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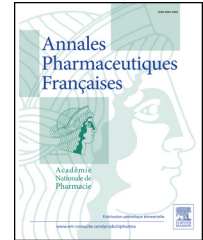


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ORIGINAL ARTICLE

Hospital compounding to face shortage: A case study of the development of a lopinavir-ritonavir oral suspension during the first wave of SARS-COV-2 in France



Maîtrise de la préparation hospitalière pour répondre à un contexte de pénurie : exemple du développement d'une suspension orale de lopinavir-ritonavir lors de la première vague de SARS-COV-2 en France

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HIGHLIGHTS

- Shortage of lopinavir-ritonavir during first wave of SARS-COV-2.
- Uncontrolled degraded mode of preparation may induce poor exposure.
- Compounding from tablets to face lopinavir-ritonavir oral solution shortage.
- Hospital product development and risk-based control strategy.
- Convenient preparation kits to permit controlled treatment continuation.

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KEYWORDS

Pharmaceutical compounding;
Oral suspension;
Lopinavir;
Ritonavir;
Control strategy;
Shortage

Summary The potential usefulness of lopinavir-ritonavir on Covid 19 infection during the first wave of contamination in France had boosted Kaletra® syrup prescription to the point of causing its national shortage. In the intensive care units of Parisian hospitals in charge of patients with life-threatening viral contamination, caregivers had to resort to lopinavir-ritonavir-based tablets, crushing them and then dispersing the powder in milk to facilitate administration by nasogastric tube. The difficulties and poor control of this degraded mode, which does not always ensure control of the amount of the drug in the prepared dose and may induce insufficient antiviral exposure, led us to develop in a very short time, while ensuring quality control proportional to the risk, a liquid form as an alternative to Kaletra® oral solution shortage. For this purpose, we describe this compounding formulation and its preparation process, while justifying the quality control strategy adapted to the risk as well as its chemical and physical stability. Based on the chemical and physical studies, the preparation was showed to be stable during at least 2 months between +2 °C and +8 °C and 1 week at room temperature. This has resulted in the design of kits that include multi-dose packaging and a measuring device and contain the appropriate quantities of drugs to ensure at least one week's treatment for each patient, during which time the kit in use can be stored at room temperature. The intensive care team used this treatment under conditions that they considered well adapted until the imported specialty became available.

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MOTS CLÉS

Préparation hospitalière ;
Suspension orale ;
Lopinavir ;
Ritonavir ;
Stratégie de contrôle ;
Pénurie

Résumé Lors de la première vague de contamination par le SARS-COV-2 en France, l'efficacité potentielle du lopinavir-ritonavir sur l'infection au Covid 19 a fait fortement augmenter la prescription du sirop Kaletra® au point de provoquer sa pénurie nationale. Dans les services de réanimation des hôpitaux parisiens en charge des patients présentant une contamination virale potentiellement mortelle, les soignants ont donc dû employer des comprimés à base de lopinavir-ritonavir, en les écrasant, puis en dispersant la poudre dans du lait pour faciliter l'administration par sonde nasogastrique. Les difficultés et la mauvaise maîtrise inhérentes à ce mode dégradé, qui n'assure pas toujours de pouvoir contrôler la quantité de médicament dans la dose préparée et peut induire une exposition antivirale insuffisante, nous ont conduit à développer une préparation hospitalière liquide comme alternative à la pénurie de solution orale Kaletra® dans un délai très court tout en assurant un contrôle de la qualité proportionnel au risque. Nous décrivons ici la formulation et son processus de préparation, la stratégie de contrôle adaptée au risque ainsi que les études de stabilité chimique et physique de cette préparation. Les études physico-chimiques ont montré que la préparation était stable pendant au moins 2 mois entre +2 °C et +8 °C et 1 semaine à température ambiante. Cela a conduit à la conception de kits comprenant un emballage multidose et un dispositif de mesure et contenant les quantités appropriées de médicaments pour assurer au moins une semaine de traitement pour chaque patient. Jusqu'à ce que la spécialité importée soit disponible, l'équipe de soins intensifs a utilisé cette préparation qu'elle a jugée bien adaptée.

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Introduction

Combined lopinavir-ritonavir is approved for use in combination with other antiretroviral drugs for the treatment of HIV infection in adults, adolescents, and children [1]. The current available dosage forms consist of tablets and oral solutions.

In the context of the SARS-CoV-2 infection, the combination of lopinavir-ritonavir has been proposed as a potential agent to treat patients [2]. For patients who receive invasive mechanical ventilation, the combination needs

to be administered in liquid form [3], most suitable for administration by nasogastric tube. This massive use of the lopinavir-ritonavir combination in the context of the COVID-19 pandemics, combined to the fact that crushing tablets is not recommended by the drug manufacturer [4] has led in France to a shortage of Kaletra® syrup. To ensure continuity of treatment, medical teams used lopinavir-ritonavir tablets, which are particularly bulky and had a large powder mass, by crushing and then dispersing them in a liquid vehicle such as milk for administration through the tube. However, the use of this degraded mode may increase the

Table 1 Drug composition.
Composition de la préparation.

Pharmaceutical ingredients	Unitary composition	Composition per multidose bottle
Drug tablets (200 mg lopinavir + 50 mg ritonavir)	1 tablet	10 tablets
Absolute ethyl alcohol	1.58 g	15.8 g
Propylene glycol	1.04 g	10.4 g
Glycerol	1.26 g	12.6 g
Purified water	0.25 g	2.5 g
Total volume	4 mL	40 mL

risk of underdosing lopinavir and ritonavir [5] due to loss during the grinding steps, poor dispersion in the liquid vehicle and incomplete recovery of the suspension by the delivery syringe, such as already reported for other drugs [6].

It was in these situations that hospital compounding takes on its full meaning and this is why we have proposed to the healthcare teams a ready-to-use formulation in order to help them in their task to ensure the best possible control of the quality of the treatment administered to the patients. Through this successful experience, we present here this compounding formulation and its preparation process, while justifying the quality control strategy adapted to the risk as well as its physical chemical stability.

Material and method

Chemical and reagents

All the excipients used were of pharmaceutical grade and purchased from Cooper (Melun, France). The reagents were purchased from Sigma Aldrich. The solvents of analytical grade were obtained from Merck (Fontenay-sous-bois, France) whereas the ultrapure water was provided from Carlo Erba (Val De Reuil, France). The tablets came from Mylan (Paris, France).

Product preparation

The unitary and mass compositions are reported in Table 1. To protect the intermediate and the final product from cross contamination as well as microbiological contamination, all operations before the obtention of the blend were performed under a laminar flow hood (Erlab® Captair Filtair 806). For each multi-dose bottle, 10 tablets were crushed with a mortar and a pestle so to obtain a fine powder. The corresponding amounts of all the excipients (absolute ethyl alcohol, propylene glycol, glycerol and purified water) were weighed and blended in another recipient. The powder resulting from tablets grinding was progressively added to the excipient solution under magnetic stirring kept for 5 minutes after all the powder has been added. Parafilm was used to avoid substantial ethanol evaporation during the magnetic stirring. The blend was then vigorously stirred by a high-performance dispersing instrument (IKA® Ultraturrax® T25 basic) until the particles of the suspension were very thin. Finally, the blend was centrifuged (5000 rpm.min⁻¹ for 10 min) and the supernatant was allocated to the primary packaging for the lopinavir-ritonavir oral liquid mixture,

which consists of a 50 mL amber moulded type III glass vial with a moulded polypropylene thread, dip tube and screw cap. Once prepared, the formulation was kept at +4°C.

Assay conditions, validation protocol and particle size analysis

The assay of lopinavir and ritonavir was performed by use of a chromatography coupled to UV detection. The method was adapted from reference [7] where conditions are proposed to perform the quantitative determination of lopinavir and ritonavir in syrup preparation by liquid chromatography. The stationary phase consisted of a Interchim Uptisphere strategy HQ SUM (250 × 4,6 mm; 5 µm). Mobile phase contained a mix of acetonitrile (60%) and ammonium acetate buffer (40%; 5 mM adjusted to pH=7 with sodium acetate). The injection volume, the mobile phase flow rate and the detection wavelength were set at 40 µL, 1 mL.min⁻¹ and 245 nm, respectively.

The validation protocol mainly aimed at assessing if the methods responded to the ICH recommendations. Three series of stock solutions independently were prepared by extracting tablets in dimethyl sulfoxide (DMSO) to reach final concentrations of 20 mg.mL⁻¹ and 5 mg.mL⁻¹ for lopinavir and ritonavir, respectively. Linearity and accuracy were studied across concentration range 100–140 µg.mL⁻¹ for both lopinavir and ritonavir. Intermediate precision and repeatability were tested by injection of six individual solutions of 110 µg.mL⁻¹ and of 130 µg.mL⁻¹ for both ritonavir and lopinavir. The absence of co-elution of excipients and/or degradation products with lopinavir and ritonavir was checked by investigating the peak purity of the two peaks in every chromatogram by use of diode array detection.

Regarding particle analysis, 20 mL of solutions were analysed by use of LIXELL apparatus (Sympatec GmbH, France) combined with the QICPIC image analyser.

Stability protocol

Regarding chemical stability, three formulations kept between +2°C and +8°C were assayed by HPLC at different periods (0–1–2–3–4–6–8 weeks). At each sampling time, for every formulation, two aliquots were weighed and diluted in the mobile phase. Assays of ritonavir and lopinavir were then carried out by preparing fresh stock solutions in dimethyl-sulfoxide (20 mg.mL⁻¹ of lopinavir and 5 mg.mL⁻¹ of ritonavir) and diluting them in the mobile phase. Chemical

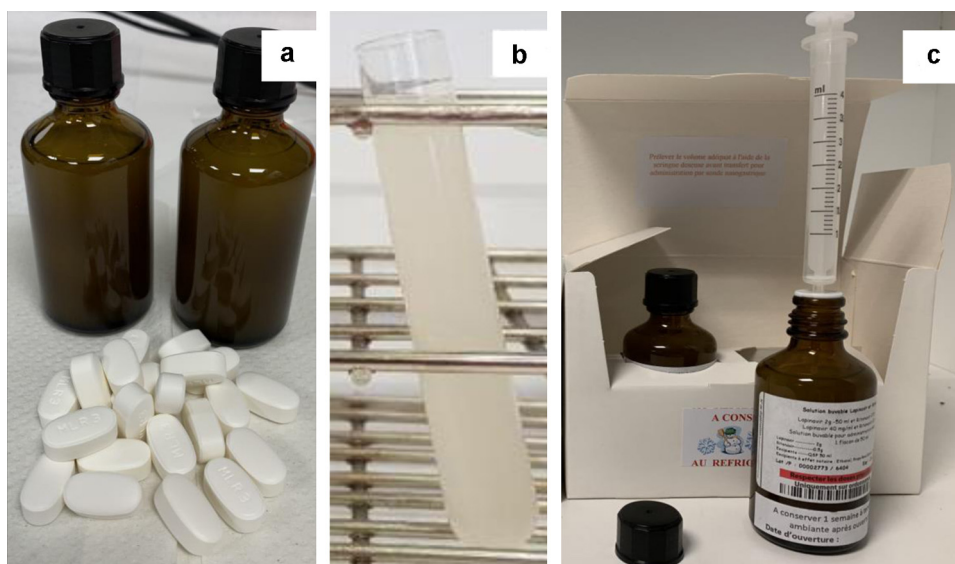


Figure 1. Lopinavir (200 mg)-ritonavir (50 mg) tablets and primary packaging used for two multi-dose bottles containing the liquid formulation (inset a), liquid bulk formulated from tablets (inset b) and the ready-to-use finished compounded preparation (inset c). *Comprimés de lopinavir (200 mg)-ritonavir (50 mg) et conditionnement primaire utilisé pour la formulation liquide (encart a), liquide formulé à partir des comprimés (encart b) et préparation prête à l'emploi (encart c).*

stability at room temperature was also assessed for one-week storage. Results were compared using paired *t*-test.

Regarding physical stability, to assess the impact of freezing on the potential formation of insoluble lopinavir or ritonavir particles, aliquots of three formulations were frozen for three days. There were then thawed in a refrigerator until no visible particles could be detected (6 hours in our case). Aliquots of the fine suspension were then centrifugated (5000 rpm, 5 minutes) and the upper part of the container were analysed and compared to that of the formulations that did not undergo a freeze-thaw cycle. As for the potential sorption of lopinavir or ritonavir on the primary packaging, it was assessed by comparing the results of the drugs assays obtained immediately after preparation and one week between +2°C and +8°C after keeping the drug in the primary packaging upside down. Results were compared using paired *t*-test. For all tests, the chosen level of significance was 0.05.

Results and discussion

Preparation of one-week kits from the available lopinavir-ritonavir tablets

In any case, it is much easier to design a product from scratch when the choice of excipients is based on a rational approach guided by a target quality profile of the product, taking into account the pharmaceutical dosage form envisaged, the strength and the route of administration. But the time required to prospect for lopinavir and ritonavir Active pharmaceutical ingredients (APIs) involving the qualification of their suppliers, their purchase and delivery was incompatible with the immediate need. Therefore, the use of lopinavir-ritonavir tablets (Fig. 1, inset a) as a source of both APIs was at the time the only viable solution,

especially since the lopinavir-ritonavir strength and ratio were consistent with the desired preparation (200 mg–50 mg per tablet versus 40 mg–10 mg per ml) (Fig. 1, inset a).

Our choice was to use a solvent system (ethanol, propylene glycol and glycerol) close enough to that of Kaletra® syrup [4], but without the aromas, sweetening and surfactants agents, to disperse and at most dissolve a large mass of powder resulting from the grinding of the tablets, so as to achieve a fine suspension (Table 1 and Fig. 1, inset b). The taste was not an issue given the nasogastric tube administration. To avoid treatment discontinuation, based on Kaletra® typical dose regimen (two tablets per day, corresponding to 10 ml of suspension per day), we proposed kits containing two multi-dose packaging as well as a measuring device (Fig. 1, inset c).

Risk-based control strategy

Since it was not possible to integrate quality at the design stage, we focused on controlling the final product to ensure that it met expectations. The risk-based strategy control consisted of performing the assay of lopinavir and of ritonavir in the formulation in the recommended storage conditions at release and at expiry date as well as assessing all the phenomena likely to decrease it. In the later the potential risks of precipitation of ritonavir and lopinavir as well as the potential physisorption of the APIs on the primary packaging materials in contact with the suspension were included. Further, the assay was systematically complemented by the analysis of the HPLC profile in search of compounds not explained by the ingredients present. In addition, to assess the risk of settling during storage and clogging the nasogastric tubes during administration, the particle size was measured. At last, given the route of administration and the nature of the solvent system used, no microbiological control was considered.

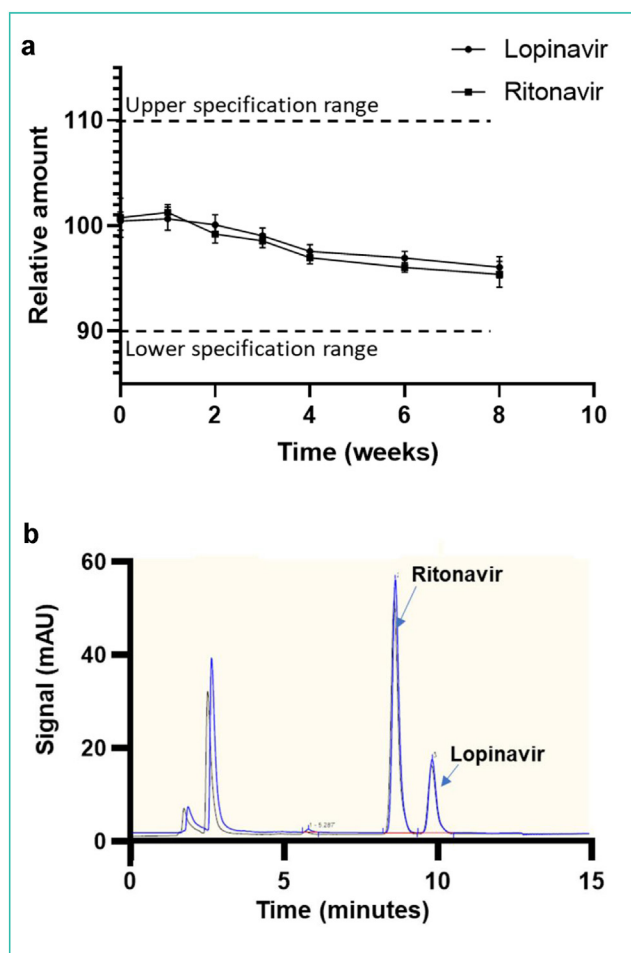


Figure 2. Inset a: relative amount of lopinavir and ritonavir as a function of time; inset b: overlaid HPLC purity chromatograms of the formulation at release (in black) and at expiry date (in blue). *Encart a : quantité relative de lopinavir et de ritonavir en fonction du temps ; encart b : chromatogrammes des formulations à la libération (en noir) et à la date d'expiration (en bleu).*

Assay of lopinavir and ritonavir at release and the expiry date

With no qualified controls available, the average levels of the two APIs present in Kaletra[®]'s specialty tablets were determined after extraction in DMSO and used as a target values to control the assay in the batch-release compounded preparation and at different periods of the stability study. For both lopinavir and ritonavir, the assay method used was validated as per the ICH guidelines and the results are provided in the supplementary material.

Thus, both the release and expiry assays, on three batches, comply with the specification range 90.0–110.0%, i.e. 100.4% (relative standard deviation, RSD=0.44) and 96.1% (RSD=0.7) respectively, for lopinavir and 100.8% (RSD=1.86) and 95.4% (RSD=1.22) respectively, for ritonavir (Fig. 2, inset a). These specifications correspond to the limit acceptable of most compounded preparations that has been established by the USP [8]. At the same time, the HPLC purity profiles obtained at expiry is comparable in all respects to that obtained just after manufacture (Fig. 2,

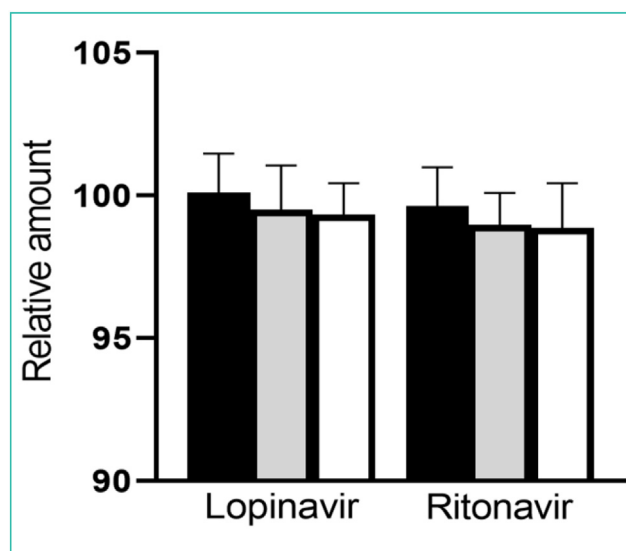


Figure 3. Relative lopinavir and ritonavir amounts in three drug formulations analyzed extemporaneously (black), after three freeze thawing cycles (grey), and when in contact with all the materials of the container for one week between +2 °C and +8 °C (white). *Quantités relatives de lopinavir et de ritonavir dans 3 formulations analysées extemporanément (en noir), après trois cycles de congélation (en gris) et mises au contact avec l'ensemble des matériaux du conditionnement primaire pendant 1 semaine +2 °C and +8 °C (blanc).*

inset b), suggesting no degradation products were quantitatively formed.

Further, the assays of lopinavir and ritonavir of three batches stored at room temperature for one week were not statistically different with that of the assays at release ($P=0.42$ for lopinavir and $P=0.59$ for ritonavir, respectively). Thus, the product can be stored at room temperature during its week of clinical use.

As the decrease could then be due to physical rather than chemical phenomena, we have then investigated this aspect by additional studies presented below.

Physical aspects of the formulation

In addition to monitoring on the chemical degradation of APIs likely to lead to underdosing and the formation of new products in the compounded preparation, we also wanted to ensure that physical phenomena did not affect much the content of lopinavir and ritonavir, such as their potential adsorption on the materials making up the primary packaging and precipitations in relation to storage of the product at low temperature.

After one freezing and thawing cycle of three preparations present in their primary packaging, on the one hand, the visual appearance of the preparations was unchanged and on the other hand, the assays for both lopinavir and ritonavir did not decrease significantly compared to the initial value ($P=0.22$ and $P=0.37$, respectively; Fig. 3). When three drug formulations were turned upside down to allow the preparation to come into contact with all the materials in the container, no statistical difference in terms of drug assay ($P=0.51$ for lopinavir and $P=0.91$ for ritonavir, respec-

tively) nor visual appearance change were perceived. Thus, overall, no significant risk of physisorption of precipitation or physisorption of the APIs was perceived (Fig. 3).

When analyzing 20 ml of three formulations before and after a freezing and thawing cycle, no particle of size beyond 50 μm were detected in the samples before and after a freezing and thawing cycle (Fig. S1 and Fig. S2). Thus, the risk of settling of suspended particles during storage during this short supply period of this preparation is negligible due to the high density of the liquid part resulting from the use of glycerin and propylene glycol, and the solubilization of a part of tablets excipients. Besides from this, it can also be considered that even in the advent of the use of very small sized nasogastric tubes, such as a round tube of 3 French catheter scale (of which the external diameter is 1000 μm), the initiation of a clogging event, due to the APIs and/or excipients agglomerates, seems unlikely.

Practical considerations for the use of this preparation

It was clear that given the urgency of the availability of this preparation, we did not have all the data from the planned 8-week stability study to perfectly guarantee this period of validity as stated on the label. However, to limit and manage this risk in this particular context, we have provided for weekly monitoring of the stability of the preparation and in the event of a lack of stability of the formulation, the batch put into service is then immediately recalled and we have trained the operators in this recall process so that they are as reactive as necessary.

Based on the results presented above and this risk management plan, we considered that the provision of this compounded preparation did not present any risk to the patient.

As for its use in the clinic, this liquid form, which very quickly took over from the tablets administered after grinding, not only allowed the healthcare team to concentrate on treatment procedures, but also to continue adapting the dosage according to the plasma dosage results, until the availability of imported specialties.

Conclusion

Based on a risk-based control strategy, we were able to quickly propose to the caregivers a ready-to use formulation to limit the duration of the use of a less adapted temporary answer. This degraded mode of operation may constitute an interesting alternative answer to the context of a Kaletra® oral solution shortage and help caregivers to provide a controlled amount of drug and to save valuable time.

Although *a posteriori* this drug does not bring convincing results in the treatment of Covid 19, this work, taken in its pharmaceutical context, can testify to the interest of maintaining a know-how in the field of hospital preparation where the quality remains satisfactory thanks to the implementation of a risk-based control strategy.

Author contributions

Conceptualization: B.D., PH.S., M.P., and O.T.; methodology: PH.S., B.D., M.P., J.S., K.R. and O.T.; writing — original draft preparation: PH.S., B.D., M.P. and O.T. writing — review and editing: M.P., O.T.; supervision: PH.S., B.D. and M.P.; funding acquisition, M.P. All authors have read and agreed to the published version of the manuscript.

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Ethical approval

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Randomized controlled trial

Not applicable.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.pharma.2021.09.002>.

Disclosure of interest

The authors declare that they have no competing interest.

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