

# Common medicines for PRN use: Stability considerations in DAAs

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After reading these articles, the learner should be able to:

- understand the factors affecting physical stability of metoclopramide and Coloxyl with Senna when packed in dose administration aids.

Competencies addressed:

1.2, 1.4, 1.5, 7.2, 8.1



Accreditation number: CX140001P

Upon successful completion of the associated assessment, this activity has been accredited for 0.5 hours of Group 2 CPD (or 1 CPD credits) suitable for inclusion in an individual pharmacist's CPD plan.

## METOCLOPRAMIDE AND COLOXYL WITH SENNA ARE FREQUENTLY REPACKAGED INTO DOSE ADMINISTRATION AIDS FOR PRN USE WITH IMPLICATIONS FOR STABILITY AND STORAGE OF MEDICINES.

**COMMONLY ASKED QUESTION:** If unused, can the 28-day expiry be safely extended and for how long?

### INTRODUCTION

Dose administration aids (DAAs), also known as multi-compartment compliance aids (MCCA or MCA) or monitored dosage systems (MDS), are designed to assist patients in managing their medicines by organising individual doses according to the prescribed dosing schedule.

A recent update by the Pharmaceutical Services Negotiating Committee (PSNC) (England and Wales)<sup>1</sup> has emphasised that whenever a decision is made to provide medicines in a DAA, it must: (i) be appropriate for the patient and (ii) preserve the integrity of the medicine.

A recent report by the Royal Pharmaceutical Society, *Improving patient outcomes: the better use of multi-compartment compliance aids*,<sup>2</sup> again highlighted that there is insufficient data in the published literature and no up-to-date authoritative resource that provides data on the stability of medicines, when stored outside of the manufacturer's original packaging.

Medicines are expected to meet their specification for identity, purity,

quality and strength throughout their defined storage period at specific conditions. Repackaging a medicine requires removal from its primary packaging, which invalidates the guarantee of stability by the manufacturer. Despite their widespread use, there is a lack of comprehensive data on the stability of drug products when repackaged into such devices. The authors have however previously reported on the stability of aspirin,<sup>3</sup> clozapine,<sup>4</sup> frusemide,<sup>5</sup> paracetamol,<sup>6</sup>—including for prn use,<sup>7</sup> prochlorperazine<sup>8</sup> and sodium valproate<sup>9</sup> when repackaged into DAAs and stored under a variety of conditions, including those of elevated temperature, light conditions and relative humidity (RH).

Repackaging medicines remains a challenge for pharmacists and they require appropriate in-use stability data to make an informed judgment as to the effect on the quality and safety of the repackaging process.

The stability data for six months storage of the antiemetic, metoclopramide (Maxolon and Pramin) and laxative, Coloxyl

(docusate sodium) with Senna, commonly repackaged into DAAs are presented.

### METHODS

Physicochemical studies were performed on 10mg metoclopramide tablets (Maxolon and Pramin), and physical stability studies on Coloxyl with Senna, (Aspen Pharma) repackaged in a DAA (WebsterPak). The DAAs were stored at controlled room temperature ( $25 \pm 1^\circ\text{C}$ ) and accelerated ( $40 \pm 1^\circ\text{C}$ ;  $75 \pm 1.5\%$  RH) conditions for a period of six months. The results were compared to a control, which was at time = 0 minutes ( $t = 0$ ) on removal from the manufacturer's pack.

Physical stability of the tablets, including weight uniformity, physical appearance, thickness, hardness, friability and disintegration rates, were evaluated according to the *British Pharmacopoeia* (BP) compendial requirements and the dissolution of metoclopramide according to the *United States Pharmacopoeia* (USP). The chemical stability was confirmed for the metoclopramide tablets using a validated high performance liquid chromatography (HPLC) method at time = 0, 1 month, 3 months and 6 months.

### RESULTS AND DISCUSSION

#### Stability of repackaged metoclopramide (Maxolon and Pramin)

The physical stability for repackaged metoclopramide (Maxolon and Pramin) was met under all storage

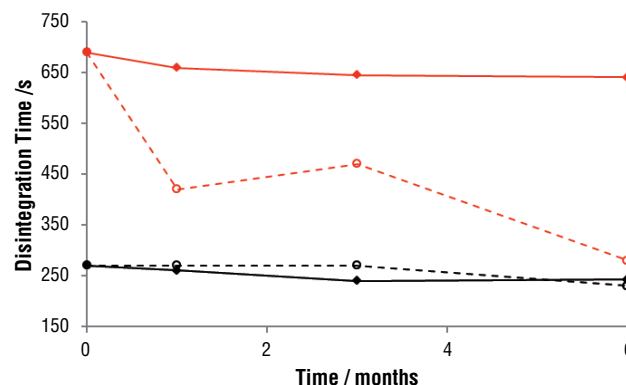
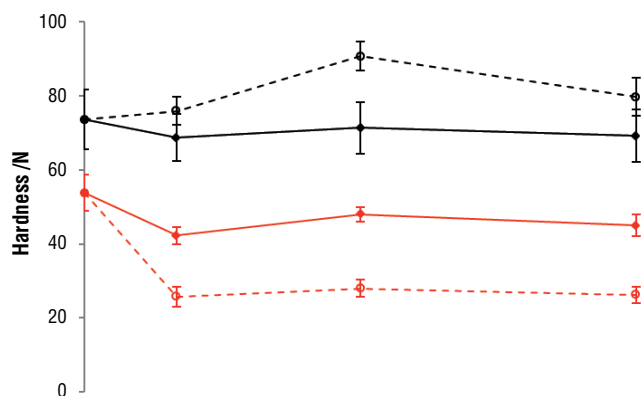


Figure 1: Effect of exposure to various storage conditions (◆ = 25°C, ○ = 40°C/75%RH) on the physical stability (hardness and disintegration) of metoclopramide tablets (Black = Maxolon, Red = Pamin) repackaged in DAAs. Values expressed for hardness as the mean ±95% confidence interval (n = 10); and disintegration as the time taken for six tablets to disintegrate.

conditions for a period of six months as follows:  
 (i) *Friability*—maximum loss of 1% of the tablet’s mass is acceptable;  
 (ii) *Disintegration*—all tablets disintegrated after 15 minutes;<sup>10</sup>

(iii) *Dissolution*—amount of metoclopramide in solution after 30 minutes is not less than 80% of the stated amount.<sup>10</sup>  
 Tablet hardness and disintegration data for the metoclopramide tablets

stored repackaged in DAAs, under controlled room temperature and accelerated conditions (40°C; 75%RH), are shown in Figure 1. Although for the Pamin tablets, a decrease in hardness under

accelerated conditions accompanied by a decrease in disintegration time was observed, these results for hardness and disintegration and also friability (0.31% loss) remained within compendial requirements.

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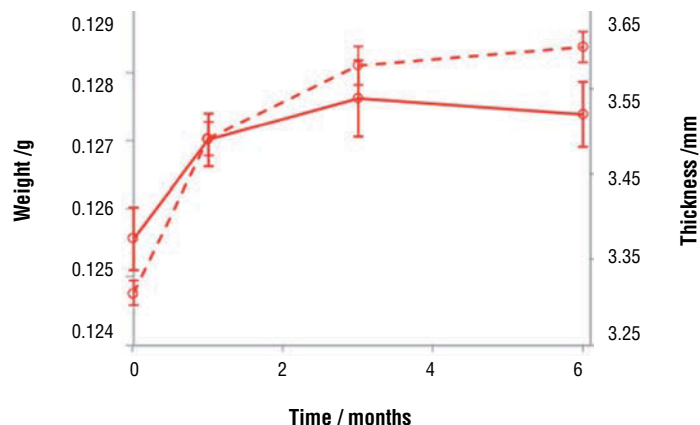


FIGURE 2: Effect of exposure to accelerated storage conditions (O = 40°C/75%RH) on the physical stability (weight = solid line; thickness = dotted line) of Pramin tablets repackaged in DAAs. Values expressed for weight ( $n = 20$ ) and thickness ( $n = 10$ ) as the mean  $\pm$  95% confidence interval.

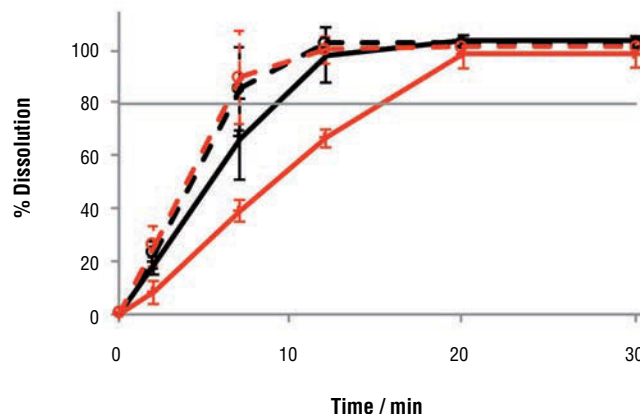


FIGURE 3: Dissolution rate profiles for repackaged Maxolon (Black) and Pramin (Red) at  $t = 0$  (solid line) and stored for six months at 40°C/75%RH (dotted line). Grey horizontal line shows the required dissolution (80%) of metoclopramide to be achieved at 30 minutes. Values expressed as the mean  $\pm$  95% confidence interval for six tablets.

No significant differences were seen in tablet weight and thickness of Maxolon and no organoleptic changes were observed for both brands over the storage period of six months. However, for Pramin, the change in weight and thickness over the six-month period was significant as shown in Figure 2, with most of that change occurring in the first month.

Dissolution rate profiles at  $t = 0$  (dissolution under controlled room temperature was similar to that at  $t = 0$ ) and six months under accelerated conditions for Maxolon and Pramin are shown in Figure 3, with the required 80% dissolution of the metoclopramide after 30 minutes for all tablets achieved.

Chemical stability results showed that the metoclopramide content was within the range (90–110% of labelled amount) specified in the BP monograph<sup>11</sup> for both brands of metoclopramide tablets (Maxolon and Pramin) under all storage conditions over a period of six months.

#### Stability of repackaged Coloxyl with Senna

Tablet hardness and weight uniformity data for repackaged Coloxyl (docusate sodium) with

Senna tablets, stored under controlled room temperature and accelerated conditions (40°C/75%RH), are shown in Figure 4. As shown in the graphs, an increase in weight under accelerated conditions is accompanied by a decrease in hardness, although these results remain within compendial requirements. This compliance with compendial requirements is also confirmed by the results for friability, with only a 0.02% weight loss after six months under accelerated conditions. No dissolution test for docusate

sodium tablets is described,<sup>12</sup> due to the sparingly soluble nature of docusate sodium in water.<sup>13</sup> Due to complexity of senna, a plant extract of senna glycosides, or sennosides containing a number of anthraquinone derivatives,<sup>13</sup> chemical analysis using HPLC was not performed.

#### CONCLUSION

The quality of the metoclopramide tablets (Maxolon and Pramin) was confirmed under both ambient and

accelerated conditions for a storage period of six months in a DAA that provides appropriate protection from air and moisture. The physical stability for Coloxyl with Senna tablets, in relation to weight uniformity, hardness and friability also complied with compendial requirements.

Metoclopramide hydrochloride, the active ingredient in Maxolon (supplied in a blister pack) and Pramin (supplied in an opaque white plastic bottle), is required to be stored protected from light in an airtight

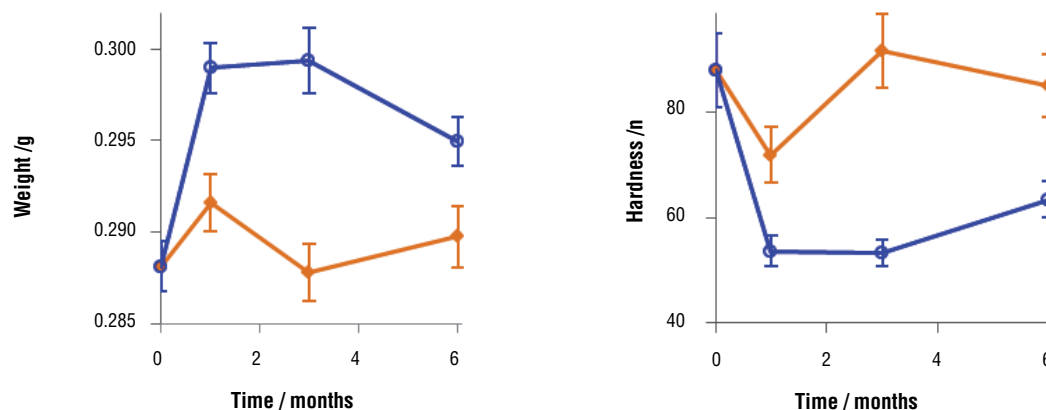


FIGURE 4: Effect of exposure to various storage conditions (Orange = 25°C, Blue = 40°C/75%RH) on the physical stability (weight uniformity and hardness) of Coloxyl with Senna tablets repackaged in DAAs. Values expressed for weight uniformity ( $n = 20$ ) and hardness ( $n = 10$ ) as the mean  $\pm$  95% confidence interval.

### RECOMMENDATIONS FOR REPACKAGING INTO DAAs

Store DAAs in a cool, dry place protected from light, for example inside lockable cabinets or medicines trolleys. Avoid high humidity areas such as bathrooms.

Monitor the integrity of the DAA throughout the usage period since DAAs may be subjected to a reasonable amount of handling and accidental rupture of the blister seals may occur, allowing tablets to be exposed to increased humidity and air.

Pharmacists must continue to use their professional judgement as part of individual patient assessment in deciding whether they should supply medicines in a DAA based on the benefits and risks to the individual patient.<sup>2</sup>

Pharmacists can play an important role in advising patients, carers and other members of the health care team on the stability of medicines and the importance of storing and using their medicines correctly.

container.<sup>13</sup> The Consumer Medicine Information (CMI) for both brands of metoclopramide states to 'keep your tablets in the bottle/pack until it is time to take them', and 'if you take the tablets out of the bottle/pack they may not keep well'.<sup>14,15</sup> For Coloxyl with Senna tablets, supplied in an opaque white plastic bottle, senna is required

to be protected from moisture and light,<sup>13</sup> while docusate sodium should be stored in an airtight container.<sup>13</sup>

This study provides new evidence of the stability of commonly repackaged medicines stored, beyond the 28-day expiry in a DAA affording suitable protection against air, moisture and light. ■

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