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9. Degree of hermeticity of a multicompartment compliance aid: Implications for the quality of professional pharmaceutical services

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Abstract. A multicompartment compliance aid (MCA) is a blister-type repackaging system that aims to facilitate drug administration and thereby increase patient adherence. One of the characteristics of the MCA that should be taken into account is the moisture permeability, since this atmospheric condition is one of the most important factors that can modify the stability of medicines. In the current paper we report the moisture permeability tests performed on a MCA according to the US Pharmacopeia. This information on the suitability of the device will help pharmacists implement a high-quality professional service.

Introduction

The scale of the problem posed by low levels of adherence to drug therapy represents a major concern for all health systems. A report published

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by the WHO indicates that in developed countries, 50% of patients who suffer from chronic conditions fail to comply; and in developing countries this figure is even higher [1].

Despite the fact that problems of adherence occur independently of the condition, type of patient and socioeconomic level, geriatric patients are more vulnerable to incorrect use of medicines; this is mainly due to a reduction in their functional capacity and the large number of drugs that they take long term [2]. According to Kendrick and Bayne [3], expected adherence to a treatment regimen for a person of advanced age who takes just one medicine is 65%; this is reduced to 54% when the patient takes four medicines; and it drops to below 7% as the number of medicines increases. In addition, the lack of adherence to the dosage schedule on the part of the geriatric patient is directly related to periods of hospitalisation [4]. Moreover, the current demographic situation, with a constantly increasing life expectancy, means that the incidence and prevalence of complex chronic conditions also increase, and it is these patients who consume large numbers of medicines [5]. Therefore, it is becoming ever more important to use tools and develop plans of action aimed at improving adherence and contributing to the increased safety, effectiveness and efficiency of drugs and of healthcare resources in general [6].

1. Multicompartment compliance aid

A multicompartment compliance aid (MCA), also called a monitored dosage system, is a blister-pack system into which drugs are re-packaged and which is used to organise all the solid medicines that a given patient takes over a week, following the prescribed dosage schedule. In accordance with the manufacturer's certificate, the MCA is safe, hygienic and made of innocuous materials that do not interact at all with the medicines. The MCA is a tool designed to facilitate the administration of medication and therefore to increase patient compliance, as well as to reduce drug administration errors. The Pharmaceutical Services Negotiating Committee, which represents community pharmacies in England and Wales, already recommends the use and monitoring of this type of pack for all patients with problems when it comes to taking their medication [7]. Similarly, in 2005, the Australian Government's Department of Health and Ageing, under the 4th Community Pharmacy Agreement, founded a specific MCA programme with the idea of reducing hospitalisations related to medication and improve treatment adherence in the population where it is required [8].

In Spain, Royal Decree Law 9/2011 of 19th August consisting of measures to improve the quality and cohesion of the national health system

[9] modified Section 1 of Article 84 of Law 29/2006 of 26th July regarding the guarantees and rational use of medicines and healthcare products [10]. The regulations pertaining to MCA use currently declaim: "In pharmacies, the pharmacists, being those responsible for the dispensing of medicines to citizens, will encourage compliance with the schedule established by the physician responsible for prescribing medicines to the patient, and will aid in treatment adherence through pharmaceutical care procedures that contribute to ensuring efficacy and safety. The pharmacist will also take part in a series of activities designed to enhance the rational use of medicines, in particular through informed dispensing to the patient. Once the medicine has been supplied, the pharmacist may provide monitored dosage systems to patients who ask for them, in order to improve treatment compliance, for those treatments and with the attendant conditions and requirements that the competent health authorities establish." In September 2012, the first guide to drug therapy adherence with MCA use was published under the coordination of the regional Council of Pharmaceutical Colleges in Catalonia [11]. More recently, in May 2013, at the national level the General Pharmaceutical Council approved distribution of the Standard MCA Working Procedure [12]. The elements necessary for the pharmacist in a community pharmacy to provide professional MCA service are defined in both documents.

2. Selection of the multicomparment compliance aid

The MCA is required to conform to a series of characteristics, including: "… preserving the stability of the medication they contain; … The manufacturer must guarantee (through supplying the corresponding certificate) that it is made of innocuous materials that do not interact with the contents; … The degree of hermeticity specified in the US Pharmacopeia (USP)". However, despite the fact that different devices are available on the market, is the pharmacist, or in general the healthcare professional, who decides which to choose to work with, as well as assigning a use date after re-packaging the medication into the MCA [13].

One of the characteristics of the MCA that should be taken into account is the degree of protection from moisture, since this atmospheric condition is one of the most important factors that can modify the stability of medicines. In accordance with the USP [14], the so-called moisture permeability test establishes whether a MCA meets the hermeticity or moisture impermeability requirements specified for this type of device (Class B). In the current paper we report the results of moisture permeability tests performed on a MCA. This information on the suitability of the device will help healthcare professionals implement a high-quality professional service.

3. Moisture permeability test

The material used to perform the moisture permeability test included: the MCA and a support for the repackaging supplied directly by the distributor (Fig. 1).

It consists of a lamina of polyethylene terephthalate plastic with 28 compartments or blisters (divided into four vertical columns —to indicate the doses—and seven horizontal rows —to indicate the days of the week) and a piece of cardboard. One side of the piece of cardboard has a sheet of a greaseproof aluminium compound stuck to it covered in a water-based self-adhesive material to strongly hold in place or glue porous supports to plastic surfaces, which is protected by what appears to be silicon-coated paper. It is cold sealed using a suitable support which the plastic lamina is placed on. The piece of cardboard is placed on top of the plastic lamina (once the silicon-covered paper has been removed), in such a way that the side with the aluminium is in contact with the plastic lamina, sealing the two parts of the system by applying pressure to the cardboard. In this way the containers or blisters of the device are individually sealed.

We also used: desiccant pellets (TK-1002L), 8 mm in diameter × 10 mm, in accordance with the specifications of the USP, supplied by Medical Packaging Inc.; two stability chambers, Memmert mod.100 and Kötterman mod. 2736, one to perform the test and one to activate the pellets; a precision balance (Precisa mod.125 A) to weigh both the test MCA and the controls; a desiccator, to keep the pellets isolated from atmospheric humidity once activated; a maximum and minimum mercury thermometer (Celsius®) to monitor temperature in the chamber, and a digital maximum and minimum

Figure 1. Multicompartment compliance aid (MCA) assayed (a) and support used for repackaging (b).

thermo-hygrometer (TFA®) to monitor the humidity. Solutions of 35 g of NaCl (Panreac, Castellar del Vallés, Barcelona) per 100 ml of water were prepared to maintain the relative humidity (RH) constant within the chamber (75% ± 3%).

The test was performed in accordance with the USP, section 671 [14] of which details the method to be followed to determine the moisture permeability of devices (packs) that incorporate a number of single-dose individually-sealed blisters (Method II). The packs are classified, according to the results, from the least to the most permeable as Class A, Class B, Class C and Class D. A package is designated Class A if no packs tested exceeds 0.5 mg/day in average blister moisture permeation rate; it is designated Class B if no pack tested exceeds 5 mg/day in average blister moisture permeation rate; it is designated Class C if no pack tested exceeds 20 mg/day in average blister moisture permeation rate; and it is designated Class D if the packs tested meet none of the above average blister moisture permeation rate requirements. The test was performed on 12 MCA for each Class (A, B, C or D), depending on the moisture permeability. The procedure was the same for all of them:

- 6 of them were filled at random with the desiccant pellets (test MCA) and the other 6 were tested as controls (control MCA) (Fig. 2).
- All the packs were stored at 23ºC ± 2ºC and 75% ± 3% RH for 24 h, at which time they were removed from the chamber and left to equilibrate for 45 min.
- The initial weighing was then carried out (the test MCA were weighed individually and the control MCA together to find their average weight) and then they were again placed into the chamber, for the appropriate time for each Class (24 h for Class D, 48 h for Class C, 7 days for class B and at least 28 days for Class A). If, during the procedure, any pellet turned pink or there was a 10% increase in the average weight of the pellets in any test pack, the assay was considered over, with the prior determination being taken as valid.
- The average rate of moisture permeation, in mg/day, for each container or blister in each MCA was calculated by applying the following formula:

$$\mathbf{(1/NX)\ [(Wf–Wi) – (Cf–Ci)]}$$

where:

N is the number of days expired (beginning after the initial 24-hour equilibration period);

X is the number of separately sealed units per pack (in the MCA assayed is 28);
(Wf –Wi) is the difference, in mg, between the final and initial weights of each test pack; and
(Cf –Ci) is the difference, in mg, between the average final and average initial weights of the control packs.

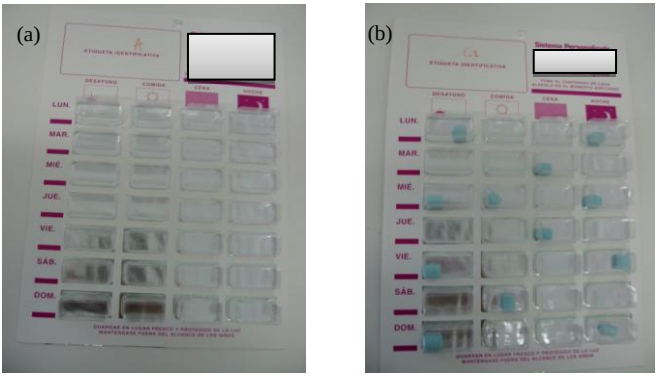

Figure 2. Test multicompartment compliance aid (MCA) (a) and control MCA (b).

4. Results of the permeability test

In accordance with the method described and based on the design of the study, the results are shown in Tables 1-4.

Table 1. Moisture permeability test for Class D packs.

Test MCA		Control MCA		Average rate of moisture permeation (mg/day)
Initial weight (mg)	Final weight (mg)	Initial average weight (mg)	Final average weight (mg)	
32210	32363			5.000
32344	32479			4.357
32080	32217	26892	26905	4.429
32810	32933			3.929
32510	32650			4.536
32707	32862			5.071

Table 2. Moisture permeability test for Class C packs.

Test MCA		Control MCA		Average rate of moisture permeation (mg/day)
Initial weight (mg)	Final weight (mg)	Initial average weight (mg)	Final average weight (mg)	
32712	32983	26690	26751	3.750
32380	32611			3.036
32854	33115			3.571
32448	32660			2.696
31822	32043			2.857
32018	32221			2.536

Table 3. Moisture permeability test for Class B packs.

Test MCA		Control MCA		Average rate of moisture permeation (mg/day)
Initial weight (mg)	Final weight (mg)	Initial average weight (mg)	Final average weight (mg)	
32894	33573	26705	26798	2.990
32791	33430			2.786
32574	33190			2.668
32786	33405			2.684
32593	33201			2.628
32844	33476			2.750

Table 4. Moisture permeability test for Class A packs.

Test MCA		Control MCA		Average rate of moisture permeation (mg/day)
Initial weight (mg)	Final weight (mg)	Initial average weight (mg)	Final average weight (mg)	
32094	32899	26692	26839	0.839
32915	33792			0.931
32561	33374			0.849
32688	33306			0.601
32769	33428			0.653
32714	33547			0.875

5. Implications for the quality of professional pharmaceutical services

Royal Decree Law 9/2011 [9] authorizes Spanish community pharmacists to prepare MCA for those patients who need them, and therefore it foresees that the use of this type of device will spread over the coming years, and moreover that this should happen in a standard way throughout the whole country. Taking into account that one of the basic functions of a MCA is to ensure that the medicines remain in similar conditions to those of their primary packaging, it is of utmost importance to know the different degrees of protection against environmental conditions that the MCA available on the market guarantee. The permeability test for packs that incorporate a number of individually sealed single-dose blisters is the first test that should be performed on this type of devices to establish whether they meet the requirements of hermeticity given in the pharmacopeia. The type of material the MCA is made of together with the loading process and the type of seal will determine the degree of protection against moisture the pack offers [15]. The results of the present study are based on the method described above with the objective of guaranteeing the highest standard for a professional service that uses these MCA. The results show that the MCA tested can be considered as Class D packs, since none of the average blister moisture permeation speeds was more than 20 mg/day after 24 h. They also meet the requirements for Class C and Class B packs, since all the average blister moisture permeation speeds were less than 20 mg/day after 48 h, and less than 5 mg/day after 7 days, respectively. However, they did not meet the Class A pack requirements, as over the 28 days of study all the average moisture permeation speeds were more than 0.5 mg/day. Despite the fact that the MCA studied here did not offer maximum barrier protection against atmospheric moisture (Class A), it does meet the conditions of hermeticity that the pharmacopeia demands for this type of packs (Class B).

The technical stage of re-packaging medicines into a MCA involves removing the medicine from its primary packaging of presentation, which annuls the manufacturer's stability guarantee, and it is the responsibility of the pharmacist who prepares and dispenses it to establish a use date for the MCA once it has been loaded. That date indicates the moment after which the MCA should not be used (and therefore the medicines re-packaged) and in order to establish that date it is important to take into account, among others, the following information [13,15]: the nature of the medicine re-packaged into the MCA, available information about drug stability, the primary

packaging in which it was presented by the manufacturer and its expiry date, the characteristics of the MCA into which it has been loaded, the expected storage conditions the medicines will be exposed to, and the useful life the MCA is expected to have (Fig. 3).

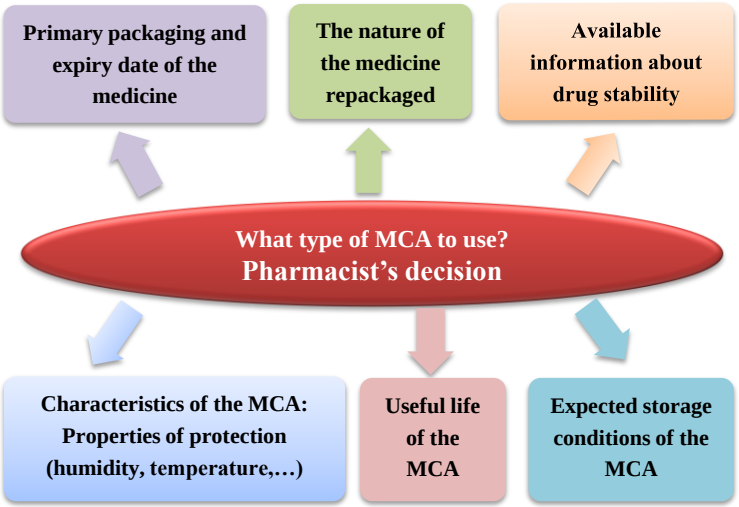

Figure 3. Some relevant aspects to consider by pharmacists in the decision of what type of multicompartment compliance aid (MCA) to use.

6. Conclusions

We performed a study to determine the degree of hermeticity of a cold-sealed MCA. In accordance with the USP and the method detailed above, we can conclude that the MCA tested meets the hermeticity requirements specified by the pharmacopeia for this type of device.

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