

LC-Mass as a Complementary Method in Detecting Drug-Excipient Incompatibility of Pharmaceutical Products

Monajjemzadeh F*

Department of Pharmaceutical and Food Control, Tabriz University of Medical Sciences, Tabriz, Iran

Stability of a drug in a pharmaceutical formulation is a critical issue and should be guaranteed by the manufacturer prior to commercialization of a product. Regulatory authorities in each country are responsible for carefully monitoring the compliance with the accepted guidelines for example the ICH ones [1]. Formulator pharmacists of pharmaceutical industries always make sure about the drug stability in “preformulation” process [2].

Recent studies on the interaction of drug with excipients have highlighted the need for monitoring such incompatibilities inside a formulation matrix. Different types of interactions such as transacylation, the Maillard browning reaction, acid base reactions and physical changes are discussed in the literature [3]. Among these the Maillard type reaction will be referred as a model interaction in the following text.

The most common methods in detecting the drug-excipient incompatibility include; Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR) [4-14]. DSC is a fast and reliable technique in detecting drug stability. Samples in this method are always prepared as binary and or tertiary mixtures including the drug substance combined with only one of the excipients in each experiment [4,15]. The argument is performed by disappearing or partially diminishing the melting endotherm of the drug in its 1:1 “W/W” binary mixtures with excipients [11-13,16]. Care should be done because this event may be related to another phenomenon such as dissolution of the drug in the molten excipient [17]. The enthalpy calculations can be made to show any difference of the observed thermal events in the presence of the excipient. Although this method introduces useful data, it is still so far from providing real incompatibility documentation. A problem with DSC method is that it only provides a simple distinguish between compatible and incompatible excipients.

Despite DSC, the FTIR analysis can open a way to understanding the type of incompatibility. Samples for FTIR can be in liquid, solid and or semisolid state. As in DSC, the components are reduced to binary or tertiary mixtures to be able to realize the type of the interaction. It is common to use isothermal stress conditions for all sample types to decrease time needed to initiate the reaction. In solid samples it is recommended to add small quantities of water, again to accelerate the chemical reaction along with the isothermal stress conditions [15].

FTIR can track the changes and report the disappear or creation of vibrational peaks in the spectrum of the reaction mixture. In the Maillard type incompatibility the formation of Imine vibration and diminish in amine vibrations is expected [12,18].

So far, the possible incompatibility is detected and some probable mechanisms have been proposed successfully using DSC and FTIR techniques.

Reaction of a drug with excipient can be studied on a full adduct mixture or on the completely separated adduct, using extraction, Micro-extraction and or any other separation methods. Other than the most common HPLC method, Liquid-Liquid Extraction (LLE) and

Solid Phase Extraction (SPE) techniques are most prevalent separation methods used in drug excipient interaction studies [19].

Liquid chromatography (LC), Mass Spectroscopy is a confirmatory method to prove the proposal [20]. First a good separation should be performed using LC. In this step a PDA detector is a useful equipment because it can produce an important factor called “peak purity”. The importance of this factor can be explained by the presence of degradation products due to drug instability or incompatibility with the formulation matrix (Excipients). Thus a key factor in further estimations is the purity of the observed peaks in the chromatograms to ensure that only one analyte is eluted in each peak. This process leads to setting a stability indicating HPLC method [14,16,21-23]. Then the method can be transferred to a preparative column in order to prepare excess amounts of each analyte according to the observed peaks in the resulted chromatogram [24]. The collected peaks can be analyzed by FTIR, Mass and or NMR (Nuclear Magnetic resonance) to reach a good explanation of the reaction mechanism [23].

Sometimes researchers only report the remaining drug content in each formulation without explaining the possible interaction products and or pathways. This is also truth if the LC method used in the study was confirmed to be a stability indicating one.

The LC method with a mobile phase free from salts can be successfully transferred to an ESI-LC-Mass system [25]. If the PDA detector was not used to check the peak purity in the initial method set up, here in LC-Mass the same can be down with checking the Single ion current (SIC). LC mass can confirm the mass of the resulted peaks using m/z values and provides some fragmentation patterns that can be used to prove the chemical structure of a analyte. LC/Mass-Mass is another powerful method to track the fragmentation patterns in detail and also to provide multiple reactions monitoring (MRM) chromatograms [11-13,25]. In this mode, a collision cell is placed between the first and the second quadrupole to induce collision between ions using an inert gas. Thus a forced fragmentation will be produced and the system can be programmed accordingly to record the presence of each ion related to its major fragmented ion.

Although it is not a common method in monitoring drug stability in pharmaceutical formulations due to almost large and pure samples, if needed NMR studies add a more detailed argument to what was proposed so far [14].

*Corresponding author: Farnaz Monajjemzadeh, Department of Pharmaceutical and Food Control, Tabriz University of Medical Sciences, Tabriz, Zip code: 5166414766, Iran, Tel: +984113392606; Fax: +984113344798; E-mail: Monajjemzadeh@tbzmed.ac.ir

Received March 17, 2014; Accepted March 20, 2014; Published March 27, 2014

Citation: Monajjemzadeh F (2014) LC-Mass as a Complementary Method in Detecting Drug-Excipient Incompatibility in Pharmaceutical Products. J Mol Pharm Org Process Res 2: e110. doi: 10.4172/2329-9053.1000e110

Copyright: © 2014 Monajjemzadeh F. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

Acknowledgement

The author would like to Thank Dr Thomas Robertson for his practical consult in LC Mass technique.

References

1. Bakshi M, Singh B Singh A, Singh S (2001) The ICH guidance in practice: stress degradation studies on ornidazole and development of a validated stability-indicating assay. *J Pharm Biomed Anal* 26: 891-897.
2. Aulton ME, Taylor KM (2013) *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*. (4th edn) Elsevier Health Sciences, USA.
3. Bharate SS, Bharate SB, Bajaj A N (2010) Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients a comprehensive review. *Journal of Excipients & Food Chemicals* 1: 1-3.
4. Marini A, Berbenni V, Pegoretti M, Bruni G, Cofrancesco P, et al. (2003) Drug-excipient compatibility studies by physico-chemical techniques; the case of atenolol. *Journal of Thermal Analysis and Calorimetry* 73: 547-561.
5. Verma R K, Garg S (2005) Selection of excipients for extended release formulations of glipizide through drug-excipient compatibility testing. *J Pharm Biomed Anal*. 38: 633-644.
6. Tomassetti M, Catalani A, Rossi V, Vecchio S (2005) Thermal analysis study of the interactions between acetaminophen and excipients in solid dosage forms and in some binary mixtures. *J Pharm Biomed Anal* 37: 949-955.
7. Abdoh A, Al-Omari M, Badwan A, Jaber A (2004) Amlodipine besylate-excipients interaction in solid dosage form. *Pharm Dev Technol* 9: 15-24.
8. Mura P, Manderioli A, Bramanti G, Furlanetto S, Pinzauti S (1995) Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients. *International Journal of Pharmaceutics* 119: 71-79.
9. Hartauer KJ, Guillory JK (1991) A comparison of diffuse reflectance FT-IR spectroscopy and DSC in the characterization of a drug-excipient interaction. *Drug Development and Industrial Pharmacy* 17: 617-630.
10. Kiss D, Zelkó R, Novák C, Éhen Z (2006) Application of DSC and NIRS to study the compatibility of metronidazole with different pharmaceutical excipients. *Journal of Thermal Analysis and Calorimetry* 84: 447-451.
11. Monajjemzadeh F, Hassanzadeh D, Valizadeh H, Siahi MR, Shahbazi Mojarrad J, et al. (2009) Assessment of feasibility of Maillard reaction between baclofen and lactose by liquid chromatography and Tandem mass spectrometry, application to Pre formulation studies. *AAPS PharmSciTech* 10: 649-659.
12. Monajjemzadeh F, Hassanzadeh D, Valizadeh H, Siahi-Shadbad MR, Mojarrad JS, et al. (2009) Compatibility studies of acyclovir and lactose in physical mixtures and commercial tablets. *Eur J Pharm Biopharm* 73: 404-413.
13. Monajjemzadeh F, Hassanzadeh D, Valizadeh H, Siahi-Shadbad MR, Mojarrad JS, et al. (2011) Detection of gabapentin-lactose Maillard reaction product (Schiff's Base): Application to solid dosage form preformulation. Part 1. *pharmind: Die Pharmazeutische Industrie* 73: 174-177.
14. Harmon PA, Yin W, Bowen WE, Tyrrell RJ, Reed RA (2000) Liquid chromatography-mass spectrometry and proton nuclear magnetic resonance characterization of trace level condensation products formed between lactose and the amine-containing diuretic hydrochlorothiazide. *J Pharm Sci* 89: 920-929.
15. Serajuddin AT, Thakur AB, Ghoshal RN, Fakes MG, Ranadive SA, et al. (1999) Selection of solid dosage form composition through drug-excipient compatibility testing. *J Pharm Sci* 88: 696-704.
16. Chadha R, Bhandari S (2014) Drug-excipient compatibility screening-Role of thermoanalytical and spectroscopic techniques. *J Pharm Biomed Anal* 87: 82-97.
17. Hamishehkar H, Valizadeh H, Alasty P, Monajjemzadeh F (2013) Spray Drying as a Fast and Simple Technique for the Preparation of Extended Release Dipyridamole (DYP) Microparticles in a Fixed Dose Combination (FDC) Product with Aspirin. *Drug Res (Stuttg)* 64: 104-112.
18. Namli H, Turhan O (2006) Background defining during the imine formation reaction in FT-IR liquid cell. *Spectrochim Acta A Mol Biomol Spectrosc* 64: 93-100.
19. Wirth DD, Baertschi SW, Johnson RA, Maple SR, Miller MS, et al. (1998) Maillard reaction of lactose and fluoxetine hydrochloride, a secondary amine. *J Pharm Sci* 87: 31-39.
20. Lim CK, Lord GA (2002) Current developments in LC-MS for pharmaceutical analysis. *Biol Pharm Bull* 25: 547-557.
21. Carstensen JT, Rhodes CT (2000) *Drug Stability: Principles and Practices*. (3rd edn) Marcel Dekker, New York.
22. Bhutani H, Singh S, Vir S, Bhutani K, Kumar R, et al. (2007) LC and LC-MS study of stress decomposition behaviour of isoniazid and establishment of validated stability-indicating assay method. *J Pharm Biomed Anal* 43: 1213-1220.
23. Bhardwaj S P, Singh S (2008) Study of forced degradation behavior of Enalapril maleate by LC and LC-MS and development of a validated stability-indicating assay method. *J Pharm Biomed Anal* 46: 113-120.
24. Mistry N, Ismail IM, Smith MS, Nicholson JK, Lindon JC (1997) Characterisation of impurities in bulk drug batches of fluticasone propionate using directly coupled HPLC-NMR spectroscopy and HPLC-MS. *J Pharm Biomed Anal* 16: 697-705.
25. Cole RB (1997) *Electrospray Ionization Mass Spectrometry: Fundamentals, Instrumentation, and Applications*. (1st edn) Wiley-Interscience, USA.