



LETTERS TO THE EDITOR

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Selected evidence and cherry picking pharmaceutical compounding

Evidencia seleccionada y cherry picking en formulación magistral

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Dear Editor-in-Chief:

We have read Ramos Martínez *et al.*'s interesting review article¹, which mistakenly concludes that the introduction of cyclodextrins is not a viable alternative for their use in extemporaneous formulations.

First of all, the authors point to the complexity inherent in selecting cyclodextrins to be incorporated in an extemporaneous formulation. Numerous cyclodextrin-based compounds have been described in the literature, with their own routes of administration, safety profiles and physical compositions, conceived for different kinds of extemporaneous formulations (liquid, semi-solid or solid)². Pharmacists are not mere transcribers of already developed formulas; our role is to find, select and interpret the published scientific knowledge indispensable for preparing new extemporaneous formulations. This is the only way in which scientific advancement and innovation are possible in these areas.

At the same time, it is not true that there is great variability across the different suppliers and batches. There are of course differences regarding the degree of substitution, in the same way as there are differences between polymers or macromolecules with different molecular weights, or with different degrees of crosslinking. Polyethylene glycol 300 does not behave in the same way as polyethylene glycol 50,000, nor does low-molecular weight hyaluronic acid with its proinflammatory effect behave in the same way as high-molecular weight hyaluronic acid with its anti-inflammatory properties. If we opt for a variety with a certain degree of substitution we shall not observe any variety beyond the ones present in any pharmaceutical excipient³.

In addition, the statement on the "high complexity required for preparing inclusion compounds" is not correct. Preparing the majority of inclusion compounds in solution is as easy as dissolving the corresponding cyclodextrin, and then the active ingredient, at the desired concentration. This was shown by the authors of this letter in the research they published on the subject, all of it implemented in galenics and in clinical practice⁴.

Another striking aspect about the review article discussed here is a comment it makes on the potential change in the bioavailability of the drug as a result of the use of cyclodextrins. However, it is obvious that any hydro-solubilization technique, using either cyclodextrins or other methods used

in extemporaneous formulations (pH changes or the use of co-solvents), will result in increased bioavailability. Moreover, the review indicates that cyclodextrins may increase membrane patency, with an ensuing increase in bioavailability. Again, this is not observed only in cyclodextrins: surfactants may also modify the dermal, nasal or ocular patency of many drugs. Moreover, co-solvents such as polyethylene glycols, propylene glycol or even ethanol may also modify the lipid layer of the skin or the mucosae as well as inhibit the Pgp efflux system and the action of cytochromes related with the metabolism of active ingredients in the gut and in the liver. All of them are used in extemporaneous formulations⁵.

Lastly, the argument that the use of cyclodextrins increases the cost of extemporaneous formulations does not hold together. A case in point is that of a recent development by the authors of this letter with a tacrolimus-based eye drop formulation solubilized with hydroxypropyl-β-cyclodextrin. Addition of cyclodextrin not only resulted in an improvement at galenic level, increasing the compound's tolerability (by making it unnecessary to use irritating excipients) and biopermanence on the ocular surface, but also allowed annual savings of €9,000 as a result of using tacrolimus as an active ingredient instead of the usual intravenous formulation. Given its higher efficiency, this new development has been incorporated to the formulary of the pharmacy department⁴.

There are many aspects of extemporaneous formulations that require further improvement. However, adopting a negative approach to the aspects currently backed by the largest body of evidence may not be the most appropriate strategy to allow the development of this activity. Rejecting the



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latest advances in the field of extemporaneous formulations would send us back to the era of alchemy.

For all the reasons above, we cannot agree with the conclusions drawn in the review article discussed.

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Authors' reply

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Dear Editor-in-Chief,

In response to the letter to the editor submitted in response to the conclusions of the review article "Application of cyclodextrins as excipients for pharmaceutical products: why not in extemporaneous formulations?"¹, we would like to make the following remarks:

It was never my intention to disparage or contradict the research into cyclodextrins (CDs) carried out by my colleagues working on extemporaneous formulations in an attempt to develop and investigate new pharmaceutical products¹. Our goal was simply to come up with excipients that could constitute an alternative to those widely used in extemporaneous formulations in order to enhance the solubility and improve the palatability of some medicines, including CDs¹. Solubility and palatability are in fact particularly important properties for the oral liquid formulations such as those administered to the pediatric population. These are the most common nonsterile formulations compounded in hospital pharmacy departments. However, although the number of publications and research papers on CDs has increased in the last few years, the roster of industrially manufactured CD-based medicines targeted at the pediatric population is still very limited². In this regard, only one ibuprofen solution dosage form is commercially available in Spain that contains beta cyclodextrin (Dolorac for pediatric use[®]).

In its latest consensus document on CDs, the European Medicines Agency (EMA) issued a warning about the uncertainties around the safe use of CDs in pediatric patients under the age of 2 years and in patients with renal failure. This could explain why no commercially available pediatric dosage forms include them³. We consider all the expert reports prepared by the EMA extremely important and highly valuable and have the highest regard for the pharmaceutical industry's experience of including new excipients in their medicines to make them stable, traceable, safe and innocuous enough to be applied in extemporaneous formulations.

At the same time, systematic reviews typically synthesize the available evidence (with its strengths and weaknesses) and serve as fundamental decision-making tools in the realm of healthcare. Indeed, in the context of galenics, they constitute the starting point for the development of, and investigation into, new formulations. Pharmacy and therapeutics committees are responsible for deciding on the inclusion of new medicines into hospitals on the basis of published evidence, even if they lack previous experience of their use. This is exactly the same thing we did in our review with respect to the inclusion of CDs in extemporaneous formulations¹.

The authors of the article, as members of the Galenics Working Group of the Spanish Society of Hospital Pharmacists (SEFH), work indefatigably to address the unmet therapeutic needs of many patients, including pediatric ones, through extemporaneous formulations. Drawing on the International Conference of Harmonisation (ICH) guidelines, we perform physical-chemical and microbiological stability studies to guarantee the quality, safety and efficacy required by these kinds of formulations⁴. We have also collaborated with the Spanish Agency for Medicines and Medical Products (AEMPS) in standardizing and publishing the Spanish Formulary, selecting the safer and most appropriate excipients on the basis of the available scientific evidence.

In a nutshell, the indiscriminate use of CDs in extemporaneous formulations could be considered premature and even precipitous. This statement is not at odds with the idea that further research be made into the development of new formulations that incorporate CDs, with special emphasis on the study of their safety, efficacy and stability in different dosage form, in accordance with the ICH guidelines⁴. The ultimate goal should be to make the most of the benefits of these excipients and improve the extemporaneous formulations administered to our patients.

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