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Limited Influence of Excipients in Extemporaneous Compounded Suspensions

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Abstract

Objective: The objective of this study was to identify whether compounding oral suspensions with SyrSpend SF based on tablets or capsules is a suitable alternative for using raw pharmaceutical materials. **Methods:** Suspensions based on 5 different tablets and capsules were studied in SyrSpend SF. The summary of product characteristics of these different tablets and capsules were obtained from the manufacturer. Our hypothesis was that, if the maximum beyond-use date of the study was reached, the excipient did not seem to have an influence on the stability of the active pharmaceutical ingredient (API) within the studied time frame. **Results:** All excipients used in flecainide acetate, labetalol HCl, and tiagabine HCl tablets as well as in celecoxib and oseltamivir capsules did not seem to influence the beyond-use date of the overall suspension based on SyrSpend SF. **Conclusion:** Although using raw materials as API sources is preferred, oral suspensions with SyrSpend SF prepared from crushed tablets or opened capsules could be a possible alternative. Based on this study, a wide range of different excipients does not seem to impact the beyond-use date of different APIs compounded in SyrSpend SF.

Keywords

compatibility, stability, oral suspension, compounding, excipients

Community and hospital pharmacists are often required to compound extemporaneous oral liquids in case of patients with dose adjustments, for patients unable to swallow oral solid medication or when patients are receiving their medication via an enteral feeding tube.[1] To assure patient safety and compliance, a number of aspects need to be considered, including chemical, physical, and microbiological stability and palatability of the compounded medication.

In practice, due to convenience or availability of raw pharmaceutical ingredients, (hospital) pharmacists often resort to capsules or tablets as the source of their active pharmaceutical ingredient (API). These commercial solid dosage forms are formulated with—among others—excipients promoting dilution, flow and disintegration, colorants, flavors, and binding agents.[2] Stability of the oral liquid is therefore no longer just determined by the interaction of the API with the vehicle alone, but also by the chemical and physical interaction of the API with the excipients.[1,3] As formulation of oral liquids is often only partially supported by pharmacopoeia and other scientific evidence, assigning a beyond-use date (BUD) by the (hospital) pharmacist can be challenging.

A wide range of APIs is currently being studied in SyrSpend SF, a commercial oral suspension base. Compatibility results with SyrSpend SF have been published for more than 70 different APIs.[4-21] In all of these studies, the compatibility was assessed by measuring the percentage recovery at varying time points throughout a 90-day period at controlled room and/or at controlled refrigerated temperature. The majority of the compatibility studies have been performed with raw pharmaceutical APIs. In case of celecoxib, flecainide acetate, labetalol hydrochloride, oseltamivir phosphate, and tiagabine hydrochloride where no raw pharmaceutical material was available, commercially available tablets or capsules were used. High-performance liquid chromatography with diode array detection was used for both the compatibility study and a forced degradation study. The latter was executed with the aim of identifying all degradation products that may be produced during storage of the samples. All APIs except for

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Table 1. Summary of all the Excipients Present in the Celecoxib, Flecainide Acetate, Labetalol Hydrochloride, Oseltamivir Phosphate, or Tiagabine Hydrochloride Tablets and Capsules Tested With SyrSpend SF.

Excipient
FD and C Blue 2 (indigo carmine, E132)
Ascorbic acid (E300)
Cellulose microcrystalline (E460)
Corn starch
Carnauba wax
Quinoline Yellow aluminium
Croscarmellose sodium (E468)
Crospovidone
Edible inks
Erythrosine
Gelatin
Hydrogenated vegetable oil (Type 1)
Hydroxypropylcellulose (E463)
Hypromellose
Lactose, anhydrous
Lactose, monohydrate
Magnesium stearate
Macrogol 400
Microcrystalline cellulose
Polyethylene glycol
Polysorbate 80 (E433)
Povidone
Pregelatinized starch (derived from maize starch)
Propylene glycol
Red iron oxide (E172)
Saccharose
Shellac
Silica, colloidal anhydrous (E551)
Sodium lauryl sulfate
Sodium starch glycolate
Sodium stearyl fumarate
Sorbitan monolaurate
Stearic acid
Talc
Titanium dioxide (E171)
Black iron oxide (E172)
Red iron oxide (E172)
Quinoline yellow (E104)
Yellow iron oxide (E172)

Note. All APIs showed a full 90-day stability in presence of the excipients listed in the table. This indicates that these excipients do not negatively impact the API stability when compounded in SyrSpend SF. API = active pharmaceutical ingredient.

oseltamivir phosphate were analyzed with the HP Agilent Series 1100; oseltamivir phosphate was studied using a Varian Prostar. Analytical grade chemical reagent and standards were used throughout the study. During validation of the method, linearity, fit, limit of detection (LOD), limit of quantification (LOQ), and recovery were determined. In the compatibility study, the appropriate amount of API was levigated with SyrSpend SF PH4 (liquid) using geometric dilution to form a smooth suspension. The API concentration was determined in 6-fold at predefined time points until $T = 90$ days. The oral liquid formulation was considered stable when the content was between 90% and 110% of the declared amount.

Although the compatibility studies were set up to determine the BUD of the APIs, we believe that the results can also be used to determine a possible influence of the excipients on the API. We postulated that the presence of excipients either accelerate API degradation or have no influence on API stability. Therefore, if the API in the study reaches the maximal studied BUD, the excipient does not seem to have an influence on the stability of the API within the studied time frame. For the study, Celecoxib (Celebrex) 200 mg capsules were obtained from Pfizer, flecainide acetate (Apocard) 100 mg tablets were obtained from Meda Pharma SAU, labetalol hydrochloride (Trandate) 200 mg tablets were obtained from Kern Pharma, oseltamivir phosphate (Tamiflu) 75 mg capsules were obtained from Roche, and tiagabine hydrochloride (Gabitril) 15 mg oral tablets were obtained from Teva Pharma BV. The list of excipients present in these oral dosage forms were acquired from the manufacturer's summary of product characteristics.[22-27]

The results of the compatibility studies are summarized in Table 1. The compatibility data show that all of the actives reached a BUD of 90 days,[4, 28] indicating no influence of the excipients present in the tested celecoxib, flecainide acetate, labetalol hydrochloride, oseltamivir phosphate, or tiagabine hydrochloride tablets or capsules.

These results found in SyrSpend SF are in concordance with the results found in published compatibility studies with other vehicles, although in general these APIs show a longer BUD when combined with SyrSpend SF than with the other vehicles (simple syrup, fruit juices, or water). These data are summarized in Table 2. The oseltamivir phosphate results in SyrSpend SF[4] were published at an intermediate time point (30 days) because of the bird flu epidemic at that time. Consecutive study results have shown a 90 days BUD.[29]

Summarizing, the data of previously performed compatibility studies indicates that commonly used excipients present in crushed tablets or opened capsules appear to have no distinct influence on the stability of celecoxib, flecainide acetate, labetalol hydrochloride, oseltamivir phosphate, and tiagabine hydrochloride when compounded in SyrSpend SF. This indicates that tablets and capsules could be a possible API source, when no raw pharmaceutical material is available. From this study, it can be concluded that a wide range of different excipients does not seem to impact the maximum BUD of different APIs compounded in SyrSpend SF.

Table 2. Overview of All Celecoxib, Flecainide Acetate, Labetalol Hydrochloride, Oseltamivir Phosphate And Tiagabine Hydrochloride Beyond-Use-Dates Published in the Literature.

Active pharmaceutical ingredient	Excipients present in the commercial dose form	Beyond-use-dates that have previously been published in the literature
Celecoxib	Croscarmellose sodium Gelatin Iron oxide E172 Lactose monohydrate Magnesium stearate Povidone Propylene glycol Shellac Sodium laurel sulfate Sorbitan monolaurate Titanium dioxide E171	90 days[30]
Flecainide acetate	Croscarmellose sodium Magnesium stearate Maize starch Microcrystalline cellulose (E460) Pregelatinized maize starch	45-60 days[31,32]
Labetalol HCl	Carnauba wax Distilled water/coloring agent Erythrosine Hypromellose Hydroxypropyl methylcellulose Macrogol 400 Magnesium stearate Methylparaben Microcrystalline cellulose Polyethylene glycol Polyvinylpyrrolidone Pregelatinized starch (derived from maize starch) Propylparaben Quinoline yellow (E104) Saccharose Silica gel Sodium starch glycolate Tartaric acid	30-60 days[33,34]
Oseltamivir phosphate	Black iron oxide (E172) Croscarmellose sodium FD and C Blue 2 (indigo carmine, E132) Gelatin Povidone Pregelatinized starch (derived from maize starch) Red iron oxide (E172) Shellac Sodium stearyl fumarate Talc Titanium dioxide (E171) Titanium dioxide (E171) Yellow iron oxide (E172)	35-92 days[35-37]
Tiagabine	Ascorbic acid (E300) Cellulose, microcrystalline (E460) Crospovidone Hydrogenated vegetable oil (Type 1) Hydroxypropylcellulose (E463) Hypromellose Lactose, anhydrous Magnesium stearate Silica, colloidal anhydrous (E551) Starch, pregelatinized (maize) Stearic acid Titanium Dioxide (E171)	42-70 days[38,39]

Declaration of Conflicting Interests

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