

RESEARCH CONCERNING THE DEVELOPMENT OF A STABLE, FIXED COMBINATION OF ASPIRINE, PARACETAMOL, CAFFEINE AND AN ANTIALERGIC COMPONENT

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Abstract

The multitude of analgesic combinations based on the synergic effect of acetylsalicylic acid, paracetamol and caffeine have in common the problem of irritative adverse effects and relative low stability. Addition of chlorpheniramine to this classical combination allowed the reduction of the usual dosage and consequently of the gastrointestinal adverse effects. The present paper aims to evaluate the stability of the quaternary combination, in both powder and tablet form. A preliminary study was performed in order to evaluate the stability of all combinations of components as well as the compatibility of the active pharmaceutical ingredients with different tableting excipients. The results allowed the development at industrial scale of a new formulation containing 125 mg acetylsalicylic acid, 75 mg acetaminophen, 15 mg caffeine and 2 mg chlorpheniramine combination. Further studies concerning the evaluation of the stability of the selected formula under International Conference on Harmonization accelerated, intermediate and real-time storage conditions (over 36 months) put in evidence that acetylsalicylic acid is the only component that presented a significant concentration decrease. Time to decreasing of acetylsalicylic acid content to 90% was found to be 41 months.

Rezumat

Multitudinea de combinații analgezice bazate pe efectul sinergic al acidului acetilsalicilic, paracetamolului și cofeinei au în comun problema apariției efectelor adverse iritante și stabilitatea relativ scăzută. Adăugarea de clorfeniramină la această combinație clasică a permis reducerea dozei obișnuite și, în consecință, a efectelor adverse gastrointestinale. Lucrarea de față își propune să evalueze stabilitatea combinației cuaternare, atât sub formă de pulbere, cât și sub formă de comprimate. A fost efectuat un studiu preliminar pentru a evalua stabilitatea tuturor combinațiilor, precum și compatibilitatea ingredientelor farmaceutice active cu excipienți de tabletare diferiți. Rezultatele au permis dezvoltarea la scară industrială a unei noi formulări care conține 125 mg acid acetilsalicilic, 75 mg acetaminofen, 15 mg cofeină și 2 mg clorfenamină. Studiile suplimentare privind evaluarea stabilității formulei selectate conform Conferinței Internaționale de Armonizare, în condiții de degradare accelerată, intermediară și în timp real (peste 36 de luni) au demonstrat că acidul acetilsalicilic este singura componentă care a prezentat o scădere semnificativă a concentrației. Timpul până la scăderea conținutului de acid acetilsalicilic la 90% a fost de 41 de luni.

Keywords: stability, new analgesic synergic combination, AAS, paracetamol, caffeine, chlorpheniramine

Introduction

Clinical evidence supports the efficacy of fixed combined analgesics with doses up to 250 - 265 mg acetylsalicylic acid (ASA), 200 - 265 mg acetaminophen, and 50 - 65 mg caffeine *per* tablet [17].

However, most of the commercial analgesic - anti-inflammatory combinations contain significantly larger than necessary amounts of the active substances. Our research led to the conclusion that the association of the chlorpheniramine results in a further increase of the well-known synergism between acetylsalicylic

acid, acetaminophen and caffeine, allowing to obtain comparable anti-inflammatory and analgesic effect as other similar drug combinations [12] but at two-three times lower doses, allowing to obtain reduced side effects and higher patient tolerance [7, 13].

The downside in increasing the number of active pharmaceutical ingredients (APIs) is however the increased risk of chemical and physical interactions between the compounds, leading to a significant decrease of stability over time for the resulting products [2-7]. As a result, despite the favourable

clinical outcome of the combination, a question associated with the formulation was related to a possible reduction of product stability [16].

The aim of the present study was to obtain drug products based on a synergic active substances combination of 100 - 125 mg acetylsalicylic acid, 75 - 200 mg acetaminophen, 20 - 50 mg caffeine (base or salt), and 1 - 5 mg antihistaminic agent with adequate stability profile. The first step towards this goal was the identification and overcoming of the main factors responsible for the known instability of acetylsalicylic acid - acetaminophen - caffeine - antihistaminic combination. The obtained results further allowed different technological approaches in order to obtain a stable pharmaceutical industrial tablet formulation. The shelf life of the optimum formulation was estimated using real-time and accelerated stability tests.

Materials and Methods

Chemicals AAS (Rhodia Organique SAS, France), acetaminophen supplemented with 4% povidone (Rhodia Organique SAS, France), anhydrous caffeine (BASF Pharma Chemikalien GMBH & Co KG, Germany), clorpheniramine maleate (Nivedita Chemic. PVT. LTD., India) and pheniramine salicylate (Sintofarm, Romania) were in accordance with the European Pharmacopoeia specifications.

The screening research concerning physico-chemical and functional stability of API powders and tablets was undertaken in the first phase of research and development of the formulations. The final research concerned a quantitative study of the evolution of the composition of tablets from industrial batches in different conditioning materials.

Preliminary screening of the main sources of instability of the fixed dose combinations of acetylsalicylic acid (ASA), acetaminophen, caffeine and the anti-histaminic agent (pheniramine and clorpheniramine) included comparative studies concerning the stability of individual, as well as of different combinations of two, three and four APIs, using as endpoints two organoleptic properties: the change in colour of the powder and the appearance of characteristic odour.

In order to further test the product stability, six different batches of a final formulation, containing 125 mg AAS, 75 mg acetaminophen, 15 mg anhydrous caffeine and 2 mg clorpheniramine maleate were stored for 3 months under International Conference on Harmonization/World Health Organisation (ICH/WHO) accelerated conditions (temperature and relative humidity (RH)) ($40^{\circ}\text{C}/75\% \pm 5\% \text{ RH}$) for 6 months under intermediate storage conditions ($30^{\circ}\text{C}/65\% \pm 5\% \text{ RH}$), and for 3 years in real storage conditions, at $25 \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{ RH}$ [18].

Influence of light on stability of the selected formulation was also assessed. The quantitative determination of all APIs as well as their impurities was selected as main stability-indicating quality parameter. The quantitative analysis was performed by using an Agilent 1100 Series chromatographic system, using a diode array detector (DAD) detection [16].

The chromatographic separation was achieved on a Inertsil 5 ODS-2, 250 x 4.6 mm, (Varian) column at 40°C , using a gradient mixture of 0.01% H_2SO_4 in water and 0.01% H_2SO_4 in methanol as mobile phase delivered at 1.2 mL/min flow rate. 5 μL of each sample were injected onto the chromatographic column. The HPLC method was subjected to validation in accordance with the ICH regulations Q2(R1) [10] in terms of specificity, linearity, precision (repeatability and intermediate precision) and accuracy (data not published).

Results and Discussion

Stability of combinations of active components and excipients

A comparative study concerning stability of individual components, of combination between two, three components and four components revealed that pheniramine and acetylsalicylic acid are the least stable components, and their instability is further increased in their combination. As a technological solution, the replacement of pheniramine salicylate with clorpheniramine maleate led to a more stable combination (Table I), associated with a comparable anti-inflammatory and analgesic effect [17].

Table I

Screening of the main interactions between the active compounds, expressed in terms of changes in colour and odour after three months at $25 \pm 2^{\circ}\text{C}/60\% \pm 5\% \text{ RH}$

Composition	No. crt.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Acetylsalicylic acid		√	-	-	-	-	√	√	√	√	-	-	√	√	√	√
Caffeine		-	√	-	-	-	√	-	-	-	√	-	√	-	√	√
Acetaminophen		-	-	√	-	-	-	√	-	-	-	√	√	√	√	√
Pheniramine		-	-	-	√	-	-	-	√	-	√	√	-	√	√	-
Chlorpheniramine		-	-	-	-	√	-	-	-	√	-	-	-	-	-	√
Test Result																
Colour changes		-	-	-	+	-	-	-	+++	-	-	-	-	++	++	-
Characteristic smell		++	-	-	+	-	+	+	+++	+	+	+	+	++	++	+

In conclusion, in the absence of stabilizing excipients, pheniramine and acetylsalicylic acid proved to be unstable for time intervals longer than three months in long term storage conditions. Instability of both components is increased in their combination. Clorpheniramine and acetaminophen were stable and didn't influence the stability profile of other components. Due to the stability issues, clorpheniramine maleate was further used in the product development process. A technological problem is associated with the compression of high dosages of API powders and the necessity of using significant amounts of excipients, resulting in excessively large tablets. Since for the particular case analysed in this paper, direct compression raised difficulties due to quite

different physicochemical properties of the APIs, wet granulation was considered as an appropriate technology in the compressing process.

Consequently, a screening of the nature and quantity of excipients appropriate for tablet formulation was performed.

The effect of the proportion of water and alcohol in the hydroalcoholic polyvinylpyrrolidone (PVP) solution on agglutinant properties of separate powders and on their mixtures was studied. Representative results are presented in Table II. Cases when a larger than 2% amount of magnesium stearate was required in order to avoid adherence of the material to the tablet punches were denoted by “+”.

Table II

The influence of water/alcohol proportion on “compliance of powders mixture to tableting”				
PVP (%)	Water	Ethanol	Material adherence to the tablet punches	
5	30	70	+	
6	30	70	+	
7	30	70	+	
10	30	70	+	
5.5	28	72	–	
4.8	30	70	–	
5.6	40	60	–	
4.5	50	50	–	

The minimum quantity of magnesium stearate was found to be 1.5 g for 100 g powders. The quantity of stearate is “critical” since it is well documented since a very long time [3, 8] that both magnesium and calcium stearate produce a high degree decomposition of ASA, leading to change in organoleptic properties of the formulation. Moisture also led to a stability decrease, but surprisingly, high moisture caused less decomposition [15]. Replacement of 0.5 g of magnesium stearate with Aerosil didn't significantly

influence the powders flowing behaviour or the disaggregation of resulted tablets.

Stability of the tablet batches

The studies concerning three years stability of the tablets highlighted that ASA is the only component rising stability issues over time: in accelerated storage conditions ASA is falling by 5.62% whereas salicylic acid is reaching 5.13% in 3 month (Figure 1); in intermediate storage conditions ASA is falling by 2.54% and salicylic acid is reaching 4.63% in 6 month (Figure 2).

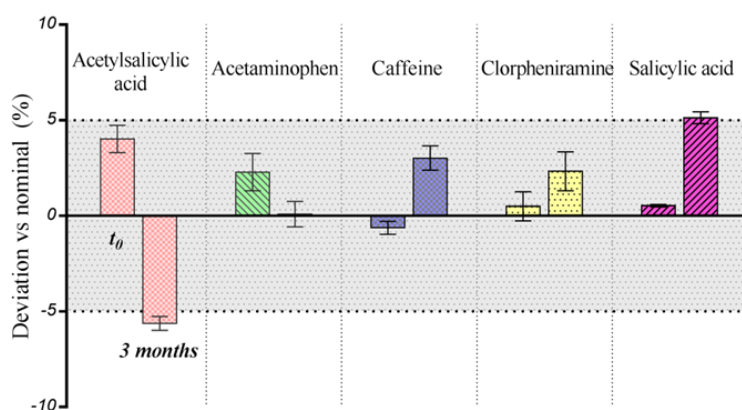


Figure 1.

Stability of the APIs under ICH/WHO accelerated storage conditions (40°C/75% ± 5% RH), evaluated on six different product batches, at 0 and 3 months

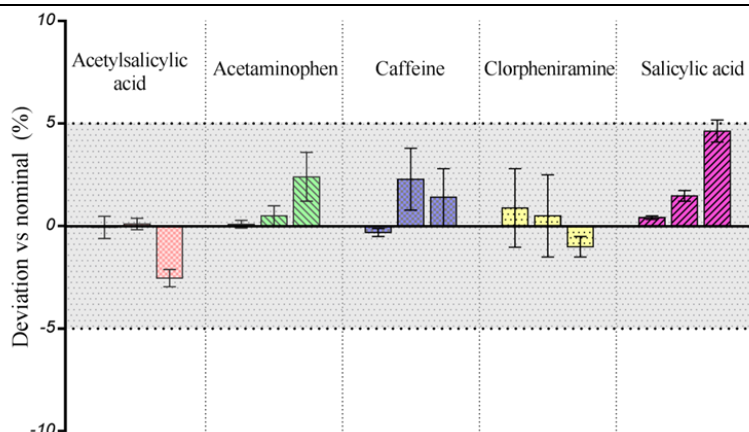


Figure 2.

Stability of the APIs under ICH/WHO intermediate storage conditions (30°C/65% ± 5% RH), evaluated on six different product batches, at 0, 3 and 6 months

Under real time stability testing conditions, ASA was falling by 3.75% and salicylic acid reaching 3.79% within the study period (Figure 3).

Degradation followed zero order kinetics and point wise estimation of T90% was found to be 41 months.

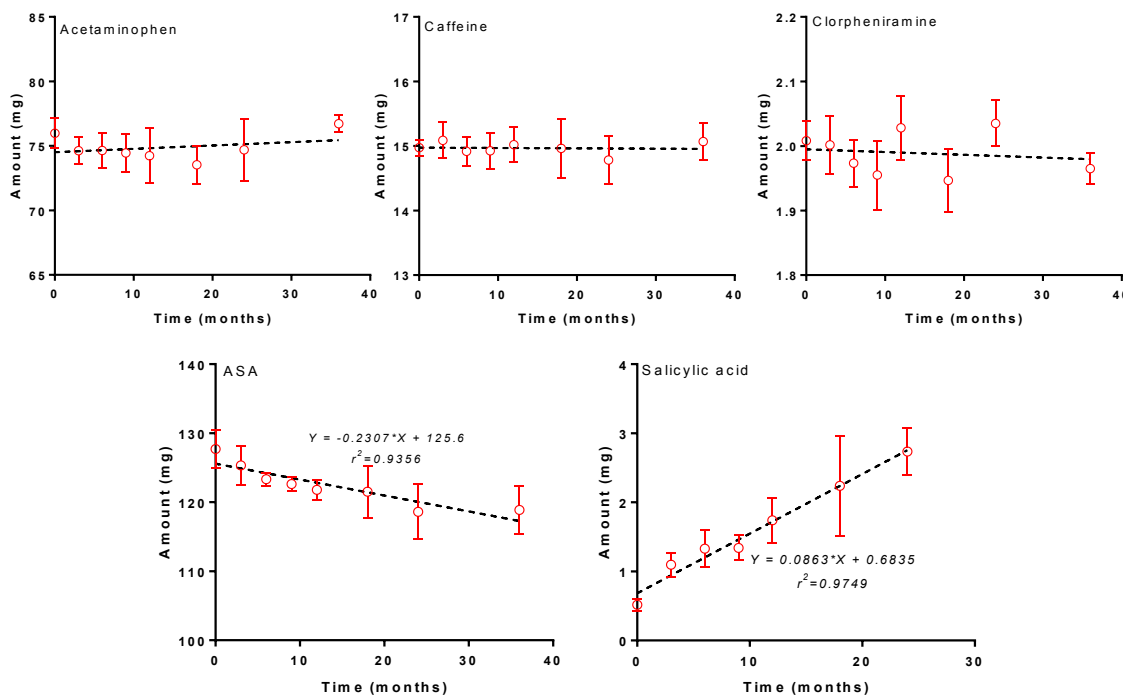


Figure 3.

Stability of the APIs under ICH/WHO real time storage conditions (25 ± 2°C/60 ± 5% RH), evaluated on six different product batches

Barrier coatings are frequently employed on solid oral dosage forms under the assumption that they prevent moisture sorption into tablet cores thereby averting premature degradation of moisture-sensitive active ingredients [1, 9, 14]. Additional protection from moisture by using PVC-PVDC/Al conditioning material improved stability, T90% being increased from 41 to (when using only PVC/Al) to 55 months (Figure 4).

In terms of degradation kinetics, it is to observe a few differences from what is found in literature. Extensive researches published in three papers by Carstensen *et al.* [5-7] concerned decomposition of ASA powders in the solid state in the presence of limited amounts of moisture, by using the Leeson-Mattocks model which is based on the assumption that initially the decomposition rate is proportional to the amount of moisture at time t and to the solubility (S) of the ASA in the adsorbed aqueous

layer [11]. One assumption by Carstensen was that salicylic acid forms a layer between the water and the ASA and that the decomposition rate-determining step is the diffusion of water through this layer. However, the solubility is influenced by the appearance of degradation products and decrease of the amount of water, making difficult to predict the ASA decomposition behaviour in combination of powders, therefore comparison of data is not simple since experiments were performed in different conditions.

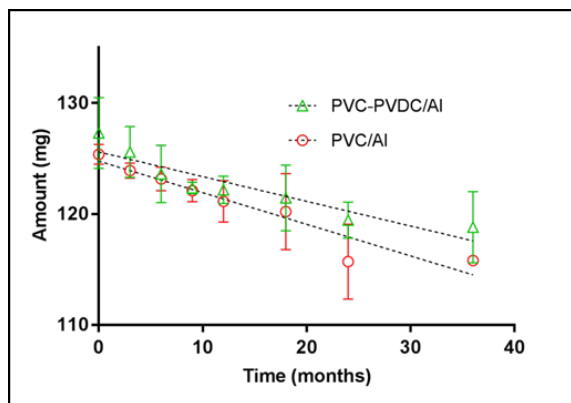


Figure 4.

Degradation kinetics of ASA in PVC/Al and PVC-PDVC/Al conditioning materials

Conclusions

The study results pointed out that no stability interactions between ASA, acetaminophen, caffeine and chlorpheniramine maleate were identified.

Over a three years' timeframe, the degradation process affected only ASA. Disappearance of ASA followed a zero order kinetic model and was correlated with the appearance of salicylic acid. Point wise estimation of T90% for ASA degradation kinetics was found to be 41 months. The increase of the protection against humidity was achieved by the change of the conditioning material, with an additional increase of the T90 % to 55 months. At 36 months in real time storage conditions, the quality requirements of the European Pharmacopoeia were met by all the active substances.

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