1-2023

Drug-Excipient Interactions

Maria Ballester
Nova Southeastern University, mballest@nova.edu

Drug – Excipient Interactions

Dr. Maria Ballester

1 Introduction

An excipient is a substance formulated with the active ingredient of a medication, to either bulking-up formulations (as fillers, or diluents), or to confer a therapeutic enhancement on the active ingredient (as facilitators of drug absorption or solubility). Though excipients were at one time considered to be "inactive" or “inert” ingredients, chemically and pharmacologically. They are now understood to be "a key determinant of dosage form performance", showing interactions that prevent absorption and bioavailability. The most frequently used drug delivery method is the compressed tablet, generally built around one of these types of excipients:

1. Cellulose
2. Lactose
3. Other sugars as sucrose
4. Starch and starch derivatives
5. Inorganic salts
6. Polyols

There is now a growing appreciation of the role that pharmaceutical excipients play in the production, shelf stability, dispensability, patient dosage acceptability, bioavailability, and delivery of the active pharmaceutical ingredient to the target organ. In fact, over the years some excipients are used as food additives, and cosmetic ingredients. This has led to higher awareness, making regulation and proper testing a necessity.

Drug-excipient incompatibility is usually detected through thermal analysis techniques, such as TGA and DSC, since they are fast, reliable, and have extremely high sensitivity for detecting changes in composition, thermal stability, and structure. DSC increases or automatically decreases the temperature of the system at a given rate, while monitoring any temperature differential that arises between the two cells. The heat absorbed or releases can be measured and related to the test material. TGA is a method of thermal analysis where physical and chemical properties of material are measured as a function of increasing temperature and/or constant mass loss. It provides information on physical and chemical phenomena as vaporization, sublimation, dehydration, and decomposition.

2 Materials

- Itopride HCl.
- Acetylsalicylic acid.
- Magnesium stearate.
- Sodium bicarbonate, citric acid and methyl cellulose.

3 Experimental

Experiments will be performed using a Shimadzu Gas Chromatograph GC-2010 System, using DSC and TGA thermal analysis techniques. In the *thermogravimetric analysis* (TGA) changes in physical and chemical properties of materials are measured as a function of increasing temperature (with constant heating rate), or as a function of time (with constant

temperature and/or constant mass loss). In the *differential scanning calorimetry* (DSC) the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature.

Using these two methods, the sequence and test parameters of experiments are as follows:

1. **Part I**: Using TGA, and DSC method, you will use multiple heating rates is to determine if the crystalline drug and/or excipient undergo true melting or lose crystalline structure as a result of decomposition.
   a. *TGA method*: perform experiments at 1, 3 and 9 $℃/\mathrm{min}$ with approximately 5 mg sample.
   b. *DSC method*: analyze approximately 2 mg of the separate drug and excipient at 1, 3 and 9 $℃/\mathrm{min}$ in hermetic pans.
2. **Part II**: Using the DSC method you will compare the results with the pure active pharmaceutical ingredient (1 $℃/\mathrm{min}$ run). If the melting point or apparent melting temperature are reduced by more than $2-5\ ℃/\mathrm{min},$ this indicates interaction.
   a. *DSC method*: analyze approximately 5 mg of a 50/50 mixture of the drug and excipient at 1 $℃/\mathrm{min}$ in a hermetic pan.

4 Results and Analysis

Discuss your results based on the TGA and DSC methods results, according to drug stability and the thermal behavior of the binary mixtures of drug and excipients. Remember the comparison should be done using the data of the drug and excipient with those of the drug and excipient alone. These are the possible questions that should be able to answer in your discussion:

1. You should keep a record of the results using the DSC method using the following table. Perform a preliminary analysis and indicate apparent interaction, incompatibility or any decomposition observed from these combinations.

Drugs	Magnesium stearate	Sodium bicarbonate	Citric acid	Methyl cellulose
Itopride HCl				
Acetylsalicylic acid				

Table 1. Preliminary analysis of the different mixtures.

2. What does the combination of itopride HCl and sodium bicarbonate at 195 ℃ reflects?
3. Are there any interactions between aspirin and Magnesium stearate?

5 References

1. Privalov PL, Potekhin SA. Scanning microcalorimetry in studying temperature-induced changes in proteins. Methods Enzymol 1986; 131:4–51. [PubMed]
2. Weber PC, Salemme R. Applications of calorimetric methods to drug discovery and the study of protein interactions. Curr Opin Struc Biol 2003; 13:115–121. [PubMed]
3. Haynie DT. Biological Thermodynamics. Cambridge, UK: Cambridge University Press, 2008.
4. Haines PJ, Reading M, Wilburn FW. Differential thermal analysis and differential scanning calorimetry. In Brown ME, editor. (ed): Handbook of Thermal Analysis and Calorimetry, vol 1 The Netherlands: Elsevier Science BV; 1998;279–361.