ORIGINAL ARTICLE

Paediatric Galenic Preparations at the Saint Damien Hospital in Haiti: Formulative Study, Stability and Quality

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ABSTRACT

Objective: *The Aid Progress Pharmacist Agreement (A.P.P.A.®) project, a program of International Health Cooperation, is the result of collaboration between the University of Turin and Community Pharmacists in order to set up galenic laboratories in medical facilities located in developing Countries. In the laboratory established in Haiti at the Saint Damien Hospital, given the low availability of paediatric medicines, it was necessary to study and then introduce several specific galenic formulas.*

Methods: *The main active principles were identified in agreement with local medical doctors taking into account World Health Organization Model Lists of Essential Medicines and cost–benefit relationships. Then, a formulative study was launched preferring liquid pharmaceutical forms, more suitable for children. For each preparation, absorption spectrophotometry in the visible and ultraviolet spectra was applied to test the formulas' quality and stability, respectively, in accordance with the European Pharmacopeia and European Medicines Agency guidelines.*

Results: *All formulations have proved to be stable in 'Refrigerated' conditions (*T = 5°C ± 3°C*) and in 'Standard' conditions (*T = 25°C ± 2°C, RH: 60% ± 5%*) for 12 months, and in 'Accelerated' conditions (*T = 40°C ± 2°C, RH: 60% ± 5%*) for 3 months.*

Conclusion: *The galenics are made at the lab in Haiti according to specific standard procedures and they are used to treat patients. The process is constantly checked.*

Keywords: Developing countries, galenic labs, International Health Cooperation, medicine quality and assurance control

INTRODUCTION

The Aid Progress Pharmacist Agreement (A.P.P.A.®) is a non-profit association (1) whose main activity is the *A.P.P.A.®* project (2). The project began in 2005 and is the result of the cooperation between the University of Turin (Italy) and the Italian Community Pharmacists. The project focuses on Galenic Laboratories (GLs) established in medical facilities located in developing countries (DCs). The project complies with both the European and guest Country's legislation. The project is structured in different steps (Table 1) through which an effective and functional lab can be set up. After 12 years of work, several projects have been established: two in Angola, Cameroon, Chad and Madagascar and one in Haiti (2).

Regarding the *A.P.P.A.®* galenic lab in Haiti, it was established in 2012 at the Saint Damien Paediatric Hospital of 'Nos Petits Frères et Sœurs' in the Tabarre district, one of the poorest neighbourhoods of Port-Au-Prince. In the Haiti lab, it was necessary to introduce

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Table 1: *A.P.P.A.*® project steps

Steps	Description
0—Pharmacoeconomic study	Preliminary pharmacoeconomic study. It implies a trip of the *A.P.P.A.*® staff on site to assess the local situation and recipient areas. Some medicines are purchased in local pharmacies and sent to the laboratory of the University of Turin to determine if these medicinal products reflect the declared characteristics or are counterfeit.
1—Choice of lab location, active ingredients and pharmaceutical forms	Choice of GL location. The Chief MD in charge of the medical centre will highlight local diseases, so appropriate A.P.I.s can be selected and correct pharmaceutical forms can be planned.
2—Students' internship to learn how to prepare galenics	Internship at the galenic *A.P.P.A.*® lab at the University of Turin for Pharmacy students completing a relevant experimental thesis. The internship teaches students how to prepare the required medicinal products.
3—Internship of the local staff to learn how to prepare galenics	A member of the local hospital staff comes to Italy (about one month) to learn the procedures of galenic preparations under the supervision of Italian Pharmacy students. During this period, the material for the GL is sent to the hospital.
4—Training on site	A two-month training period in the DC hospital during which the work of the lab technician, who was in Italy to learn galenic methods and procedures, will be coordinated by the Italian Pharmacy students
5—Quality controls	Quality control of medicinal products routinely prepared in new GL; some samples will be sent to the University of Turin where they will be quality tested.
6—Supervision and introduction of new formulas	Regular 40 days or more internships for students of the University of Turin—during their experimental thesis—these internships are organized each year both to guarantee an ongoing supervision of the medicinal products prepared in the lab and to study new formulations according to the Chief MD's demands which might change over time.

GL = galenic laboratory. MD = medical doctor. A.P.I.s = active pharmaceutical ingredients.

several formulations for paediatric use because the number of young patients is high, and the availability of preparations designed for them is limited.

MATERIALS AND METHODS

Drug selection and formulative study

The main active principles, needed to meet the hospital's needs, were identified in agreement with local medical doctors (MDs) taking into account the World Health Organization Model Lists of Essential Medicines (3, 4) and the related relationship between costs and benefits. Considering the high incidence of heart disease on site (5), the list of the selected active ingredients included a number of preparations for the cardiovascular system. Once this list of active ingredients had been drawn up considering local needs, a formulative study was launched. This took into consideration the fact that the hospital's user base is mostly children. For this reason, it made more sense to provide liquid pharmaceuticals such as syrups, drops, solutions and suspensions. These liquid pharmaceutical forms are easier to administer and allow modulating the dose more simply according to the weight of the patient. The first step of the formulative study was to evaluate the chemical and physical characteristics of each active ingredient with the aim of identifying the most appropriate excipients to use in preparations as well as the most appropriate excipients for paediatric use. Where possible, the active ingredients were dissolved in water, if necessary co-solvents were added, and the pH of the formulation was controlled with a buffer system. In order to try to limit the costs of buying and transporting materials, the same excipients were used for as many formulations as possible.

Stability and quality control

The introduction of a complete list of liquid formulas for paediatric use brought about the need to identify specific ways of measuring the stability of the new formulas, as well as the method for carrying out quality controls on medicines prepared in the GL.

With the intention of analysing the stability of all the studied formulations and evaluating the possibility to use them in the extreme conditions of temperature and humidity like those commonly found in DCs, all formulas were analysed to obtain values that represent the initial condition (T0). These results were used for reference and comparison during the stability study, and for the successive quality controls that were carried out on the formulations prepared on site.

Following this, each medicine was divided into aliquots, and each separate aliquot was conserved in different environmental conditions (Table 2) at different temperatures (T) and relative humidity (RH%) based on the guidelines set by the European Medicine Agency (EMA) (6). The refrigerated conditions (RC) were applied to evaluate the need for this type of storage, the standard conditions (SC) were applied to define the stability of samples under storage conditions accepted by the Eur. Ph.. The stability tests carried out in the accelerated conditions (AC) can be used with two objectives. Firstly, they can reduce the times of analysis, as a

Table 2: Samples storage conditions during the stability tests

Storage condition	T (°C)	RH%	Period covered by data
Standard	25 ± 2	60 ± 5	Analysis at time zero (T0), every 45 days for 3 months (T2 and T3), after 6 and 12 months (T6 and T12)
Refrigerated	5 ± 3	–	Analysis at time zero (T0), every 45 days for 3 months (T2 and T3), after 6 and 12 months (T6 and T12)
Accelerated	40 ± 2	60 ± 5	3 months, analysis at time zero (T0) and every 45 days for 3 months (T2 and T3)

T0 = initial condition; T2 = 45 days; T3 = 3 months; T6 = 6 months; T12 = 12 months.

month of conservation in these conditions is equivalent to four months of conservation in standard conditions (7). Secondly, they reflect the typical climatic conditions of tropical countries and, therefore, they help predict the stability in environments where conservation at controlled temperature and humidity cannot be guaranteed.

Absorption spectrophotometry in the visible (VIS) and ultraviolet (UV) spectra was chosen as the analytic method for the stability tests. The medicines are suitable when the percentage error is ≤ 10% in relation to the absorbance (Abs) obtained at T0. The scientific literature usually proposes high-performance liquid chromatography (HPLC) as a suitable method for medicinal product analysis (8). Taking into account that the Eur. Ph. (9) does not prescribe a specific analytical method to test the active ingredient content of a medicinal product (the Ph. Eur. stating that a 'suitable analytical method' should be applied), we applied an UV–VIS spectrophotometric method. This choice was determined by the lower costs and, therefore, by the opportunity to apply this technique in DCs. In any case, in order to evaluate the equivalence between the two methods, in a past study (10), different samples were analysed using both the HPLC and UV–VIS methods.

Once the stability of each galenic formulation had been verified, the same method of analysis was applied to test the uniformity of content (Eur. Ph., assay 2.9.6) of the medicines prepared at the Haiti lab since 2012. Overall, the quality controls were carried out according to guidelines set out in Eur. Ph. (9). Some of the tests were carried out on site at the hospital, and others were carried out at the University of Turin, depending on the availability of equipment needed to carry out each test.

RESULTS

Drug selection and formulative study

Considering local needs, the chosen active principles were as follows: aluminium hydroxide, ascorbic acid, B vitamins (B_1, B_2, B_3, B_6), captopril, ferrous sulphate, furosemide, ibuprofen, magnesium hydroxide, nifedipine, potassium canrenoate, propranolol, ranitidine and salbutamol.

Based on the need to prepare medicines suitable for paediatric use, according to the different chemical–physical properties of the various active ingredients, 18 formulas were studied.

In general, the active ingredients were dissolved in excipients suitable for paediatric use and in many cases the final volume was reached using a sucrose syrup (11) or a sorbitol solution (50%–70%). Given the low viscosity of sorbitol solutions when compared to sucrose syrup, the desired rheological properties of the final formulation were achieved through the addition of co-solvents, *eg*, glycerol.

For each formula, the optimal pH value was experimentally determined. These values are always checked by local workers at the end of the preparation process.

Following the formulative study, a specific sheet was prepared in the local language for each formula studied in the galenic lab in Haiti. The sheet contained the following information: the components of the formulation and their chemical–physical properties, the method of preparation, the indications for use and information about suitable dosages for paediatric use. All sheets were brought together in a single document, which became the handbook for the GL in the Saint Damien Hospital.

Stability and quality control

In order to evaluate the stability over time of the studied galenic preparations, samples conserved in different conditions were analysed at regular time intervals as described (Table 2). The percentage rate calculated according to T0 during the testing period conformed to what was expected (≤ 10%) from each environmental condition applied.

For each analysed sample, pH was also measured. The pH values collected during the testing period conformed to what was expected from each environmental condition applied.

Regarding quality, since 2012, all the tested medicines satisfied the tests according to the Eur. Ph. and were used to treat the Saint Damien's patients.

DISCUSSION

Regarding the formulative study, sucrose syrup was considered the better choice as it is cheaper, and the sugar is available on site. Considering the high concentrations of sugar in sucrose syrup (66.5%) and the consequent

high osmotic pressure that prevents the growth of bacteria, the use of a conservative would be not necessary. However, it was decided to use a conservative due to two factors. Firstly, during the preparation of galenics, the total concentration of sugar is reduced because other excipients are added. Secondly, the environmental conditions in Haiti meant that it was deemed the best practice to add a conservative. For some of the studied formulations, additional considerations are required.

Ferrous sulphate syrup. Ferrous sulphate was formulated with ascorbic acid to increase intestinal absorption.

Ibuprofen syrup. When preparing ibuprofen syrup, it was necessary to find an appropriate solvent. Propylene glycol was used as a co-solvent, taking into consideration the fact that the maximum dose allowed for paediatric use is 200 mg/kg (12).

Captopril solution. The literature suggests that captopril is particularly sensitive to degradation. The studied formula needed ethylenediaminetetraacetic acid (EDTA), a chelating agent that works to protect captopril which degrades in the presence of metallic ions. EDTA also has weak antimicrobial activity (13).

Furosemide solution. To prepare furosemide solution it was necessary to identify a solvent, other than water, in which the active ingredient is not soluble. Furosemide is, however, soluble in alkaline aqueous solutions. In order to make the active ingredient soluble, while keeping the pH at a suitable level for oral administration, a mix of ethanol and sodium hydroxide solution at 0.4 M was used. The quantity of ethanol used as a co-solvent is compatible with stated levels for paediatric use (14, 15).

After the formulative study, production started but always taking into account that for each medicine prepared in a GL, the quality must be guaranteed, according to the current legislation (9, 11) to ensure its safety and efficacy. With the aim to ensure quality, a key factor is the stability of the medicinal product. As a precautionary measure, it was thought appropriate to give a validity period of three months for the galenic medicines prepared, since at AC they remained stable during this period. The stability tests in AC reflect the environmental conditions of tropical countries, and therefore can help to predict the stability of medicines in environments where ideal storage conditions cannot be ensured.

Following the formulative study and stability tests in June 2012, a specific training was carried out with local operators of the GL and the production of medicines began. The practices of the lab technicians and their ability to adhere strictly to the operating procedures learned during the previous period of training were audited during periodic monitoring missions performed on site by A.P.P.A.® staff members and students of the University of Turin.

The entire process is constantly checked in order to show that it meets the quality stated by the Eur. Ph. The excellent results of the quality controls obtained since 2012 show that the continued adherence to specific operative protocols resulted in galenic preparations that fully meet the requirements of the Eur. Ph..

In addition to this, the stability of these medicines was shown to meet the EMA guidelines. Evaluation of stability according to the EMA guidelines is usually applied to industrially manufactured medicines and not to galenic preparations. In spite of this, the galenic formulas studied for the GL in Haiti were tested according to these guidelines to assess the quality of the preparations in the tropical conditions as those of Haiti. Through testing, we demonstrated that all galenic preparations may be used in total safety at home where, most probably, refrigerators and air conditioning are not present.

The principal aim of the International Cooperation is to create autonomy, and therefore, we hope that as soon as possible it will be possible to introduce on site the necessary equipment for the quality control execution according to Eur. Ph. requirements.

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