



REVIEW

Stability of chronic medicines in dosage administration aids. How much have been done?



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KEYWORDS

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Abstract Background: The prevalence of chronic diseases is increasing in Asia, therefore compliance to the medications is of utmost importance to slow disease progression and improve outcomes. Dosage administration aids (DAAs) serve as important tool to improve the compliance of patients. However, there is a dearth of data on the stability of chronic medications in DAAs. Furthermore, data presented by our Western counterparts may not be applicable to us because of our extreme humidity and temperature. In this study, we aim to summarize the data available in the literature on the stability of chronic medications in DAA.

Methods: We performed a literature search using electronic databases and related keywords.

Results: In total, 24,336 articles were retrieved and 21 articles were found to be relevant to our topic. This commentary stratified drugs according to their treatment categories and key stability conclusions, DAA and conditions used and recommendations were presented.

Conclusion: Due to the lack of specific data, pharmacists have to exercise their professional judgment with the help from professional guidelines when using DAA in repackaging medication. Manufacturers and regulators can play a greater role in filling the gap needed to provide pharmacists with necessary information to fulfill their function.

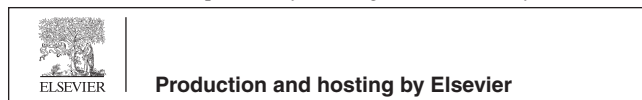
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1. Introduction

Prevalence of chronic diseases is rising in Asia and compliance to medication is necessary to ensure slowing of disease progression as well as improving healthcare outcomes (Tan, 2011). In Asia, the number of people needing dosage administration aid (DAA) to assist in medication administration is increasing (Brown and Bussell, 2011). Reminder packaging, dosette, do-set, multi-compartment compliance aids (MCAA) or compliance aid all refer to DAA. DAA is defined as a device that assists patients in managing their medicines by having patients, caregivers, or pharmacists, to arrange individual doses according to their prescribed dose regime throughout the day for certain duration of time. There were many studies that had shown favorable outcomes when patients used DAA to help them improve their adherence to medications (Rivers, 1992). Studies had shown that DAA helped to reduce medication error rates during medication administration in nursing homes, useful to simplify patients' medication regime and may overcome barriers to adherence such as difficulties in reading pharmacy labels and opening medication containers (Roughhead et al., 2003; Cramer, 1998; Kippen et al., 2005; van Eijken et al., 2003). There were reports showing that DAA use helps to improve clinical outcomes like glycemic, blood pressure and lipids control (Simmons et al., 2000; Lee et al., 2006).

In Asia, especially Singapore, the weather is extremely humid and of high temperature all year round. An average relative humidity (RH) in Singapore can range from 80% to 100%, while temperature ranges from 25 to 30 °C (Pinto et al., 2011). World Health Organization's stability guidelines stated that certain Asian countries have long-term stability conditions of 30 °C and 75% RH (Bott and Oliveira, 2007). This differs greatly from the conditions of the Western countries and therefore, may need a different set of stability data so that pharmacists can determine if a particular drug will be suitable to be stored in a DAA. Repackaging of a medicine requires removal from its primary packaging, thus invalidates the stability guarantee by the manufacturer. Manufacturers also tend to discourage repackaging because there is little data to support this action (Church and Smith, 2006). As far as we know, there are very limited studies on the stability of drugs when repackaged into a unit dosing system and this is especially so in the context of Asia. With the increase in the prevalence of chronic diseases in Asia, data for repackaging of medicine into DAA will be essential so that the medicine manufactured will be of suitable physical, chemical and photo stabilities.

Therefore, the aim of this commentary is to provide readers a summary of the types of stability data available. Manufacturers and regulators, especially that of Asian countries, will be able to conduct more region specific stability studies to fill the gap needed to provide the pharmacists with essential data to support their operations. In turn, the patients' compliance can be improved, disease progression can be slowed and improved healthcare outcomes can be delivered.

2. Methods

An electronic database search was performed using Pubmed, Google Scholar, Web of Science, Scopus and ScienceDirect. Hand searches were also conducted using the references of related articles. Searches were current as of June 2013. The keywords utilized were (“dosage administration aid” OR “reminder packaging” OR dosette OR do-set OR repackaged OR “compliance aid”) AND (stability OR duration OR characteristics OR degradation OR “color changes”). There were no exclusion criteria due to the dearth of literature on the topic and all related articles were reviewed.

3. Results

3.1. Search results

A total of 24,336 articles were retrieved from our searches. Twenty-one articles were found to be relevant to our topic.

3.2. Cardiovascular medications

Studies were found for 4 cardiovascular drugs, namely metoprolol, atenolol, frusemide and aspirin. A summary can be found in Table 1.

Metoprolol is a beta-blocker used to treat several diseases of the cardiovascular system such as hypertension. From the study published by Yang et al., controlled and accelerated test conditions are 25 °C/60% RH and 40 °C/75% RH, respectively. The DAA of interest was the United States Pharmacopoeia (USP) Class A unit dose blister pack. Tablets were stored at accelerated and controlled conditions for 52 weeks and 12 weeks respectively. USP standards for chemical stability were met for all conditions and packaging. However, water uptake and tablet hardness increased for repackaged tablets stored in accelerated conditions (Yang et al., 2010).

The next drug of concern is Atenolol, which is another beta-blocker. From the study published by Chan et al., the tablets were stored at different containers and subjected to 4 storage conditions. They were stored for 4 weeks in the original blister pack at controlled condition, in 28 chambers plastic MCCA in both controlled and accelerated conditions and in petri dish at controlled conditions. Results showed that USP standards for chemical stability were met for all packaging and storage conditions. However, changes were observed in disintegration, dissolution and physical appearance for the MCCA at accelerated conditions. Therefore, the authors recommended that DAA might not be suitable for countries with hot and humid conditions (Chan et al., 2007). In another study atenolol was investigated on, 2 different atenolol brands co-stored with aspirin at controlled and accelerated conditions using opaque and transparent DAA. The DAA of interest was Dosett® Maxi and Medidos®. Results showed that USP standards for chemical stability were met for all storage and packaging conditions. However, changes in tablet hardness were observed in a particular brand of atenolol in controlled conditions with higher changes in the transparent DAA. Also, co-storage at accelerated conditions resulted in non-coated aspirin tablets had a change in appearance. Therefore, the authors concluded that multi-factorial experimental conditions, such as brand of the drug, type of DAA used and co-storage in different storage conditions might affect the physical stability of the drug (Donyai, 2010).

Furosemide is a diuretic that is used for symptomatic relief in fluid overload patients. There were 2 studies retrieved that had done stability studies in DAA for furosemide. One study was conducted by Asafu-Adjaye et al. with furosemide being stored in the original high-density polyethylene (HDPE) bottle and USP Class A unit dose blister pack at both controlled and accelerated conditions. Tablets were stored for 52 weeks at controlled conditions and 12 weeks at accelerated conditions. Results showed that chemical stability was met for all packaging and storage conditions. In terms of physical stability, there were no differences seen for loss on drying and dissolution rates and no change in tablet hardness across all conditions. There was also no difference in the physical appearance of the tablets and no discoloration was observed for both the original and repackaged product stored in different conditions. However, the authors concluded that these results were only applicable to tablets using low moisture excipients, such as magnesium stearate, lactose monohydrate and corn starch, and cannot be generalized to tablets using hygroscopic excipients (Asafu-Adjaye et al., 2011). Another study involving furosemide used Webster-Pak® as DAA of interest. The repackaged tablets were stored for 8 weeks at controlled conditions while protected from light or at home conditions exposed to either a standard 60 W tungsten light bulb with indoor indirect daylight or at pharmacy conditions exposed to a fluorescent lighting with indoor indirect sunlight. Results showed that chemical and physical stabilities were confirmed at all storage conditions. However, progressive yellow discoloration was observed when stored in the simulated pharmacy conditions. Therefore authors had proposed that repackaged tablets should be protected from light by placing in a light-protecting sleeve (Bowen et al., 2007).

Aspirin is an antiplatelet used in many cardiovascular diseases as a primary or secondary prevention medication. There were 2 studies retrieved regarding stability studies of aspirin in DAA. One study by Mylrea et al. used halved tablets of aspirin stored in controlled, accelerated, natural variations in daylight

exposure and internal temperature fluctuations (23–26 °C at 45–60% RH) and refrigerated conditions (–8 to 2 °C) in dosette boxes for 1 week. Aspirin content did not meet the British Pharmacopoeia (BP) standards for the accelerated condition and physical appearance compromised for tablets stored in dosette boxes and in accelerated conditions. Also, when split tablets were used, the degradation of aspirin was comparable to the whole tablet (Mylrea et al., 2012). Another study by Yamazaki et al. used experimental conditions of 27 °C with 55% RH or 65% RH in a unit dose packing for 12 weeks. Results showed that color changes occur at 65% RH and the color change and rate of decomposition become higher as time passed. Therefore, authors concluded that maintenance of RH to 55% or less by storing in a plastic or aluminum pack with drying agent may be needed to maintain the quality of product (Yamazaki et al., 2010).

3.3. Central nervous system medications

Studies were found for 4 neurological drugs, namely gabapentin, clozapine, carbamazepine and sodium valproate. A summary can be found in Table 2.

Gabapentin is used as an adjunct for seizures as well as for neuralgia management. A study by Gupta et al. that used controlled and accelerated conditions at 52 and 13 weeks respectively had shown that repackaged drug in a unit dose blister pack stored under both conditions showed significant increase in weight. There was no significant difference in terms of potency and level of degradation between the original and repackaged units. The authors concluded that Gabapentin in the original bottle and repackaged blister were stable up to one year under long term storage conditions and up to 3 months under accelerated conditions (Gupta et al., 2009).

Clozapine is an antipsychotic drug and is commonly used in the treatment of schizophrenia. Perks et al. conducted a study to investigate the stability of clozapine repackaged into Webster-Pak® at controlled and accelerated conditions for 12 weeks. Results showed that clozapine was physically and chemically stable for up to 6 weeks with no discoloration observed (Perks et al., 2012).

Carbamazepine is an anti-epilepsy and mood-stabilizing drug. A study by al-Zein et al. compared carbamazepine of different brands at varying conditions. Tegretol® and Tegral® were stored at 40, 50, and 60 °C at 75% RH for 6, 3 and 1 month(s), respectively. Tegretol® and Tegral® tablets were also removed from the original strip package and then placed into bottles. The tablets were then exposed to conditions of 97% RH at 40 °C for 5 min daily. The other brand, Finlepsin® was stored in a bottle and the bottle was opened to expose the tablets for 5 min daily at 40 °C or 25 °C at 97% RH for 1 month. Results showed that USP standards for chemical stability were met for all packaging and storage conditions. Changes in dissolution rate were observed for Tegral® and Finlepsin® brands but not for Tegretol® brand. Therefore, the authors concluded that the effect of storage was largely formulation dependent with factors such as sensitivity to moisture of different excipients may play a role in tablet performance (Al-Zein et al., 1999).

Another anti-epileptic medication that was investigated on was sodium valproate. A study conducted by Llewelyn et al. compared controlled and accelerated conditions for a heat-sealed DAA for 56 days. Results showed that chemical

Table 1 Summary of cardiovascular drugs' stability in dosage administration aids.

Drug	DAA	Conditions (weeks)	Conclusions for stability	Recommendations	References
Metoprolol tartrate	USP Class A unit dose blister pack	Controlled (52) Accelerated (12)	<ul style="list-style-type: none"> • USP standards for chemical stability met for all packaging and storage conditions • Water uptake and tablet hardness increased for repackaged tablets stored in accelerated conditions 	NA	Yang and et al. (2010)
Frusemide	USP Class A unit dose blister pack	Controlled (52) Accelerated (12)	<ul style="list-style-type: none"> • USP standards for chemical stability met for all packaging and storage conditions • No change for loss on drying, tablet hardness and dissolution rates for all packaging and storage conditions • Increase in tablet hardness for repackaged tablets stored in accelerated conditions 	Results can only be extrapolated to non-hygroscopic excipients.	Asafu-Adjaye and et al. (2011)
	Webster-Pak®	Control; Home; Pharmacy (8)	<ul style="list-style-type: none"> • Physical and chemical stabilities were confirmed for all storage conditions • Progressive yellow discoloration was observed for the tablets stored in the simulated pharmacy condition, starting from week 1 	Frusemide tablets repackaged into DAA should be protected from light in the pharmacy and in patients' homes by placing the DAA into a light-protecting sleeve and/or stored away from light.	Bowen and et al. (2007)
Atenolol	28 chamber plastic MCAA	Controlled; Accelerated (4)	<ul style="list-style-type: none"> • USP standards for chemical stability met for all packaging and storage conditions • Changes in disintegration, dissolution and physical appearance were observed for the plastic MCAA at accelerated conditions 	Certain formulation of atenolol tablets is not suitable for storage in hotter, humid weather	Chan and et al. (2007)
Atenolol (2 different brands) co-storage with aspirin	Dosett® Maxi, Medidos®	Controlled; Accelerated (4)	<ul style="list-style-type: none"> • USP standards for chemical stability met for all packaging and storage conditions • Changes in tablet hardness in controlled conditions were observed for Alpharma, with storage in Dosett® exerting a greater impact than storage in Medidos® • Co-storage at elevated temperature and humidity also impacted on the appearance of non-coated aspirin tablets 	Multi-factorial experimental conditions impacted differently on the physical stability of tablets stored within MCCAs	Donyai (2010)
Aspirin	Dosette boxes	Controlled; accelerated; In use condition; Refrigerated (1)	<ul style="list-style-type: none"> • Only in accelerated storage condition, the aspirin content did not meet BP specifications • The split tablets did not display any additional aspirin degradation when compared to the whole tablets under the same conditions • Physical appearance compromised for dosette boxes and accelerated conditions 	NA	Mylrea and et al. (2012)
	Unit dose packing	27°C/55% RH; 27 °C /65% RH (12)	<ul style="list-style-type: none"> • Prevents color changes and preserves the quality by maintaining the humidity as 55% • It was revealed that the color changes became greater and the decomposition rate became higher as time passed 	To maintain the humidity as 55% or less and storage with drying agent in a plastic or aluminum pack	Yamazaki and et al. (2010)

Abbreviations: Relative humidity (RH), United States Pharmacopoeia (USP), British Pharmacopoeia (BP), multi-compartment compliance aid (MCAA), dosage administration aid (DAA), nonapplicable (NA). Conditions: controlled (25 °C /60% RH), accelerated (40 °C/75% RH), in use (23–26 °C/45–60% RH), refrigerated (2–8 °C).

Table 2 Summary of central nervous system drugs' stability in dosage administration aids.

Drug	DAA	Conditions (weeks)	Conclusions for stability	Recommendations	References
Clozapine	Webster-Pak [®]	Controlled; accelerated (12)	<ul style="list-style-type: none"> Chemically and physically stable for up to 6 weeks Discoloration of tablet not observed USP standards for chemical stability met for all packaging and storage conditions 	NA	Perks and et al. (2012)
Carbamazepine of different brands	Glass bottle	40 °C/97% RH (4)	<ul style="list-style-type: none"> Changes in the dissolution rate were observed for the Tegral[®] and Finlepsin[®] but not Tegretol[®] brand 	Effect of storage is largely formulation dependent with factors such as sensitivity to moisture of different excipients used and the moisture content	Al-Zein et al. (1999)
Gabapentin	Unit dose blister strips	Controlled (52) Accelerated (13)	<ul style="list-style-type: none"> Repackaged drug product stored under all conditions showed significant increase in weight No significant differences in potency between the original and repackaged drug products were detected Lactam degradation product levels were within the acceptable level for all storage conditions 	NA	Gupta and et al. (2009)
Sodium valporate	Heat sealed DAA	Controlled; accelerated; refrigerated (56 days)	<ul style="list-style-type: none"> Chemical stability observed at all the storage conditions Variation in weight observed in accelerated conditions Variation in dissolution observed for all storage conditions 	Since tablets stored in compliance aid may be exposed to uncontrolled temp and humidity during use in patients' home, it is inappropriate to repackage sodium valporate in a DAA	Mangan and et al. (2006)

Abbreviations: Relative humidity (RH), multi-compartment compliance aid (MCAA), dosage administration aid (DAA), non-applicable (NA). Conditions: controlled (25 °C/60% RH), accelerated (40 °C/75% RH), refrigerated (2–8 °C).

Table 3 Summary of other drugs' stability in dosage administration aids.

Drug	DAA	Conditions (weeks)	Conclusions for stability	Recommendations	References
Mesalazine	Polyethylene laminated cellophane and glassine films	Controlled; refrigerated (4)	<ul style="list-style-type: none"> • 1% weight increase of the mesalazine tablets in controlled conditions • Changes in color occur in controlled conditions 	Mesalazine CR is not recommended for repackaging in one dose packaging due to discoloration and absorption of moisture	Harada and et al. (1999)
Mebeverine, mesalazine, sulphasalazine, dispersible aspirin	Venalink Monitored System [®]	Protected from light and heat (5)	<ul style="list-style-type: none"> • The 4 medicines remain stable in the Venalink[®] blister packs for at least 5 weeks. 	During normal handling, rupture of remaining tabs results in increased level of air and humidity. Advise patient to be careful when handling the blister pack and to store away from heat, light and humidity	Elmasry and et al. (2011)
Prochlorperazine	Webster-Pak [®]	Controlled; accelerated; in-use conditions with fluorescent light; in situ conditions with indirect daylight (8)	<ul style="list-style-type: none"> • BP standards were met for chemical and physical stabilities in all storage conditions • Progressive gray discoloration of the tablet observed from week 2 	Photodegradants may potentially lead to adverse effect. Pharmacists need patients to store it away from light, heat and humidity	Glass and et al. (2009)
Paracetamol	Webster-Pak [®]	Controlled; accelerated (12)	<ul style="list-style-type: none"> • BP standards were met for chemical and physical stabilities in all storage conditions 	Repackaged paracetamol offers sufficient protection against moisture and will remain stable for a reasonable period in use of approximately 6 weeks	Mangan and et al. (2006)

Abbreviations: Relative humidity (RH), multi-compartment compliance aid (MCAA), dosage administration aid (DAA), British Pharmacopoeia (BP). Conditions: controlled (25 °C/60% RH), accelerated (40 °C/75% RH), in use/in situ (23–26 °C/45–60% RH), refrigerated (2–8 °C).

stability was observed at all storage conditions. However, there was a variation in weight for accelerated conditions and a variation in dissolution for all storage conditions. Therefore, the authors recommended that it was inappropriate to repackage sodium valproate in a DAA.

3.4. Other medications

Studies were found for 5 other medications, namely mesalazine, mebeverine, sulphasalazine, prochlorperazine and paracetamol. A summary can be found in [Table 3](#).

Mangan et al. investigated on paracetamol, a commonly used drug over the counter pain medication. In the study, Webster-Pak® was the DAA of choice and the storage duration was 3 months. Results showed that repackaged paracetamol met BP standards for chemical and physical stabilities for both controlled and accelerated conditions. From their analysis, the author recommended that paracetamol is suitable for repackaging into a DAA for approximately 6 weeks ([Mangan et al., 2006](#)).

Prochlorperazine is an anti-emetic, usually used for the treatment of severe nausea and vomiting. A study by Glass et al. that used multi-dose Webster-Pak® as the DAA at controlled, accelerated, under fluorescent light and indirect day light for 8 weeks had shown that BP standards for chemical and physical stabilities were met for all storage conditions. However, progressive graying of the tablets was observed from week 2 onwards. Therefore, the authors recommended pharmacists to be wary of adverse effect from photodegradants and to protect the tablets from light, heat and humidity ([Glass et al., 2009](#)).

Mesalazine is an anti-inflammatory drug for treating ulcerative colitis. A study by Harada et al. used polyethylene laminated cellophane and glassine films as the container. They were stored in room conditions (22–25 °C at 50–70% RH with 350 lux fluorescence white light for 12 h or in darkness) and control (4 °C at 29% RH) for 4 weeks. Results showed that 1% weight increase in Mesalazine tablets were seen in room conditions accompanied by changes in color. The authors therefore concluded that the tablets were not appropriate for repackaging ([Harada et al., 1999](#)).

The last study done by Elmasry et al. involved co-storing mebeverine, mesalazine, sulphasalazine and aspirin together and assessing their stability. The Venalink Monitored System® was used as the DAA and protected from heat and light for 5 weeks. Results showed that the 4 medications remain stable for up to 5 weeks in this DAA. However, the authors cautioned that the handling method might cause rupture of blister seals; affecting humidity and performance of tablet, therefore advised counseling for patients to help them better manage DAA ([Elmasry et al., 2011](#)).

4. Discussion

4.1. Chemical stability

From the studies retrieved, only 1 study showed chemical stability to be affected by repackaging in DAA. However, as not much had been done in this field, we cannot determine the exact extent and the clinical impact of chemical instability of chronic medications when repackaged into DAA.

4.2. Physical stability

From the studies retrieved, 7 studies indicated physical instability when drugs were repackaged into DAA. It was observed in some studies that an increase in moisture absorption could in turn lead to an increase in tablet hardness. The implications of increased tablet hardness are decreased dissolution and this affects the bioavailability of the medication. However, we are unable to conclude that repackaged medications stored in accelerated conditions will experience an increase in moisture absorption that will affect the tablet integrity. Physical stability is affected by multiple factors and some important factors to consider is the excipients that are used in the manufacture of the tablet, the moisture barrier properties of the storage device. Exploration into the type and amount of hygroscopic excipients used, type of DAA used, storage and handling conditions should be taken into account when deciding if a drug should be repackaged into DAA.

4.3. Recommendations for manufacturers and regulators

From the results of this literature search, it is evident that data on drug stability in DAA is clearly lacking in Asia. With the extreme humidity and temperature compared to our Western counterparts, we hope that all manufacturers, generic and branded, can allocate some resources so that stability data can be obtained and compliance to their medication can be improved.

Regulators in Asia can come together and request for stability data in compliance aid when drug companies seek to enter the individual markets. Licenses of previously approved drugs can be renewed only upon provision of crucial essential stability data.

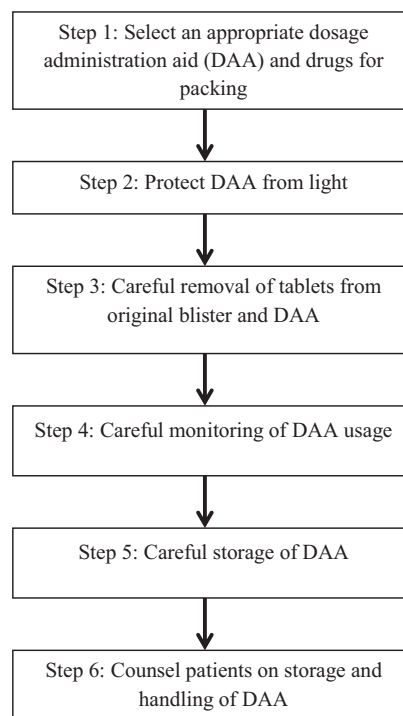


Figure 1 Steps to guide a pharmacist on how to handle cases involving repackaging of drugs into DAA.

4.4. Recommendations for pharmacists and patients

Pharmacists on the ground can gather information on which are the most popular and important medications so that focused studies can be done on those drugs. Hospitals should also come up with algorithms to guide pharmacists on how to select drugs to pack into DAA so as to maintain the stability of the medication. One algorithm that was proposed with the Australia Professional Practice Guideline in mind is shown in Fig. 1 (Australia PSo, 2010). Step 1 will be to select an appropriate DAA with appropriate permeability for the environment. There should also be considerations on whether the drugs being repackaged will be stable for the DAA. Step 2 will be to protect the DAA repackaged with medicine from light in the pharmacy or patients' house to maintain photo stability. This can be done by putting in suitable light-protecting sleeves such as black bags or foils. Step 3 involves careful removal of tablets from blister to prevent neighboring blisters from rupturing. Step 4 involves careful monitoring of the DAA packaging from repackaging, dispensing and when patient is using it. Step 5 involves choosing an appropriate location to store the product to minimize heat, humidity and light exposure while keeping away from children. Step 6 involves counseling the patient the right way of using and storing DAA.

5. Conclusions

A literature search on the stability of chronic drugs in DAA had been summarized. Manufacturers, regulators, and researchers should seek to close the gap by conducting stability studies on highly used and essential chronic medications in Asia. Pharmacists should adhere to professional guidelines and exercise their professional judgment while acknowledging the dearth in data when packing chronic medications into DAA.

References

- Al-Zein, H. et al, 1999. Effect of packaging and storage on the stability of carbamazepine tablets. *Drug Dev. Ind. Pharm.* 25, 223–227.
- Asafu-Adjaye, E.B. et al, 2011. Comparative stability study of unit-dose repackaged furosemide tablets. *Clin. Res. Regul. Aff.* 28, 38–48.
- Australia PSo. 2010. Professional Practice Standards. Version 4 Standard 7: Dose Administration Aids Service, ed.
- Bott, R.F., Oliveira, W.P., 2007. Storage conditions for stability testing of pharmaceuticals in hot and humid regions. *Drug Dev. Ind. Pharm.* 33, 393–401.
- Bowen, L. et al, 2007. Stability of frusemide tablets repackaged in dose administration aids. *J. Pharm. Prac. Res.* 37, 178–181.
- Brown, M.T., Bussell, J.K., 2011. Medication adherence: WHO cares? *Mayo Clin. Proc.* 86, 304–314.
- Chan, K. et al, 2007. Pilot study of the short-term physico-chemical stability of atenolol tablets stored in a multi-compartment compliance aid. *Eur. J. Hosp. Pharm. Sci. Pract.* 13, 60–66.
- Church, C., Smith, J., 2006. How stable are medicines moved from original packs into compliance aids? *Pharm. J.* 276, 75–81.
- Cramer, J.A., 1998. Enhancing patient compliance in the elderly. Role of packaging aids and monitoring. *Drugs Aging* 12, 7–15.
- Donyai, P., 2010. Quality of medicines stored together in multi-compartment compliance aids. *J. Clin. Pharm. Ther.* 35, 533–543.
- Elmasry, M.S. et al, 2011. Quantitative HPLC analysis of mebeverine, mesalazine, sulphasalazine and dispersible aspirin stored in a Venalink monitored dosage system with co-prescribed medicines. *J. Pharm. Biomed. Anal.* 54, 646–652.
- Glass, B. et al, 2009. Prochlorperazine tablets repackaged into dose administration aids: can the patient be assured of quality? *J. Clin. Pharm. Ther.* 34, 161–169.
- Gupta, A. et al, 2009. Stability of gabapentin 300-mg capsules repackaged in unit dose containers. *Am. J. Health Syst. Pharm.* 66, 1376–1380.
- Harada, Y. et al, 1999. Coloration and stability of the controlled-release mesalazine tablets repackaged by the one-dose packaging machine for dispensing. *J. Nipp. Hosp. Pharm. Assoc.* 25, 399–406.
- Kippen, S. et al, 2005. As time goes by: issues for older people with their medication use. *Australas. J. Ageing* 24, 103–107.
- Lee, J.K. et al, 2006. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA* 296, 2563–2571.
- Mangan, M. et al, 2006. Stability implications of repackaging paracetamol tablets into dose administration aids. *J. Pharm. Prac. Res.* 36, 25–28.
- Mylrea, M. et al, 2012. Stability of dispersible aspirin tablets repacked into dosette boxes. *J. Pharm. Prac. Res.* 42, 204–207.
- Perks, S. et al, 2012. Clozapine repackaged into dose administration aids: a common practice in Australian hospitals. *Int. J. Pharm. Pract.* 20, 4–8.
- Pinto, E. et al, 2011. The influence of climate variables on dengue in Singapore. *Int. J. Environ. Health. Res.* 21, 415–426.
- Rivers, P.H., 1992. Compliance aids-do they work? *Drugs Aging* 2, 103–111.
- Roughead, E.E. et al, 2003. Quality use of medicines in aged-care facilities in Australia. *Drugs Aging* 20, 643–653.
- Simmons, D. et al, 2000. Can medication packaging improve glycemic control and blood pressure in type 2 diabetes? Results from a randomized controlled trial. *Diabet. Care* 23, 153–156.
- Tan, D.A., 2011. Changing disease trends in the Asia-Pacific. *Climacteric* 14, 529–534.
- van Eijken, M. et al, 2003. Interventions to improve medication compliance in older patients living in the community: a systematic review of the literature. *Drugs Aging* 20, 229–240.
- Yamazaki, N. et al, 2010. The most appropriate storage method in unit-dose package and correlation between color change and decomposition rate of aspirin tablets. *Int. J. Pharm.* 396, 105–110.
- Yang, Y. et al, 2010. Comparative stability of repackaged metoprolol tartrate tablets. *Int. J. Pharm.* 385, 92–97.