Stability over time of in-hospital compounded amoxicillin capsules and ceftriaxone patch tests for drug allergy testing

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Drug hypersensitivity reactions account for 15% of adverse drug reactions [1]. For both immediate and non-immediate reactions, re-exposure to the culprit drug through skin testing and/or oral drug challenge is part of the diagnosis process. Since patch test batteries do not include all the drugs involved in hypersensitivity reactions and no commercial drug provocation tests are available to date, compounding tests is often necessary prior to the exploration of drug hypersensitivity reactions [2]. Compounding activity raised two major issues, especially in the setting of allergy specialized centers. First compounding is time consuming, the tests being mainly manufactured for a single patient and kept no more than one day. Second, compounded drugs may undergo chemical degradation from their compounding to their use, either in liquid, semi-liquid, or solid forms [3], leading, at least in theory, to false negative tests if the incriminated drug is degraded into inactive metabolite(s), or in contrast to false positive tests if degradation products are irritants or act themselves as allergens. Manufacturing batches of standardized tests, stored prior to use, with an expiry date based on stability studies, would then appear to be a valuable solution to fulfill unmet needs by the pharmaceutical companies for the exploration of drug hypersensitivity reactions.

In this pilot work, we studied the physico-chemical stability of amoxicillin drug provocation tests and ceftriaxone patch tests in water and petrolatum since betalactams are the antibiotics most frequently reported to cause hypersensitivity reactions [4].

To compound amoxicillin capsules, available capsules of amoxicillin (Clamoxyl® 500 mg) were opened, and the powder contents were ground with colloidal silica and carmine powder in a mortar. Mixed powder was then distributed in gelatin hard capsules using a manual capsule filling machine. Three different batches of amoxicillin hard capsules were packaged in individual bags away from light. Studies were conducted for 12 months at room temperature (*i.e.*, 15-25°C). On each pre-determined time point, three hard capsules from each batch were

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opened and sampled for subsequent visual examination and amoxicillin quantification. To compound ceftriaxone patch tests, ceftriaxone powder (Ceftriaxone 1g Mylan®, powder for solution for injection) was either diluted in water to reach 0,1 g/mL or mixed with petrolatum to reach 0,1 g/g. Cetriaxone 10% in water or petrolatum was then distributed in 3 mL-syringes. Three batches of syringes containing ceftriaxone 10% in water or petrolatum were stored at -20°C for 90 days in individual bags away from light. On each pre-determined time point, three syringes for each batch and each condition (pet. and wat.) were thawed. One for immediate analysis and two for storage 48 hours more before analysis, the first at 25°C and the second at 4°C. Analyses included visual examination and ceftriaxone quantification **(See supplemental for extended material and methods)**.

Protocols for graded oral challenge with amoxicillin imply oral administration of increased doses, *e.g.* ranging from 5 mg (1:100) to 250 mg (1:2) until the reach of the full dose (500 mg), the latter being available [5]. We therefore compounded 5 mg and 250 mg hard capsules for further study. Amoxicillin content quantified by high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) remained above 90% of the expected quantity in hard capsules of both dosages after a 12-month storage period at room temperature (**Figure 1A**). We did not observe any change in the aspect of intact capsules, as well as powder, between day 0 and month 12 (**Supplemental Figure 1A**)

Ceftriaxone was compounded at 10% in water (wat.) or petrolatum (pet.) for patch testing in 3 mL-syringes to be applied on the skin and occluded [6]. Ceftriaxone, quantified by HPLC-MS/MS, remained above 90% of the expected quantity, either in petrolatum or in water (**Figure 1B**). Furthermore, we did not detect any change in visual aspect throughout the study (**Supplemental Figure 1B**)

To the best of our knowledge, we reported here the first long-term stability study of betalactam tests compounded to fulfill a need unmet by pharmaceutical companies. In our institution, the manufacturing activity is carried out in the pharmacy department to remove this time-consuming activity from the nurses, and to guarantee a quality close to industrial guidelines (*i.e.*, Good Manufacturing Practice, GMP). We compounded capsules from commercial 500 mg amoxicillin doses since no bulk forms were available. It was then necessary to add a diluent excipient to the formulation to fill the capsules, allowing compounding large series of capsules at once. For this purpose, we decided to use colloidal silica since it is widely used in oral and topical pharmaceutical products and is generally considered as nontoxic and nonirritant [7]. In

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a similar manner, we compounded patch tests in water or petrolatum containing 10% commercial form ceftriaxone in the absence of bulk form. However, lyophilized ceftriaxone we used could be considered as pure substance since a vial contains 1193 mg of sodium ceftriaxone, *i.e.* 1000 mg of pure ceftriaxone, without any additional excipient than sodium. This is in line with current guidelines that recommended diluting the drug at 5% to 10% in water or petrolatum [8–10]. A literature review highlighted the variability in stability of compounded and commercial patch test allergens and found that many degrade when in storage [11]. We decided to store ceftriaxone patch tests at -20°C since ceftriaxone is particularly susceptible to degradation, which is dependent on the temperature and concentration [12,13].

Amoxicillin drug provocation tests and ceftriaxone patch tests compounded in water and petrolatum were stable respectively for one year at room temperature and 90 days in freeze conditions. This study would allow the manufacture of batches, rather than extemporaneous compounding. We envisioned that this pilot work could constitute a first step toward the development of standardized manufactured tests for drug hypersensitivity exploration.

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Conflict of interest

The authors declare no conflict of interest.

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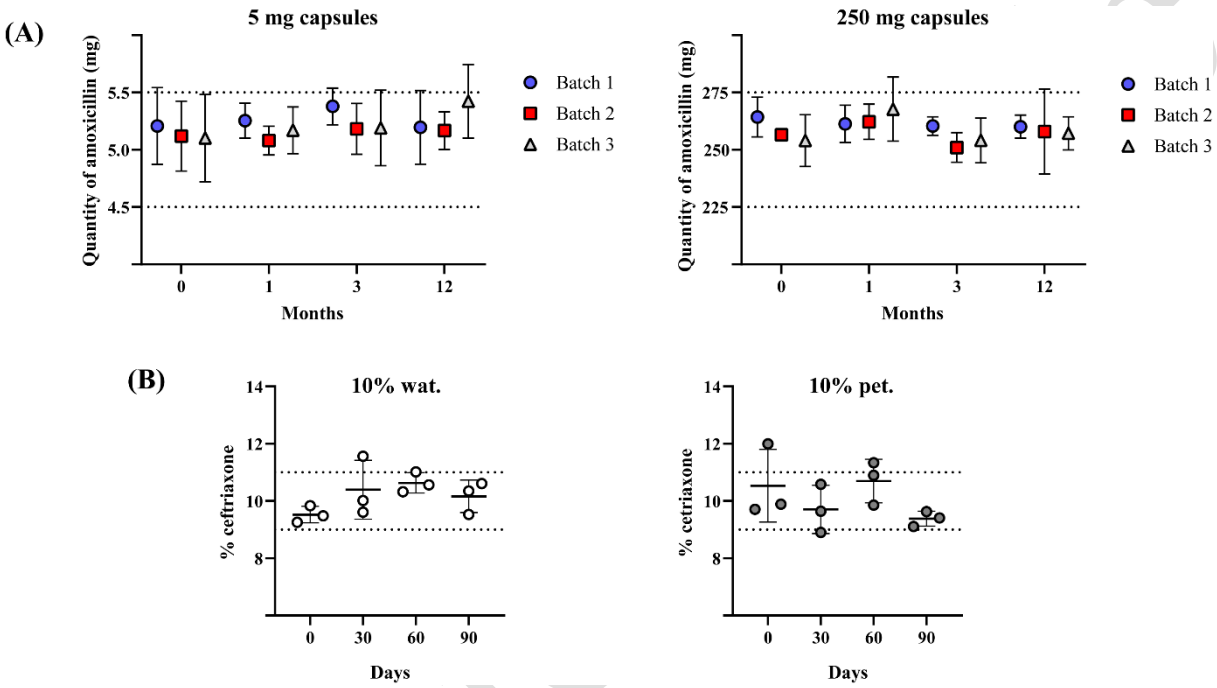
Figure. (A) Stability of 5 mg and 250 mg amoxicillin hard capsules for graded oral challenge and (B) Stability of ceftriaxone in water and petrolatum for patch testing

Horizontal lines and error bars: mean and standard deviation. Dotted lines: 10% interval from theoretical quantity.



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