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Compatibility between four anti-TB drugs and tablet excipients determined by microcalorimetry

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Received November 18, 2018; accepted February 18, 2019

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Pharmazie 74: 350-351 (2019) *doi: 10.1691/ph.2019.8189*

Previous isothermal microcalorimetry studies at 40 °C, with and without humidity (RH 75%), had shown no incompatibility between rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA) and ethambutol HCl (EMB). The purpose of this study was to explore any interactions at an increased temperature of 50 °C and also to investigate the possibility of incompatibilities between the drugs and tablet excipients used in the most commonly prescribed commercial four-drug TB FDC. No incompatibilities were observed between the excipients, or when the excipients were tested with the four drugs individually. Incompatibility was observed with the four drugs combined.

1. Introduction

IMC (isothermal microcalorimetry) is a sensitive and useful tool to study thermal activities like chemical degradation, crystallization, compound interactions, to name but just a few. Microcalorimetry proved to be highly sensitive towards heat flow (±0.1 µW) and temperature changes (Ball and Maechling 2009; Gaisford 2005; Skaria et al. 2005). According to Skaria et al. (2005), the use of isothermal microcalorimetry is not widespread in the pharmaceutical field, because the data obtained are more complex of nature and often more than one process contribute to the data obtained. We used isothermal microcalorimetry exclusively to investigate if there is a possible interaction between the different anti-tuberculosis (anti-TB) drugs as combined in a well-known four drug containing fixed dose combination (FDC) product.

Anti-TB FDC products have been reported to be unstable in formulation due to chemical interactions between the drugs. It has been previously published that ethambutol hydrochloride catalyses the degradation of rifampicin and isoniazid in the formulation due to its reported hygroscopic nature. This is said to result in the loss of rifampicin potency upon storage. The proposed incompatibility of the four anti-TB dugs has been reported to have led to two major problems, namely; (1) the decrease in bioavailability of rifampicin upon oral administration and (2) instability of drugs within the formulation environment (Bhutani et al., 2005; Sankar et al. 2003; March 2001).

2. Investigations, results and discussion

The first tested set consisted of rifampicin (RIF), isoniazid (INH), ethambutol hydrochloride (EMB) and pyrazinamide (PZA) combined in the weight ratio as present in commercial tablet formulations. Heat flow data of each individual active ingredient were measured to obtain reference heat flow curves for each of them. The obtained heat flow results obtained for the tablet mixture containing only the four active ingredients are provided in Fig. 1.

During a step-wise elimination experiment it was deduced that no interaction exists between INH, PZA or EMB, meaning that RIF is the drug interacting with the other three anti-TB drugs. This was further tested through microcalorimetry studies and it was identified that an incompatibility exists between INH and RIF (Fig. 2) at 50 °C (isothermal). An average heat flow of -64.05 µW/g and an interaction error of 73.41 µW/g were calculated. The presence of a distinctive slope and a clear difference in the physically measured and the theoretically calculated heat flow curves are indicative of an incompatibility (O'Neil and Gaisford 2011; Gaisford and Buckton 2001).

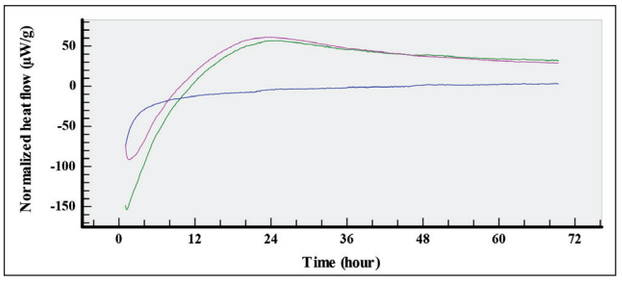

Fig. 1: Heat flow graph obtained with the combination of RIF, INH, PZA and EMB. The average interaction heat flow obtained during this run was calculated to be 29.8 µW/g with an interaction error of 44.8 µW/g. This is indicative of an interaction occurring between the different active ingredients that forms the active ingredient component of the FDC tablets.

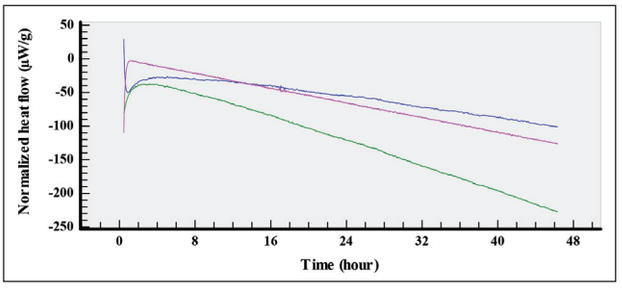

Fig. 2: Heat flow graph obtained with the combination of RIF, INH, PZA and EMB. The heat flow graph obtained for RIF+INH showed an incompatibility as measured at 50°C. An average heat flow of -64.05 µW/g and an interaction error of 73.41 µW/g were calculated. The presence of a distinctive slope and a clear difference in the physically measured and the theoretically calculated heat flow curves are indicative of an incompatibility.

No incompatibilities were observed between the excipients, or when the excipients were tested with the four drugs individually. Incompatibility was observed with the four drugs combined.

Interaction of single drugs, combined with the excipients was also excluded. Combinations of INH+PZA+EMB, PZA+EMB, INH+PZA, RIF+PZA, RIF+EMB with excipients were not observed to interact with one another.

The only incompatibility detected, whilst testing the active and inactive ingredients of a commercial anti-TB FDC using microcalorimetry at 50 °C, was between RIF and INH. Our prior testing at 40°C (with and without 75% RH) did not show this interaction. Even at 50 °C, the heat flow measured did not indicate a large or rapid reaction. Microcalorimetry is the most sensitive method of measuring chemical incompatibility, with units in µW/g or nW/g. Potential chemical interaction between RIF and INH in the absence of water has been theorized, but if it cannot be measured with microcalorimetry at 40 °C it is unlikely to be a major contributor to RIF and INH degradation in anti-TB FDCs. The rationale for testing drug-drug compatibility at higher isothermal temperature is to allow the acceleration of a possible interaction between the compounds. At a higher temperature, incompatibility detection is enhanced. Although pharmaceutical products are not necessarily stored at temperatures higher than 40 °C, it is valuable to gain the knowledge that should two compounds be incompatible, the possibility will exist for an interaction to occur during the complete shelf-life of the product, even when stored at lower temperatures. Furthermore, from the data obtained during this study it became apparent that should RIF and INH combinations be exposed to temperatures higher than 40 °C, as is often the case in South African rural clinic settings during summer, a reaction between the two drugs will occur.

3. Experimental

Different mixtures consisting of RIF, INH, PZA, EMB and tablet excipients were tested for compatibility. All drugs were purchased from DB Fine Chemicals (Johannesburg, South Africa) and had purity values higher than 95.0 %. The ratios in the mixtures were *as per* the commercial FDC product (RIF = 150 mg; INH = 75 mg; PZA = 400 mg; EMB = 275 mg). The following excipients were tested: Croscarmellose sodium = 10.5 mg; polyvinyl pyrrolidone = 7 mg; ascorbic acid = 3.5 mg; starch = 113.31 mg; lactose = 210.44 mg; sodium lauryl sulphate = 3.5 mg and magnesium stearate = 5.25 mg and was a kind donation from the Department of Pharmaceutics, School of Pharmacy, North-West University. The tablet mixture was tested in relation to the different excipients that are included in the tablet formulation.

A 2277 Thermal Activity Monitor (TAMIII) (TA Instruments, USA) equipped with an oil bath with a stability of ±100 µK over 24 h was used during this study. The temperature of the calorimeters was maintained at 50 °C (dry). Heat flow was measured for the single components as well as the mixtures. The calorimetric outputs observed for the individual samples are summed to give a theoretical response. This calculated hypothetical response represents a calorimetric output that would be expected if the two or more materials do not interact with each other. If the materials interact the measured calorimetric response will differ from the calculated theoretical response. Samples for testing were prepared by accurately weighing sufficient quantities providing a total mass of approximately 100 mg, into glass ampoules. Each ampoule was tightly sealed and used for subsequent microcalorimetric analysis.

Acknowledgements: The authors are grateful for the financial support received from the National Research Foundation (NRF) of South Africa as well as the Centre of Excellence for Pharmaceutical Sciences (Pharmacen) at the North-West University, Potchefstroom, South Africa.

Disclaimer: Any opinions, findings and conclusions, or recommendations expressed in this material are those of the authors and therefore the NRF does not accept any liability in regards thereto.

Conflicts of interest: None reported.

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