beyond-use date for repackaged medicine at 28 days per default or the remainder of the original expiration date, whichever is earlier [14]. In the UK, the Royal Pharmaceutical Society recommends a maximum of 8 weeks as an expiry date of repackaged medicines and raises simultaneously awareness of “stability issues” [9]. For further guidance, stability data of brand medicines are compiled in a UK online database with information from manufacturers' and hospitals' experience, theoretical concerns, and publications of stability studies. The information is rated with a red/yellow/green color code indicating the suitability of the solid medicine for a transfer into MCA [15].

No guideline on repackaging exists in Switzerland, besides a good dispensing practice document of a Swiss Pharmaceutical regulatory body, which mentions a 14 days beyond-use date after medicine repackaging [16].

In this context, we aimed to (1) validate a simple screening method to detect visual instability of repackaged oral solid medicines, (2) test its usefulness with known critical medicines, and (3) propose general solutions for the routine use of MCA in daily pharmacy practice.

Materials and methods

Criteria and scoring for visual stability

The International Pharmacopoeia [17] contains general monographs on capsules and tablets describing the appearance of solid oral dosage forms with ten criteria. It states that any of these criteria demonstrates evidence of physical instability. For our purpose, the two criteria “excessive powder or pieces of tablets in the container” and “fusion of tablets” were disregarded because they are suited to bulk products, but not to single repackaging. The remaining eight criteria for the visual inspection of capsules and tablets are (1) rough surface, (2) chipping, (3) cracking, (4) capping, (5) mottling, (6) discoloration, (7) swelling, and (8) crushing. A score is formed as follows: The absence of one criterion gives 1 point, and thus each of the tablets and capsules have a maximum score of 8 at the beginning of the study. Any observed alteration qualifies to refuse the point for the respective criterion. Consequently, the lower the score, the more the appearance of the tablets or capsules have been altered.

Selection of critical medicines for validation of criteria

To select critical medicines for validation of the eight criteria, a total of 5892 medicines were obtained from the

Danish Medicines Agency Dose Dispensing list [14] and a published list of medicines with manufacturers' opinion on stability after repackaging [18]. Of these medicines, 157 were critical, i.e. their repackaging was explicitly not recommended. The 157 medicines corresponded to 83 active pharmaceutical ingredients (APIs). Additional information from a publication [19] and from a personal communication from the two leading repackaging companies in Switzerland (Pharmis GmbH, Beinwil am See; Medifilm AG, Oensingen) yielded a total of 97 critical APIs. Medicines were excluded if they were unsuitable for repackaging (e.g. cytotoxic API or effervescent tablets), seldom used in Swiss practice, expensive, or not on the Swiss market. The three most often split tablets in Switzerland [20] were added (Fig. 1). The final list of critical medicines contained 22 whole tablets and capsules and three half tablets, with a total of 24 different APIs. One medicine was whole and half (Madopar®). Equivalents of the critical medicines were identified on the Swiss market. We selected brands from manufacturers that were previously reported as critical (e.g. Solian®) or that were the most often prescribed brands in Switzerland (e.g. Carvedilol-Mepha) [Table 1].

Repackaging procedure, storage conditions, and measurements

A community pharmacy in Basel, Switzerland, which provides repackaging services for out-patients and has participated in previous studies, served as the center for repackaging. Two punch cards, commercially available in Switzerland and produced from different packaging material, were selected. A third blister was self-produced with a blister packaging machine (Koch KST plus, Pfalzgrafeweiler, Germany). The water vapor transmission rate (WVTR) of polyvinyl chloride (PVC), polyethylen terephthalat-G (PETG) and polyvinyl chloride/polyethylene/polyvinylidene chloride (PVC/PE/PVDC) [Pentapharm® alfoil®] are listed in Table 2 and indicate values for the unprocessed plastic foils [21]. The specific WVTR for the processed punch cards were not available.

The investigator (V.A.) obtained all medicines on site, manually deblistered and immediately repackaged the medicines in the punch cards and triplex blister. Four capsules or tablets of each medicine were put separately in single cavities. Splitting of tablets was performed manually with a pill splitter (Wiegand® MediSplitter, Theo Frey AG). One original blister of each medicine served as control. Repackaging activities were performed in the same room at 21 ± 1 °C and $30 \pm 5\%$ relative humidity (RH).

Filled MCA and original blisters as controls were stored for 4 weeks (March/April 2016) at room temperature and protected from light at the pharmacy. Temperature was

continuously monitored every 10 min and fluctuated between 20 and 25.5 °C (with one outlier down to 11 °C for 20 min). RH fluctuated between 23 and 44%. Both correspond to usual values in Switzerland (climatic zone I). A second set of Pharmis® punch cards and controls was stored for 4 weeks (October/November 2015) in a climate chamber at accelerated conditions (40 ± 2 °C and $75 \pm 5\%$ RH) according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [22]. Storage under exclusion of light at room temperature was chosen to obtain similar conditions to the dark climate chamber.

Visual inspection of all tablets and capsules was recorded and pictures were taken (Nikon 5100) before starting the storage period and after 1, 2, 3, and 4 weeks of storage. After 4 weeks, tablets and capsules were manually pressed out of the cavities.

Results

Room temperature

Appearance did not change for any of the 24 medicines repackaged in Pharmis® or triplex blister during 4 weeks at room temperature compared to controls. All medicines maintained a score of 8. An unexpected event occurred to medicines repackaged in SureMed™. Some tablets remained stuck to residues of the cold seal glue at the edges of the cavities during storage. Three medicines were stuck after 1 week (Pantoprazol Nycomed®, Sequase®, and Xarelto®) and 13 after 4 weeks (additionally Solian®, Tegretol® CR, Plavix®, Digoxin-Sandoz®, Zandip®, Dancor®, Adalat® CR, Dipiperon®, Triatec®, and Simvastatin-Mepha). Shaking the punch card would detach the sticking tablets except for Pantoprazol Nycomed®. From the 12 detached medicines, chipping was observed for eight of them, with a small piece of tablet remaining stuck to the glue. Scores were reduced by 1 point for chipping after 1 week for Sequase®; after 2 weeks for Tegretol® CR, Plavix®, Zandip®, Xarelto®, and Simvastatin-Mepha (film-coated tablets); and after 4 weeks for Solian® and Dancor® (non-coated tablets).

Accelerated conditions

Seven medicines repackaged in Pharmis® showed changes in appearance (Table 3), with scores between 3 and 7 after 4 weeks.

Madopar® started mottling after 1 week (Fig. 2). Rough surface was observed after 2 weeks for Madopar® and Carvedilol-Mepha and after 3 weeks for Pravastatin Sandoz® and Adalat® CR. Alteration of Adalat® CR was caused by a yellow watery drop coming out of the perforation of the membrane-controlled osmotic push-pull

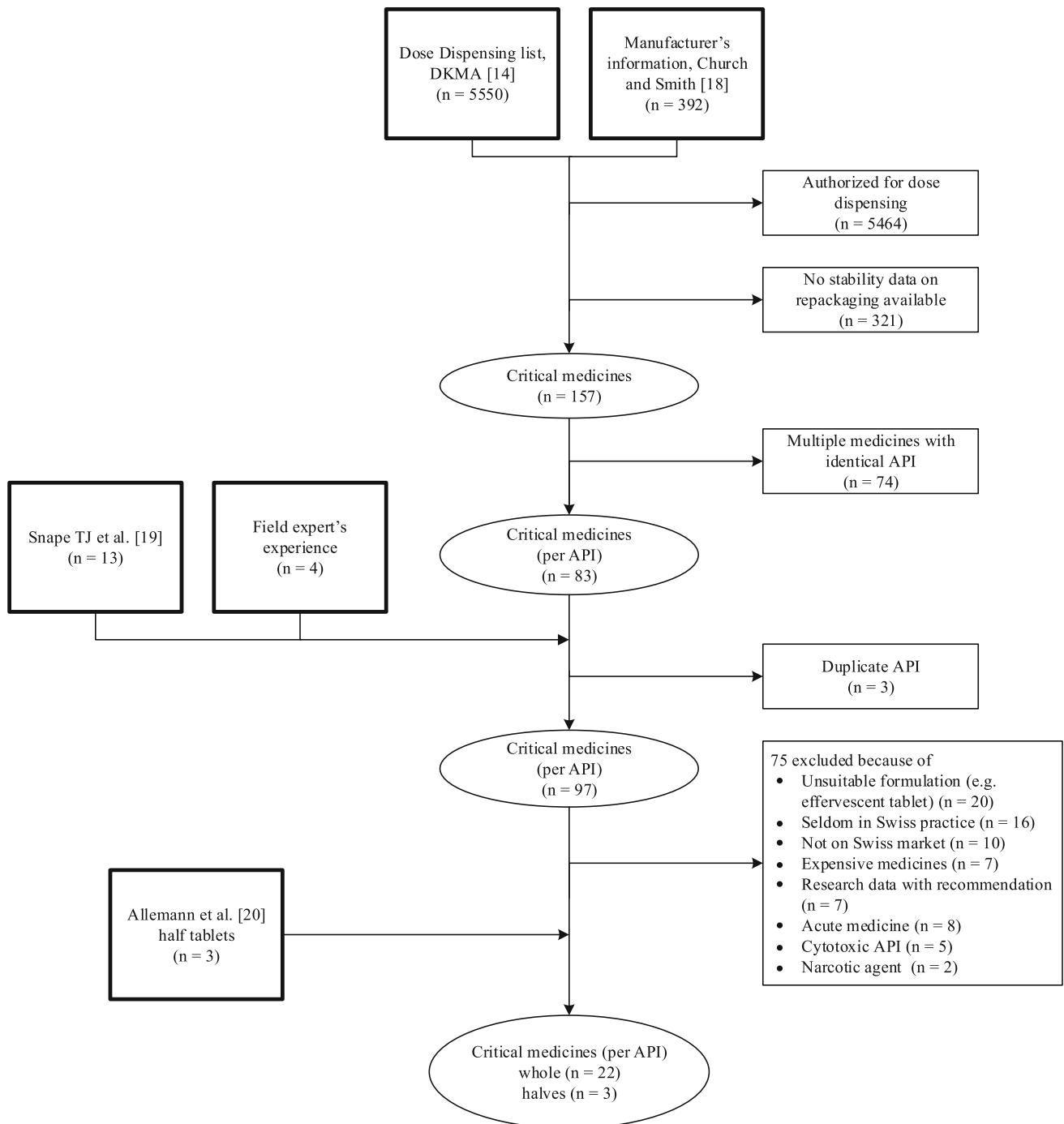


Fig. 1 Flowchart of the selection of critical medicines with sources of information. *API* active pharmaceutical ingredient, *DKMA* Danish Medicines Agency

system (Fig. 3). Cracking was observed for Pravastatin Sandoz[®] after 2 weeks, for Madopar[®] after 3 weeks, and for Plavix[®] after 4 weeks. The color of Imodium[®] capsules faded after 4 weeks. Swelling was observed for four medicines after 4 weeks (Madopar[®], Pravastatin Sandoz[®],

Carvedilol-Mepha, and Pantoprazol Nycomed[®]). Three tablets crushed when pressed out of the punch cards (Plavix[®], Pravastatin Sandoz[®], and Madopar[®]). No chipping or capping was observed. The split Madopar[®] tablets showed the same changes as the whole tablets.

Table 1 Critical APIs in alphabetic order with corresponding Swiss medicines selected for our study					
API	Manufacturer	Medicine name and strength (formulation)	Whole	Half	Expiry date mm/yyyy (AC/RT)
Alfuzosin	Sanofi-Aventis (Suisse) SA	Xatral [®] Uno 10 mg (prolonged release tablet)	x		03/2017
Amisulpride	Sanofi-Aventis (Suisse) SA	Solian [®] 100 mg (tablet)	x		10/2016
Amlodipine	Pfizer AG	Norvasc [®] 5 mg (tablet)	x		03/2016 (AC) 11/2016 (RT)
Carbamazepine	Novartis Pharma Schweiz AG	Tegretol [®] 200 mg (tablet) Tegretol [®] CR 200 mg (prolonged release film-coated tablet)	x		08/2016 (AC) 04/2017 (RT)
Carvedilol	Mepha Pharma AG	Carvedilol-Mepha 12.5 mg (tablet)	x		01/2018
Clopidogrel	Sanofi-Aventis (Suisse) SA	Plavix [®] 75 mg (film-coated tablet)	x		09/2017
Digoxin	Novartis Pharma Schweiz AG	Digoxin Sandoz [®] 0.125 mg (tablet)	x		05/2018
Donepezil	Pfizer AG	Aricept [®] 5 mg (film-coated tablet) Aricept [®] 10 mg (film-coated tablet)	x		01/2017 (AC) 02/2018 (RT)
Hydrochlorothiazide	Novartis Pharma Schweiz AG	Esidrex [®] 25 mg (tablet)	x		01/2018
Lercanidipine	Pierre Fabre Pharma AG	Zanidip [®] 10 mg (film-coated tablet)	x		03/2016 (AC) 11/2018 (RT)
Levodopa/ benserazide	Roche Pharma (Schweiz) AG	Madopar [®] 125 mg (tablet)	x	x	11/2017 (AC) 03/2019 (RT)
Levothyroxine	Sigma-Tau Pharma AG	Eltroxin [®] LF 0.1 mg (tablet)	x		08/2016 (AC) 10/2017 (RT)
Loperamide	Janssen-Cilag AG	Imodium [®] 2 mg (capsule)	x		09/2017 (AC) 09/2020 (RT)
Nicorandil	Merck (Schweiz) AG	Dancor [®] 10 mg (tablet)	x		12/2016
Nifedipine	Bayer (Schweiz) AG	Adalat [®] CR 30 mg (prolonged release tablet)	x		01/2017 (AC) 01/2018 (RT)
Oxybutynin	Sanofi-Aventis (Suisse) SA	Ditropan [®] 5 mg (tablet)	x		11/2017
Pantoprazole	Takeda Pharma AG	Pantoprazol Nycomed [®] 40 mg (film-coated tablet)	x		12/2017
Pipamperone	Janssen/Eumedica Pharmaceutical AG	Dipiperon [®] 40 mg (tablet)		x	01/2019
Pravastatin	Sandoz Pharmaceuticals AG	Pravastatin Sandoz [®] 40 mg (tablet)	x		03/2018 (AC) 06/2018 (RT)
Quetiapine	AstraZeneca AG	Sequase [®] 25 mg (film-coated tablet)		x	11/2017 (AC) 06/2018 (RT)
Ramipril	Sanofi-Aventis (Suisse) SA	Triatec [®] 10 mg (tablet)	x		12/2017 (AC) 03/2018 (RT)

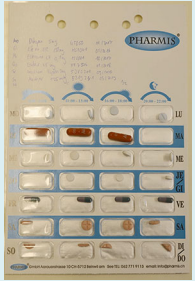


Table 1 continued

API	Manufacturer	Medicine name and strength (formulation)	Whole	Half	Expiry date mm/yyyy (AC/RT)
Rivaroxaban	Bayer (Schweiz) AG	Xarelto [®] 20 mg (film-coated tablet) Xarelto [®] 15 mg (film-coated tablet)	x		03/2017 (AC) 01/2017 (RT)
Simvastatin	Mepha Pharma AG	Simvastatin-Mepha 20 mg (film-coated tablet)	x		03/2016 (AC) 11/2016 (RT)
Venlafaxine	Pfizer AG	Efexor [®] ER 150 mg (Prolonged release capsule)	x		05/2016

Name, strength, and formulation of whole tablets and capsules ($n = 22$) and half tablets ($n = 3$) are listed with expiry date. If different packages were used for the different testing conditions, both expiry dates are indicated

AC accelerated conditions, API active pharmaceutical ingredient, RT room temperature

Table 2 Characteristics of material used for repackaging and pictures of the filled blisters

Name	Manufacturer	Sealing	Backing material	Plastic material	WVTR in $\text{g} \cdot \text{mm} \cdot \text{m}^{-2}$ (unprocessed plastic)	Pictures
Pharmis [®] size Quattro	Venalink Ltd.	Heat seal	Paperboard with aluminum foil/tissue backing	Transparent PVC	1.2	
SureMed [™] 10 × 6.5 blister	Omnice [®] (MTS)	Cold seal	Paperboard with paper backing	Light blue tinge PETG	1.5	
Triplex blister	Self-produced	Heat seal	Aluminum foil	PVC/PE/PVDC	0.06–0.16	

PE polyethylene, PETG polyethylen terephthalat-G, PVC polyvinyl chloride, PVDC polyvinylidene chloride, WVTR water vapor transmission rate

Table 3 Type of alteration of the 7 medicines with changes in appearance during 4 weeks of storage at accelerated conditions (40 °C, 75% RH) in Pharmis®. The maximum score of 8 indicates no alteration. Chipping and capping were not observed

Medicine (API)	Criteria						Score
	Rough surface	Swelling	Cracking	Crushing	Mottling	Discoloration	
Madopar® (levodopa/benserazide)	x (week 2)	x (week 4)	x (week 3)	x (week 4)	x (week 1)		3
Pravastatin Sandoz® (pravastatin)	x (week 3)	x (week 4)	x (week 2)	x (week 4)			4
Carvedilol-Mepha (carvedilol)	x (week 2)	x (week 4)					6
Plavix® (clopidogrel)			x (week 4)	x (week 4)			6
Adalat® CR (nifedipine)	x (week 3)						7
Pantoprazol Nycomed® (pantoprazole)		x (week 4)					7
Imodium® (loperamide)						x (week 4)	7

API active pharmaceutical ingredient, RH relative humidity

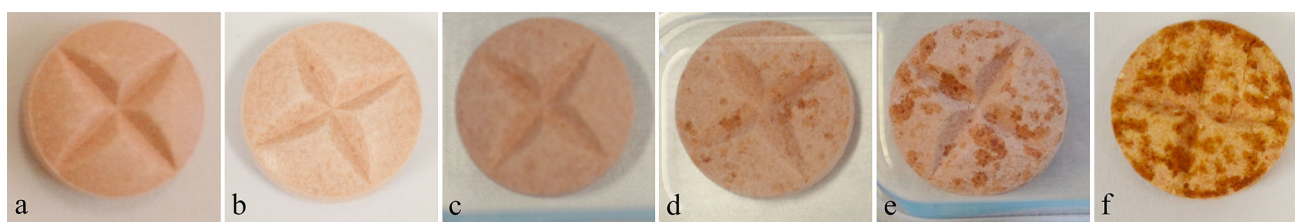


Fig. 2 Madopar® tablet at accelerated storage conditions and different storage durations: **a** before storage, **b** control after 4 weeks, **c** repackaged in Pharmis® after 1 week, **d** 2 weeks, **e** 3 weeks, and

f 4 weeks. Mottling of tablets started after 1 week of storage at accelerated conditions and intensified clearly until week 4



Fig. 3 Adalat® CR after 3 weeks of storage at accelerated conditions. A yellow watery drop is visible at the perforation of the membrane-controlled osmotic system

Discussion

According to *The International Pharmacopoeia* [17], evidence of physical instability of oral solid medicines is given by the following criteria: excessive powder or pieces of tablets in the container, fusion, appearance of crystals, discoloration, swelling, mottling, chipping, capping, or cracking. Due to our setting being independent of bulk ware, we excluded the criterion “fusion” and summarized the criterion “powder or pieces of tablets” into “crushing”. Thus, eight visual criteria were derived. We assumed that

rough surface, chipping, cracking, capping, mottling, discoloration, swelling, and crushing may serve as a screening method for visual instability of oral solid medicines. We selected critical tablets and capsules that were not recommended for repackaging to test the usefulness of the criteria. After the repackaging into MCA and storage at accelerated conditions (40 °C, 75% RH), we were able to detect swelling, cracking, crushing, discoloration, and rough surface through, e.g. leaking of fluid, and thus proved the criteria to be valid to detect visual alteration.

When community pharmacists prepare MCA to help patients manage and ultimately take their polypharmacy, they can consult existing guidelines on the process of repackaging that state, for example, to exclude hygroscopic formulations such as effervescent tablets [9]. Few stability studies exist for specific medicines and storage conditions [3]. Unfortunately, the stability of repackaged medicines, i.e. the beyond-use date of medicines outside their original packaging, is not systematically available. In the USA, stability of medicines in patient customized packaging is taken for granted for 60 days, and the Danish Medicines Agency allows 28 days beyond-use date. When Danish marketing authorization holders apply for approval of an extended storage period, they must simulate worst-case storage conditions, i.e. the medicine is stored outside the

original packaging at 25 °C and 60% RH in a single layer that does not protect against light and moisture [23]. As a consequence, pharmacists and patients who repackage medicines in MCA have a lack of information and mostly rely on personal experience or judgment.

The eight visual criteria can serve as a screening method for potential unsuitable medicines for repackaging. Observations of alterations may lead to exclusion of repackaging of these medicines or to restrictions in storage duration.

Surprisingly, only seven among the selected 24 critical medicines showed alterations of appearance after repackaging into a common MCA and storage at accelerated conditions, with Madopar[®] (levodopa/benserazide) showing the most and the fastest alterations. The reasons for alterations are manifold and lay predominantly in the peculiarity of every medicine, which is given by its API and its formulation, together with the excipients and the production process [8]. As a consequence, brands declared as critical medicines in the Danish or English markets might have identical API as their counterparts in Switzerland, but different excipients and thus different composition and different stability properties. Moreover, a critical API such as an oxygen-sensitive compound might have been processed so that the final medicine is oxygen resistant and the commercially available product is no longer critical. Finally, with the emergence of generic products, the extrapolation from one brand to another is inappropriate, and the testing of every single medicine seems unavoidable. Under these conditions, the visual criteria represent a pragmatic approach for screening for unsuitability for repackaging with high feasibility in the daily practice of pharmacists.

Not surprisingly, the most frequent observed alterations were swelling and cracking resulting from water uptake of disintegrants [24]. Solid oral formulations such as immediate release tablets must contain excipients that enable disintegration in the stomach with the presence of fluid. Consequently, moisture represents the main risk for alterations of repackaged medicines, which can finally lead to crushing when extracting the tablets from the compartment with pressure. Different climatic zones in the world were defined with corresponding long-term stability testing conditions [25], illustrating the importance of the effect of humidity on degradation and disintegration of the medicine: this factor can lead to a change in dissolution and hence bioavailability [8]. It is also conceivable that the presence of moisture can lead to a higher tendency to stick to the MCA or stick together, especially for film-coated tablets. The sticking and finally detaching of tablets can lead to a disruption of the film and a loss of functionality.

We observed no alteration of appearance after 4 weeks at room temperature for medicines repackaged in Pharmis[®]

multidrug punch cards. As expected, half and whole tablets retained the same appearance. Thus, visual integrity seems guaranteed by this MCA at room temperature. However, physical or chemical stability may be impacted. A review article summarized stability studies performed with sensitive APIs [3]. Chemical stability was tested with the determination of the API concentration by high performance liquid chromatography after storage of the medicine in MCA. At room temperature, chemical stability was met for tablets containing APIs that were moisture sensitive, light sensitive, and oxygen sensitive after storage for 1 week (aspirin dispersible tablet) and for at least 4 weeks (all others). Physical tests were partly unmet for atenolol, aspirin, clozapine, and sodium valproate (immediate release tablets). The authors concluded that alterations in appearance and physical instability were not associated with chemical degradation in the tested medicines. A similar study performed with moisture-sensitive omeprazole enteric-coated hard capsules confirmed the chemical stability after repackaging and storage up to 60 days at 25 °C and 60% RH [26]. However, even when the literature has shown that specific APIs are chemically stable despite the dosage form being physically or visually unstable after storage, extrapolation of these findings to all medicines is uncertain. Further studies are also needed to evaluate the clinical impact of the visual and physical changes of medicines after repackaging and storage at room temperature. However, given that medicines in the USA are usually delivered after bulk repackaging by health care professionals and that the latest safety alert concerning repackaging was in 2013 (dabigatran capsules [27]), it seems valid to recommend a beyond-use date up to 4 weeks, as does the Danish Medicines Agency.

An unexpected chipping of tablets was observed with SureMed[™] punch cards during storage at room temperature. Tablets stuck on a small strip of glue that remained after the closing. After precautionous shaking to release the tablets, chipping resulted for eight medicines, predominantly film-coated medicines. Since chipping only occurred after tablets had stuck to the glue, we concluded that the glue caused the chipping. Because the alteration of the surface of modified release tablets such as enteric-coated tablets can affect its dissolution and ultimately efficacy, and because residues of glue are inherent to the process of cold-sealing, the SureMed[™] device seems less advisable for daily practice. Related to this consideration, a recent study showed enteric-coated tablets of sodium valproate with a compromised integrity after 8 days of storage in MCA at accelerated conditions, denoting probable physical stability issues with enteric-coated tablets [28].

It is obvious that MCA cannot provide the same protection from environmental conditions (such as moisture) as the manufacturer's packaging, which must protect the

medicine until the expiration date. As expected, the self-produced triplex blister protected all medicines, and no alterations were observed. However, elevated costs hinder its use in daily practice. Material with a high barrier against water vapor transmission could be indicated for highly sensitive APIs. Thanks to its low price and nontoxic properties, PVC is a very common repackaging material. Although it has very little or no barrier against moisture [21], its combination with cardboard and aluminum in the Pharmis® punch card seems adequate to protect medicines from visual alteration for up to 4 weeks.

This study has several strengths. First, we selected accelerated conditions (40 °C, 75% RH) that could be experienced by patients during summer at “home conditions” even though rarely in Switzerland. Second, we chose critical medicines not recommended for repackaging with the purpose of provoking alterations. We observed visual alteration in 29% of medicines at accelerated conditions (seven out of 24), which was less than expected. However, the observed alterations confirmed that the eight criteria we had chosen can detect visual alterations. Third, physico-chemical analysis of repackaged medicines is not feasible in community pharmacies. Therefore, the eight criteria we selected represent a simple screening method to test repackaged medicines in MCA in practice.

We acknowledge some limitations. First, we did not perform chemical analysis, and consequently, possible chemical degradation of the investigated tablets and capsules (e.g. hydrolysis, oxidation) cannot be excluded. Second, we did not test physical stability parameters such as uniformity of mass, hardness or friability, which can have an impact on dissolution or ultimately bioavailability. However, according to the World Health Organization, visual alterations can give evidence of physical instability. Third, we investigated four tablets and capsules per medicine. *The International Pharmacopoeia* [17] mentions unpacking of at least 20 tablets for visual inspection. However, we did not aim to validate batches of tablets with a standardized method, but aimed to test the feasibility of visual criteria. Thus, we selected four tablets or capsules for pragmatic reasons and took into account that we could not perform statistical tests. Nevertheless, comparison with controls enabled us to detect alteration. Fourth, we did not test the influence of light. However, controls and repackaged medicines were both stored under exclusion of light, enabling us to compare results. Fifth, the additional criterion “fusion of tablets” mentioned in *The International Pharmacopoeia* was excluded for our study because we repackaged one tablet or capsule per compartment. Fusion of tablets should, however, be added to a screening method designed for tablets and capsules repackaged together in compartments of an MCA.

Conclusion

In summary, MCA are indispensable tools for patients with polypharmacy. The professional filling of MCA in community pharmacies is common practice in many countries and follows general advice for repackaging processes. In the absence of specific stability data, the eight criteria rough surface, chipping, cracking, capping, mottling, discoloration, swelling, and crushing can serve as a screening method to detect visual alteration of repackaged medicines in practice. A national website could collect and give access to information about observed alterations and help health care professionals decide which medicine to repack and for how long. It could also help future research to select critical medicines for stability studies.

Acknowledgements We thank Barbara Kursawe (CEO Pharmis GmbH, Beinwil am See) and Markus Meier (CEO Medifilm AG, Oensingen) for sharing their experience in repackaging of medicines.

Author contributions All authors contributed to the conception and planning of the work or the acquisition, analysis, and interpretation of the data. They critically revised the manuscript for important intellectual content and approved the final submitted version of the manuscript.

Compliance with Ethical Standards

Funding This study was funded by the University of Basel and University of Applied Sciences and Arts Northwestern Switzerland (investigator-initiated research).

Conflict of interest Valerie Albert, Michael Lanz, Georgios Imanidis, Kurt E. Hersberger and Isabelle Arnet declare that they have no conflict of interest.

Open Access This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Hersberger KE, Boeni F, Arnet I. Dose-dispensing service as an intervention to improve adherence to polymedication. *Expert Rev Clin Pharmacol*. 2013;6(4):413–21. doi:[10.1586/17512433.2013.811829](https://doi.org/10.1586/17512433.2013.811829).
2. Haywood A, Llewelyn V, Robertson S, et al. Dose administration aids: pharmacists' role in improving patient care. *Australas Med J*. 2011;4(4):183–9. doi:[10.4066/AMJ.2011693](https://doi.org/10.4066/AMJ.2011693).
3. Haywood A, Glass BD. Evidence of stability of medicines repackaged in compliance aids: a review. *Curr Drug Saf*. 2016;11(1):69–77.
4. Gilmartin JF, Raimi-Abraham BT, Jani Y, et al. Taking the guesswork out of supplying multicompartment compliance aids:

- do pharmacists require further guidance on medication stability? *Int J Pharm Pract.* 2015;23(5):367–9. doi:10.1111/ijpp.12183.
5. Haywood A, Mangan M, Glass B. Stability implications of repackaging paracetamol tablets into dose administration aids. *J Pharm Pract Res.* 2006;36(1):25–8.
 6. U.S. Food and Drug Administration. Draft guidance. Expiration dating of unit-dose repackaged drugs: compliance policy guide. May 2005. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070278.pdf>. Accessed 9 Dec 2015.
 7. USP-NF. United States Pharmacopeia and National Formulary (USP39-NF34), Second Supplement. The United States Pharmacopeial Convention Rockville, MD. 2016. p. Chapter 1136.
 8. Guo Y. Impact of solid-state characteristics to the physical stability of drug substance and drug product. In: Ed Huynh-Ba K, editor. *Handbook of stability testing in pharmaceutical development: regulations, methodologies, and best practices.* New York: Springer Science + Business Media; 2009. p. 241–61.
 9. Royal Pharmaceutical Society. Improving patient outcomes - the better use of multi-compartment compliance aids. 2013. <https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Support/toolkit/rps-mca-july-2013.pdf>. Accessed 10 Aug 2015.
 10. Pharmaceutical Society of Australia. Dose administration aids service - guidelines and standards for pharmacists. 2007. <https://www.psa.org.au/download/community-pharmacy-agreements/dose-administration-aids/dose-administration-service-guidelines.pdf>. Accessed 10 Aug 2015.
 11. Bundesministerium für Gesundheit Österreich. Neuverblisterungsbetriebsordnung. 2011. <https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=20007067>. Accessed 4 Sept 2015.
 12. Consejo General de Colegios Oficiales de Farmacéuticos. Sistemas personalizados de dosificación—Procedimiento Normalizado de Trabajo. 2013. http://www.portalfarma.com/profesionales/organizacioncolegial/profesionfarma/planfuturofarmaciacomunitaria/Documents/2013_10_05_Documento_Procedimiento_SPD.PDF. Accessed 4 Sept 2015.
 13. Bundesapothekerkammer Deutschland. Patientenindividuelle manuelle Neuverpackung von Fertigarzneimitteln für bestimmte Einnahmezeitpunkte. Leitlinie zur Qualitätssicherung. 2014. <https://www.abda.de/themen/apotheke/qualitaetssicherung/leitlinien/leitlinien0/>. Accessed 10 Aug 2015.
 14. Danish Medicines Agency. Dosis Dispensering Laegemidler Drug Niveau. <http://sundhedsstyrelsen.dk/en/medicines/sale/pharmacies/dose-dispensing>. Accessed 14 Oct 2015.
 15. UKMi. UK Medicines Information Medicines Compliance Aid Database. <http://www.ukmi.nhs.uk/applications/mca/>. Accessed 14 Oct 2015.
 16. Kantonsapothekervereinigung Schweiz. Regeln der Guten Abgabepaxis für Heilmittel—cGAP. 2009. http://www.kantonsapotheker.ch/fileadmin/docs/public/kav/posipapiere/regeln_der_guten_abgabepaxis_cgap_v1_maerz2010_d.pdf. Accessed 10 Sept 2015.
 17. World Health Organization. The International Pharmacopoeia. 5th ed. 2015. <http://apps.who.int/phint/en/p/about/>. Accessed 21 Apr 2016.
 18. Church C, Smith J. How stable are medicines moved from original packs into compliance aids? *Pharm J.* 2006;276(7384):75–81.
 19. Snape TJ, Aastles AM, Davies J. Understanding the chemical basis of drug stability and degradation. *Pharm J.* 2010;285(7622):2.
 20. Allemann SS, Bornand D, Hug B, et al. Issues around the prescription of half tablets in Northern Switzerland: the irrational case of quetiapine. *Biomed Res Int.* 2015;2015:602021. doi:10.1155/2015/602021.
 21. Massey LK. Permeability properties of plastics and elastomers: a guide to packaging and barrier materials. 2nd ed. New York: Plastics Design Library/William Andrew Publishing; 2003.
 22. U.S. Food and Drug Administration. ICH guidance for industry Q1A (R2) stability testing of new drug substances and products. 2003. Accessed 18 Nov 2015.
 23. Danish Medicines Agency. Application for extended storage period in connection with dose dispensing. 2012. <http://laegemiddelstyrelsen.dk/en/pharmacies/pharmacies/dose-dispensing/extended-storage-period>. Accessed 14 Oct 2015.
 24. Waterman KC, MacDonald BC. Package selection for moisture protection for solid, oral drug products. *J Pharm Sci.* 2010;99(11):4437–52. doi:10.1002/jps.22161.
 25. World Health Organization. Annex 2—stability testing of active pharmaceutical ingredients and finished pharmaceutical products. 2009. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1F/Stability_Guideline_WHO.pdf. Accessed 26 Feb 2017.
 26. Loscertales HR, Modamio P, Lastra CF, et al. Can we repackaging omeprazole capsules into multicompartiment compliance AIDS? *J Am Geriatr Soc.* 2014;62(3):569–70. doi:10.1111/jgs.12725.
 27. Therapeutic Goods Administration Australian Government. Dabigatran (Pradaxa) and risk of bleeding: information for health professionals—updated safety information. 2013. <https://www.tga.gov.au/alert/dabigatran-pradaxa-and-risk-bleeding-information-health-professionals>. Accessed 8 Aug 2016.
 28. Redmayne N, Robertson S, Kockler J, et al. Repackaged sodium valproate tablets—meeting quality and adherence to ensure seizure control. *Seizure.* 2015;31:108–11. doi:10.1016/j.seizure.2015.07.007.