Printed in the Republic of Korea
ANALYTICAL SCIENCE & TECHNOLOGY
Vol. 34 No. 2, 46-55, 2021
https://doi.org/10.5806/AST.2021.34.2.46

Gliclazide compatibility with some common chemically reactive excipients; using different analytical techniques

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(Received December 30, 2020; Revised February 20, 2021; Accepted February 24, 2021)

Abstract: Evaluation of drug-excipient compatibility is one of the basic steps in the preformulation of pharmaceutical dosage forms. Some reactive excipients have been known so far which may cause stability problems for drug molecules in pharmaceutical dosage forms. The aim of this study was to evaluate drug-excipient compatibility of gliclazide with some common pharmaceutical excipients, known for their ability to incorporate in drug-excipient interactions. Binary mixtures were prepared using lactose, magnesium stearate, polyvinylpyrrolidone, sodium starch glycolate, polyethylene glycol 2000 and dicalcium phosphate. Based on the results; gliclazide was incompatible with all tested excipients; but not with dicalcium phosphate. DSC (Differential Scanning Calorimetry) results were in accordance with HPLC (High Pressure liquid chromatography) data and were more predictive than FTIR (Fourier Transform Infrared Spectroscopy). Drug and reactive excipients incompatibility was fully discussed and documented. It is advisable to avoid incompatible excipients or carefully monitor the drug stability when incorporating such excipients in final formulation designs.

Key words: incompatibility, excipient, gliclazide, differential scanning calorimetry, fourier transform infrared spectroscopy, high performance liquid chromatography

1. Introduction

Evaluation of Drug-excipient physicochemical compatibility is one of the basic steps in the formulation of pharmaceutical dosage forms. Excipients have an inevitable role in the preparation of pharmaceutical products. They may change the release characteristics of an active agent or may protect them from environmental or manufacturing risks.[1,2] Although excipients are pharmacologically inert but they may be chemically reactive leading to a change in the functional moiety of a drug molecule and thus leading to a new chemical entity which may consequently alter the stability and drug bioavailability, efficacy and also safety.[1,3] Drug-excipient compatibility screening tests are very useful in reducing the

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quality deficits and increasing the quality assurance and are usually performed in the pre-formulation stage of all pharmaceutical dosage forms.[4,5]

In diabetes mellitus a decrease in insulin sensitivity and/or secretion or an increase in pancreas glucose secretion leads to elevated blood glucose levels. In the majority of patients with diabetes mellitus, initially, oral drug therapy is being used as mono or multidrug regimens.[2]

Gliclazide (Glc) is a sulfonylurea drug that stimulate the release of insulin from pancreatic β cells and is being administered 30 – 80 mg as a once a day dose.[6]

Drug-excipient compatibility screening tests can be performed using Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and High-pressure liquid chromatography (HPLC) coupled with different detectors, as essential methods in compatibility studies.[7] Although DSC provides main physicochemical characteristics of a pure sample such as the melting point, it has been utilized in detecting compatibilities in drug and excipient mixtures, too.[8] It should be noted that, this technique provides an intermediate performance and should be used and interpreted with caution and along with other instrumental results such as FTIR and HPLC.[9] In pre-formulation, Fourier transform infrared spectroscopy (FTIR) can detect any changes in the absorption spectra of the drug-excipient blends in drug-excipient compatibility evaluations. This needs an in depth knowledge of the IR absorption pattern of the drug molecule and excipients.[9] HPLC methodology creates a reliable final decision in drug-excipient compatibility evaluations. This essential decision depends on a number of parameters such as accuracy and reproducibility of the methods used in quantification studies.

The chemical activity of excipients and their involvement in chemical reactions with other susceptible molecules such as drug molecules, is often due to their intrinsic activity and the presence of active impurities in the excipients as raw materials.

To the best of our knowledge, the physicochemical compatibility of gliclazide with common pharmaceutical reactive excipients which are known for their ability to incorporate in drug-excipient interactions has not been investigated yet. Thus drug-excipient compatibility between gliclazide and reactive excipients (lactose, Magnesium stearate, polyvinylpyrrolidone, Sodium starch glycolate and PEG2000) is evaluated in this study using HPLC, DSC and FTIR techniques.

2. Experimental

2.1. Chemicals and reagents

Gliclazide(IUPAC:1-(3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[c]pyrrol-2-yl)-3-(4-methylphenyl) sulfonylurea) (CAS: 21187-98-4) were purchased from Hangzhou Dingyan Chem Co., LTD, China with purity fraction of 0.98 and 0.99 respectively. Excipients were all from (Merck, Germany) with pharmaceutical grade and a purity fraction above 0.97. Names classifications and CAS numbers of excipients are as follow.[10]

Filler excipients such as Lactose (Lac) (CAS: 63-42-3) and Dicalcium phosphate(DCP) (CAS: 10031-30-8), Coating agent such as Poly Vinyl pyrrolidone (PVP) (CAS: 88-12-0), disintegrant such as sodium Starch Glycolate (NaSg) (CAS: 9063-38-1) and lubricants such as Poly Ethylene Glycol 2000 (Peg) (CAS: 25322-68-3), and Magnesium Stearate (Mgst) (CAS: 557-04-0).

2.2. Preparation of binary mixtures for compatibility studies

Binary mixtures of drugs and each of the excipients were prepared in 1:1 mass ratio in micro tubes and then vortexed to be homogenized. Stress conditions were provided by adding 20 % (v/w) water to the solid samples inside the micro tubes (200 mg) and incubating at 40 ºC for 2 months. This an accepted procedure and was first introduced by *Abu T M Serajuddin* in 1999,[11,12] and have been used in several solid state studies.[13-16]

2.3. Analytical methods

2.3.1. HPLC

The Knauer HPLC system (Berlin, Germany) was made up of a Knauer controller quaternary pump and

a UV detector (Knauer No. E 4310) and photodiode array detector (PDA) (Agilent, 1260 infinity). The whole operation was controlled using EZ Chrome elite software. The system was operated at a constant UV wavelength of 200 nm with a flow rate of 1ml/min by 20 μL injection volume. The method was transferred[17] and partially validated according to ICH guidelines.[18] After reaching acceptable system suitability parameters, Linear range, accuracy, precision (repeatability), LOD and LOQ were calculated accordingly. The stationary phase was a high resolution C18 column (CLIPEUS, C18, 5 μm, 250 × 2.1 mm, USA) and the mobile phase was a mixture of acetonitrile and buffer solution (solution 0.35 g/L disodium hydrogen phosphate and 0.6 g/L potassium dihydrogen phosphate) in a 60:40 v/v ratio. Elution was performed in an isocratic mode.

Mobile phase was employed as a diluent for stock solutions of drug and consequent dilutions were made to prepare different calibration concentrations of Glc (20, 25, 50, 100, 200 μg/ml).

Mixtures were analyzed immediately after mixing and also after incubation at stress conditions, and injected into HPLC system.[17] While analyzing stressed samples the purity of the peaks related to drug molecules were checked with PDA technique.

Peak identification was performed using Mass analysis. Mass spectrometric data were assessed using a Waters ZQ Mass 2000 (Waters, USA) spectrometer equipped with electron spray ionization and a single quadrupole Mass analyzer. All data were evaluated using Mass lynx version 4.01 software. Voltage values were set for Cone (4KV), capillary (70V), extractor (3V) and RF lens (1V), temperature was also defined for source (100 °C) and desolvation (150 °C) and gas flow rate was determined for cone (150L/h) and desolvation (600 L/h) on the program.

2.3.2. DSC

DSC curves were obtained in a Shimadzu DSC-60 cells and were analyzed using TA-60 software, in closed aluminum pans. Sample weight was kept constant at 2 mg and the heating rate was defined at 10 $^{o}C.min^{-1}$ up to 300 ^{o}C under air atmosphere.

2.3.3. FTIR

FTIR spectra was recorded to detect the possible incompatibility and the type of the chemical reaction when possible. The IR spectra were obtained from each of samples with FTIR Bomem machine (MB-100 series, Quebec, Canada) and software (GRAMS/32, version 3. 04) in the spectral area of 400 −4000 cm^{-1}. KBr pellets were compressed using potassium bromide powder and solid samples in an approximate 10:1 mass ratio. The obtained IR spectra were the average of 10 consecutive scans.

3. Results and Discussion

In this section HPLC data for each binary mixture after stress condition are tabulated. FTIR spectrums and DSC curves of incompatible mixtures were also achieved. It should be noted that FTIR data were gained before and after stress but DSC data were recorded only for physical mixtures.

3.1. HPLC Results and discussion

The HPLC chromatogram of Glc standard solutions is depicted in *Fig.* 1. Validation parameters are presented in *Table* 1.

The DSC curve of Glc (*Fig.* 1-B), shows only one sharp endothermic event at 169.59 ^{o}C related to Glc melting.[19] The curve ends in 300 °C with a pattern similar to decomposition reactions. Mass spectra illustrated in *Fig.* 1-C displays the mass spectrum of pure Glc in methanol (10 μg/ml). Molecular ion of the drug is seen at an m/z value equal to 324.4 with a weak intensity. This is accordance with molecular weight of Glc, which is 323.412 g/mol.

The next ion with high intensity in about in 346.5 m/z value, indicates the molecular ion bonded with sodium, (M+23). Base peak with the highest intensity was seen in 153.3 m/z which is resulted from fragmentation under mass analysis.

All stressed binary samples of Glc were injected into HPLC system. The percentage of the remaining drug content after stress was calculated based on the calibration curve and data are depicted in *Table* 7. The drug loss less than 10 percent was estimated as a

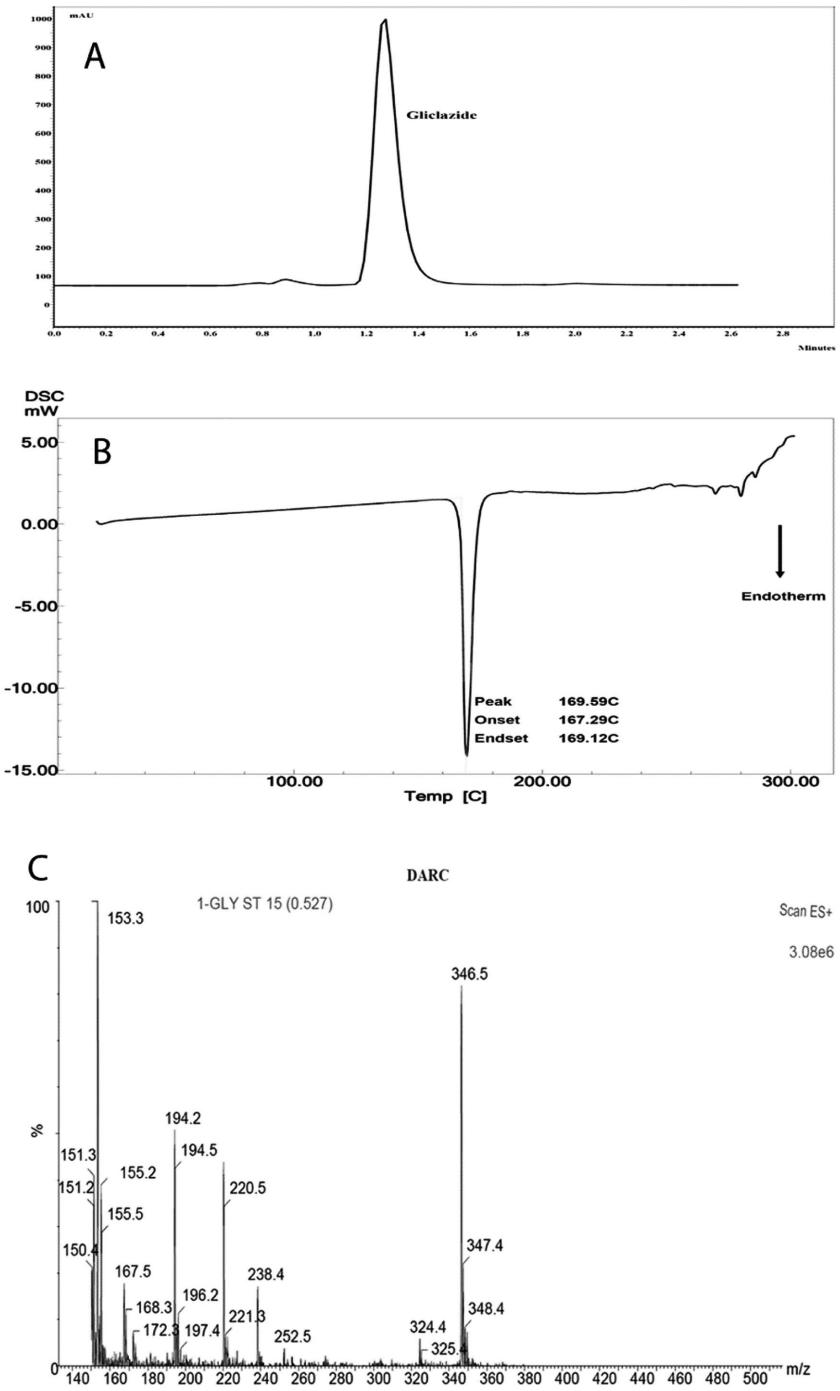

Fig. 1. Standard Glc A) HPLC chromatogram, B) DSC curve and C) Mass Spectrum.

compatible mixture.

According to results (*Table* 2), PVP, Lac, Peg, NaSg and Mgst containing binary samples were assigned as incompatible mixtures. The least stable binary mixture was determined as Glc-Mgst and Glc-Peg with about 40 % drug loss. Mixture of Glc with PVP

Table 1. Validation Parameters of HPLC method for Glc

Calibration equation	Correlation coefficient (r)	LOD (µg/ml)	LOQ (µg/ml)	Concentration (µg/ml)	Accuracy ± SD %	Repeatability (RSD %)
y = 113403x+ 01355	0.995	3.41	10.24	25	97.82 ± 4.38	3.24
				50	101.41 ± 0.07	0.06
				100	99.97 ± 3.93	3.63

Table 2. The percentage of the remaining drug content after stress in Glc binary mixtures

Samples	Remaining Percentage of Glc after stress
Glc	97.99 ± 0.12
Glc-PVP	77.60 ± 1.21
Glc-NaSg	83.02 ± 0.98
Glc-Lac	86.88 ± 1.30
Glc-Peg	65.02 ± 0.54
Glc-Mgst	57.01 ± 0.52
Glc-DCP	96.98 ± 1.85

showed more than 20 % loss and mixtures of drug with NaSg and lactose had more than 10 % loss. DCP was the only one with drug loss of about 4 percent.

Peak identification was done using photo diode detector (PDA) and Mass detectors. Drug molecules peaks had a purity factor greater than 0.997 and thus considered pure.

Mass studies were performed to ensure the peak purity of the HPLC peak related to the main drug molecule in stressed samples. For this purpose all binary stressed samples were weighed separately and dissolved in diluent prior to being mixed all together and being injected to HPLC. Several injections were performed and peak collection in the peak area of Glc were done manually. The collected fraction were separately injected to mass system to gain data. The

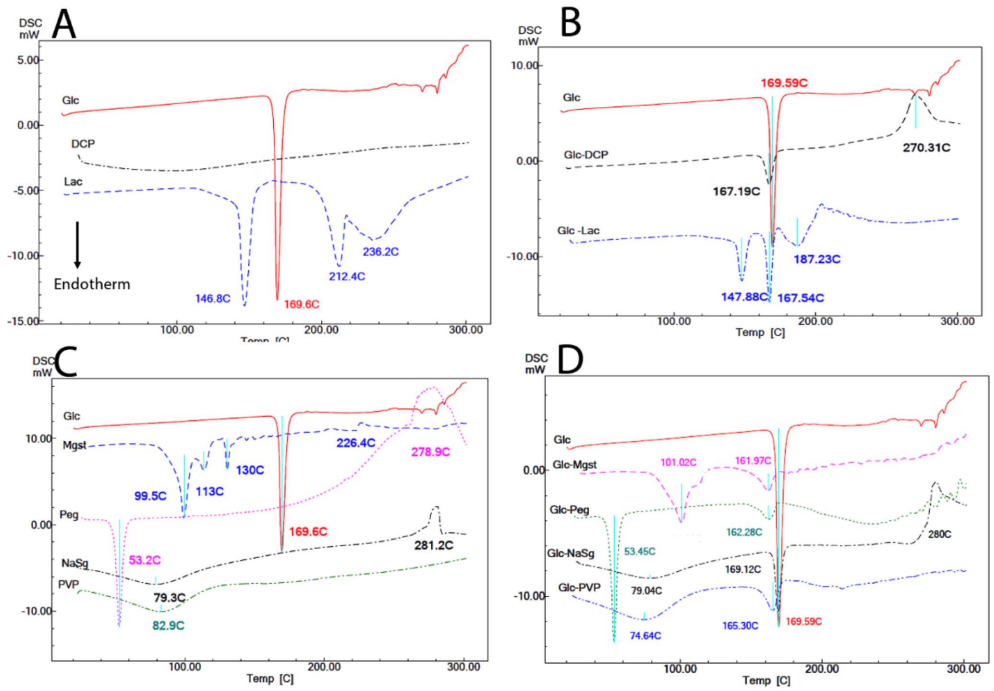

Fig. 2. DSC curves of Glc (a) with A) Pure filler excipients, B) Binary mixtures with filler excipients, C) Pure tablet lubricants, coating agents and disintegrant, D) Binary mixtures with tablet lubricants, coating agents and disintegrant.

mass spectrum of collected HPLC peaks related to Glc in stressed binary mixtures were in accordance with standard Glc shown in *Fig.* 1-C (Data not shown).

3.2. DSC Results and discussion

Fig. 2 depicts the DSC results for Glc binary mixtures. For the better illustration, excipients have been categorized according to their function in tableting process and shown as 2 main subgroups.

In *Fig.* 2, thermal behavior of Glc, pure excipients and binary mixtures has been evaluated. For ease of comparison, the thermal curve of Glc is represented in all parts of *Fig.* 2 as the upper trace. *Fig.* 2-A is related to pure tablet fillers such as DCP and Lac.

No thermal event was observed in the thermal curve of DCP (Fig 2-A). The thermal curve of Lac (*Fig.* 2-A) also had two endothermic events in 146.8 ºC and 212.4 ºC which are related to its dehydration and melting [10,13].

Fig. 2-B illustrates the DSC curve of the binary mixtures of Glc with some tablet fillers (DCP and Lac).

The intensity of the melting endotherm of the Glc in Glc-DCP binary mixture (*Fig.* 2-B) was decreased and a new peak was observed at 270 °C as an exothermic phenomenon probably related to the sample evaporation process.

In the DSC curves of Glc-Lac (*Fig.* 2-B), the water loss of Lac and endothermic peak of Glc were visible at 147 and 167 °C, respectively. A shift in Lac melting endotherm from 212 °C to 187 °C was observed. The 236 ºC endotherm of Lac is almost missing in the mixture. These results suggest the drug-excipient incompatibility.

Fig. 2-C depicts the DSC curve of pure Glc with some pure tablet lubricants, coating agents and disintegrants (Mgst, PVP, NaSg and Peg).

The curve of Mgst (*Fig.* 2-C) displays three endothermic events at 99, 130 and 113˚C, and a very small exothermic one in 226.4 ºC, respectively.

The DSC curve of Peg (*Fig.* 2-C) shows the presence of a sharp endothermic event in 53 ºC and a broad and intense exothermic event at 278 ºC. The DSC curve of Sodium starch glycolate (*Fig.* 2-C) reveals the presence of an endothermic event at 79.3 ºC and an exothermic event at 281 ºC.

In *Fig.* 2-C, The DSC curve of PVP displays the presence of a broad and weak endothermic event at 82 ºC probably related to the excipient dehydration.[10]

Fig. 2-D shows the DSC curve of the binary mixtures of Glc with some pure tablet lubricants, coating agents and disintegrants (Mgst, PVP, NaSg, Peg).

In the thermal curve of Glc-Mgst (*Fig.* 2-D), the endothermic peak of Glc decreased too much and appeared at 161.9 °C and one of the endothermic peaks of Mgst at 130°C disappeared, while two others merged and appeared at 101.2 °C probably due to drug-excipient incompatibility.

Binary mixtures of Glc with Peg (*Fig.* 2-D) revealed a very small melting endotherm of the drug molecule at 162.2 °C along with an almost unchanged peak related to Peg at 53 °C .

In the DSC curve of Glc- Sodium starch glycolate (*Fig.* 2-D), the melting endotherm of the drug molecule was almost unchanged and appeared at 169.12 °C. The thermal events of the excipient were almost unchanged at 79.04 °C.

In the DSC curve of Glc-PVP (*Fig.* 2-D), the endothermic peak of Glc was decreased extensively and appeared at 165.3 ºC.

The enthalpy of the drug melting peak in all drug – excipient mixtures were less than half of the endotherm value calculated for the melting peak in the pure drug. Enthalpy values for Glc peak in pure drug sample, Glc-Lac, Glc-DCP, Glc-Mgst, Glc-Peg, Glc-Nasg and Glc-PVP mixtures are as 131.94, 60.9, 40.5, 20.9, 19.4, 42.3 and 34 J/g respectively.

Finally the list of incompatible excipients with Glc according to DSC are: PVP, Lac, Peg, Mgst and DCP.

3.3. FTIR Results and discussion

Fig. 3 illustrate the FTIR results for Gliclazide and excipients. For better illustration, excipients are categorized according and shown as subgroups of each Figure.

Fig. 3 shows the main IR peaks of pure Glc as a

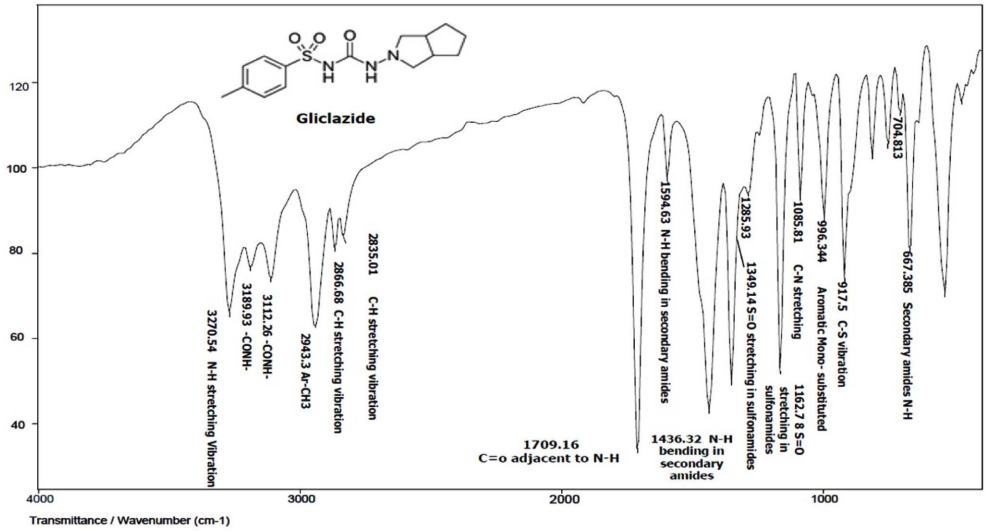

Fig. 3. FTIR spectrum of Standard Glc.

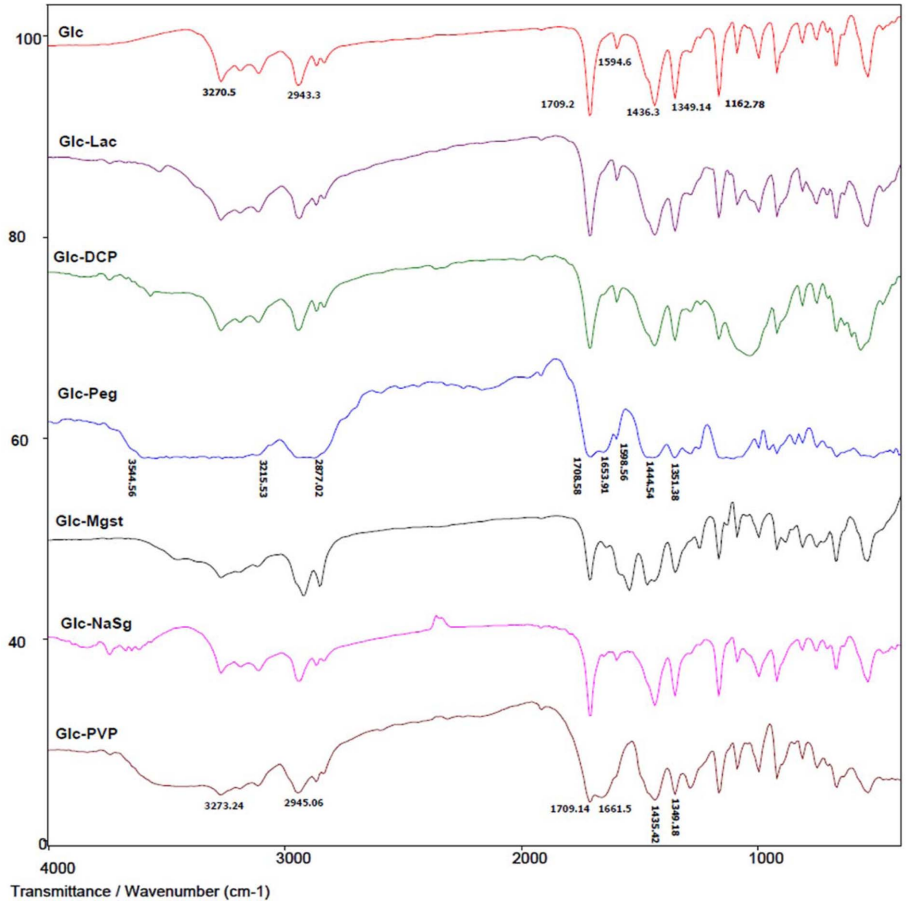

Fig. 4. FTIR spectra of Glc and binary mixtures with Lac, DCP, Peg, Mgst, NaSg, PVP.

Table 3. Summarization of DSC, FTIR and HPLC results for drug-excipient compatibility of Glc

Samples	Prediction of compatibility with different methods			Agreement		
	DSC	FTIR	HPLC	DSC with FTIR	HPLC With DSC	HPLC With FTIR
Glc + PVP	×	×	×[1]	✓[2]	✓	✓
Glc + NaSg	✓	✓	×	✓	×	×
Glc + Lac	×	✓	×	×	✓	×
Glc + Peg	×	×	×	✓	✓	✓
Glc + Mgst	×	✓	××[3]	×	✓	×
Glc + DCP	×	✓	✓	×	×	✓

[1]incompatibility
[2]compatibility
[3]intense incompatibility

standard powder. In all binary mixtures of Glc with excipients, the presence of the drug main IR peaks and the formation of any new absorption peaks were monitored.

Fig. 4 depicts the FTIR spectrum of Glc with the selected excipients after stress. For better illustration the IR peaks of Glc in pure sample without stress is inserted as the upper trace in *Fig.* 4.

The main peaks of Glc in binary mixtures with Lac and DCP, Mgst and NaSg were almost unchanged (*Fig.* 4) after stress. Thus, incompatibility of Glc with these excipients can't be concluded via FTIR spectrum.

But in the FTIR spectrum of the binary mixture of Glc-PEG2000 (*Fig.* 4), the appearance of a new peaks at 1653 cm^{-1} was observed. This observation can be interpreted as drug-excipient incompatibility based on FTIR results.

In Glc-PVP mixture, the presence of a new peaks at 1661 cm^{-1} which is appeared as a shoulder to peak at 1709 cm^{-1}, were seen after stress period. Peak deformity seen at 1700 cm^{-1} in the trace of Glc-Mgst in *Fig.* 4 have been originated form Mgst absorption at 1700 region which is being overlapped with Glc and is seen as deformity.

FTIR detected incompatibility evidences for only Peg and PVP mixtures.

3.4. Comparison table

Glc is a sulfonylurea and can be categorized to a sulfonamide part and a pyrrole substituted aliphatic type 2 amide part according to its chemical structure. In Glc, the amide like hydrogen atoms are more acidic compared to simple amides, which are very weak acids or neutral groups. Thus the most reactivity of the amide functional groups in the Glc structure can be summarized as hydrolysis and reduction reactions. All excipients which are assigned incompatible in this study can involve in hydrolysis or reduction reactions with the drug molecule.

PVP and Peg as peroxide containing excipients, NaSg as a nitrite impurity source can involve in Red-Ox reactions. Mgst with its alkaline nature can interacts via hydrolysis reactions. Lactose as aldehyde containing excipient can react with nitrogen in the drug molecule and cause instability.

DSC and FTIR assumptions are finally being proved using HPLC. In comparison table (*Table* 3) the final decision of compatibility is made based on the HPLC data.[20-21] *Table* 3 summarizes all DSC, FTIR and HPLC results. Prediction of drug-excipient compatibility is based on this Table. According to results gained by three different techniques (DSC, FTIR and HPLC), Data obtained from HPLC and DSC were more consistent than HPLC and FTIR.

It should be noted that conclusions could not be

made merely based on DSC results and interpretations should finalized by HPLC quantifications. According to *Table* 3 it seems that the stress applied in this study (40 °C for 2 months with 20 % added water) was successful to trace the incompatibilities using HPLC and DSC rather than IR spectra. Formation of very trace chemical changes may be a possible explanation for FTIR disability to detect the incompatibility.

4. Conclusions

Polyethylene glycol may also be contaminated by aldehyde impurities. Aldehydes can react with amine groups and yield N-methyl derivatives. It has been reported that in soft gels aldehydes interact with amines and forms a protein which in insoluble and this leads to slow drug release. Formic acid impurities are formed by air oxidation of formaldehyde.

Peroxides can be found in polymeric excipients such as polyvinylpyrrolidone and polyethylenglycole and form N-oxide derivatives of drugs and oxidation of thiols.

Nitrosating impurities in drug products may be originated from Nitrates and nitrites contents of some excipients such as Sodium starch glycolate (NaSg) which can form N-nitroso compounds (NOC) with Nitrogen-containing pharmaceutical compounds. NOC are carcinogenic even in trace.

Magnesium Stearate (Mgst) is another reactive excipient which may contain Magnesium oxide impurity and may cause drug degradation via alkaline pH microenvironmental effect.

Dicalcium phosphate (DCP) a common filler excipient has an alkaline nature and may cause stability problems for acidic drugs. Many drug examples and the source of such impurities in excipients are discussed in detailed elsewhere.[1,2,22]

In preformulation steps of pharmaceutical manufacturing DSC and FTIR can be easily used in evaluating drug-excipient compatibilities. The evidences suggest that; HPLC remains the gold method in such evaluations and pharmaceutical chemists can use fast techniques for screening purposes along with HPLC to reach the accurate results and decisions.

Glc incompatibility with reactive excipients (PVP, Sodium starch glycolate, PEG, Magnesium stearate and Lactose) was successfully documented.

A new approach has been established which can be useful for industrial pharmacists in similar formulation processes. Based on the results, the sophisticated, accurate and time-consuming HPLC method was in a good and moderate agreement with DSC and FTIR data as fast screening techniques, respectively.

It is recommended to avoid the use of incompatible excipient in the formulation of Glc pharmaceutical dosage forms.

Acknowledgements

This paper was extracted from Pharm.D thesis of Mohammad Shabani (no. 3862) submitted to the Faculty of Pharmacy, Tabriz University of Medical Sciences.

References

1. S. S. Bharate, S. B. Bharate and A. N. Bajaj, *J. Excip. Food. Chem.*, **1**(3), 3-26 (2010).
2. P. M. Adhikari and M. Pai, *Journal of Clinical and Diagnostic Research*, **1**(5), 440-443 (2007).
3. F. Lotfipour, H. Valizadeh, S. Shademan and F. Monajjemzadeh, *Iranian Journal of Pharmaceutical Research: IJPR*, **14**(4), 1015-1029 (2015).
4. F. Monajjemzadeh, F. Ebrahimi, P. Zakeri-Milani and H. Valizadeh, *Adv. Pharm. Bull.*, **4**(4), 329-338 (2014).
5. M. R. S. Shadbad, F. Ghaderi, L. Hatami and F. Monajjemzadeh, *AAPS PharmSciTech*, **17**, 1491-1499 (2016).
6. S. K. Sharma, S. Mohan, M. Jaimini, B. S. Chauhan and A. Chatterjee, *International Journal of PharmTech Research*, **6**(2), 607-622 (2014).
7. F. Ghaderi, M. Nemati, M. R. Siahi-Shadbad, H. Valizadeh and F. Monajjemzadeh, *Journal of Thermal Analysis and Calorimetry*, **123**(3), 2081-2090 (2016).
8. F. Monajjemzadeh and F. Ghaderi, *J. Mol. Pharm. Org. Process Res.*, **3**, e121 (2015).

9. G. Kirtansinh, P. Piyushbhai and P. Natubhai, *International Journal of Pharmaceutical & Biological Archive*, **2**(5), 1319-1326 (2011).
10. R. C. Rowe, P. J. Sheskey and P. J. Weller, 'Handbook of Pharmaceutical Excipients', 6th Ed, Pharmaceutical press, London, 2006.
11. A. T. Serajuddin, A. B. Thakur, R. N. Ghoshal, M. G. Fakes, S. A. Ranadive, K. R. Morris and S. A. Varia, *Journal of Pharmaceutical Sciences*, **88**(7), 696-704 (1999).
12. F. Monajjemzadeh and A. Farjami, *Journal of Molecular Pharmaceutics & Organic Process Research*, **2**(3), e117 (2014).
13. F. Monajjemzadeh, D. Hassanzadeh, H. Valizadeh, M. R. Siahi-Shadbad, J. S. Mojarrad, T. A. Robertson, et al., *Pharmind: Die Pharmazeutische Industrie*, **73**(1), 174-177 (2011).
14. F. Monajjemzadeh, D. Hassanzadeh, H. Valizadeh, M. R. Siahi-Shadbad, J. S. Mojarrad, T. A. Robertson, et al., *European Journal of Pharmaceutics and Biopharmaceutics*, **73**(3), 404-413 (2009).
15. F. Ghaderi, M. Nemati, M. R. Siahi-Shadbad, H. Valizadeh and F. Monajjemzadeh, *Journal of Food and Drug Analysis*, **25**(3), 709-716 (2017).
16. F. Ghaderi, M. Nemati, M. R. Siahi-Shadbad, H. Valizadeh and F. Monajjemzadeh, *Journal of Thermal Analysis and Calorimetry*, **130**(3), 1417-1427 (2017).
17. G. Bansal, M. Singh and K. C. Jindal, *Chromatographia*, **66**(9-10), 751-755 (2007).
18. S. K. Branch, *Journal of Pharmaceutical and Biomedical Analysis*, **38**(5), 798-805 (2005).
19. M. Windholz, S. Budavari, L. Y. Stroumtsos and M. N. Fertig, 'The Merck Index: An Encyclopedia of Chemicals and Drugs', 15th Ed, Royal Society of Chemistry, London, UK, 2013.
20. P. Niguram, S. N. Polaka, R. Rathod, K. Kalia and A. S. Kate, *Drug Development and Industrial Pharmacy*, **46**(2), 209-218 (2020).
21. M. Ecaterina, S. Martin and U. Livia, *The Moldovan Medical Journal*, **63**(4), 35-42 (2020).
22. Y. Wu, J. Levons, A. S. Narang, K. Raghavan and V. M. Rao, *AAPS PharmSciTech*, **12**(4), 1248-1263 (2011).

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