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A Tablet as an Environment for Investigation of the Reactions in the Solid States

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ABSTRACT

Objective

In this study, a tablet's matrix was considered a solid environment to investigate the reactions in the solid states. The tendency of molecules to each other and their interaction in the solid state was studied through the advent of impurities in the tablet caused by the interaction of the active pharmaceutical ingredient with an excipient.

Significance

Investigation of solid-state reactions and their prediction in the matrix of tablets will reveal the possible appearance of impurities in pharmaceutical dosage forms and help formulators prevent impurities in drug products.

Methods

Principal Component Analysis (PCA) was used to predict the interaction between Gliclazide as a secondary amine and Lactose in the manufactured powders. The infrared spectra of binary mixtures of Gliclazide with Lactose at different weight ratios were recorded and the obtained data matrix was analyzed with PCA. High-performance Liquid Chromatography (HPLC) was used for the identification and quantification of the impurity.

Results

The incompatibility was seen theoretically by PCA and also experimentally by HPLC. A kinetic model was proposed for this solid-state reaction in the tablets. The presence of some excipients was investigated on the appearance of the impurity and also on the kinetics of the reaction. This reaction was faster when Hydroxypropylmethylcellulose (HPMC) was present in the tablet formulation.

Conclusion

The chemical reaction in a tablet could be considered as a solid-state reaction. This reaction was predicted and modeled and the effect of the matrix of the tablet was investigated on the reaction.

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Introduction

Fifty years have passed since the publication of Chemistry of the Solid State edited by W.E. Garner, which dealt with solid-state theories, including the kinetics of solid-state reactions [1].

Jacobs and Tompkins cover the theories and derivation of several solid-state reaction models in Garner's text, in particular the nucleation and nuclear growth models. The derivation of these and other models also appears in Volume 22 of the Chemical Kinetics Series titled "Solid State Reactions" by Brown et al. Later, Galwey and Brown presented several similar models [2-4].

Solid-state chemistry has recently acquired great importance in pharmaceutical sciences, which gives importance to the topic of solid-state kinetics. However, solid-state reactions come in many forms, those that involve weight change or enthalpy change are of great interest because their kinetics can be studied through thermal analysis [5].

In pharmaceuticals, many solid-state kinetic studies focus on desolvation reactions or polymorphic transformations. Interest in these reactions is increasing as many formulated drugs, including compendial drugs, are solvates; mainly hydrates [5]. There are few reports regarding kinetic studies of the reactions in tablets.

Investigation of impurities in drug-finished products has a pivotal factor in the pharmaceutical formulations. Many studies have been performed regarding determination and identification of impurities in pharmaceutical dosage forms [6-9]. I did not see any reports considers the production of impurities as a chemical reaction between an API and an excipient in the solid state of the matrix of a tablet.

More recent studies designed to detect drug-excipient interactions generally rely upon the use of DSC or diffuse reflectance FT-IR [10,11]. Rojek and Wesolowski used factor analysis methods to investigate compatibility in pharmaceutical mixtures [12-15].

Principal Component Analysis (PCA) is the is the most common multivariate data analysis technique [16]. Its field of application

varies from theoretical physics to meteorology, psychology, biology, chemistry and technology. Applications of PCA also cover all major topics in pharmacology and biomedicine, from quantitative structure-activity relationships to data mining [17].

Pavlovi´c et al. used PCA to reveal quercetin analogues as modulators for modulating inositol phosphate multikinase (IPMK). This is utilized in lead optimization of blood–brain barrier (BBB)-penetrating IPMK modulators as neuroprotective agents [18].

Jonathan P. McMullen et al. utilized PCA for enhanced drug substance development [19]. Yang et al. accurately evaluated the fungal bioactivities by principal component analysis [20].

The Maillard reaction is named after Louis Maillard, who reported more than 80 years ago that certain amines and reduced carbohydrates reacted to produce a brown pigment [21]. It has been widely studied and reviewed, especially in the food and nutrition literature [22]. The first product of this reaction is a simple glycosylamine, which readily undergoes the Amadori rearrangement to yield 1-amino-1-deoxy-2-ketoses [23,24].

The set of experiments clearly shows that the Maillard reaction between fluoxetine hydrochloride and lactose can occur, even in the solid phase, and factors such as humidity, type of lactose, and the presence of magnesium stearate may have influenced the rate and properties of subsequent decomposition products [25]. The addition of magnesium stearate catalyzes the formylation process. Based on the pH-dependent data produced in the solution, this effect is likely due to local changes in pH rather than changes in physical mobility in the solid due to the lubricant [25]. Liew et al. showed that choosing the right excipients could be so important in pharmaceutical formulations to protect the active pharmaceutical ingredient from degradation and chemical reactions [26].

In this research, an interaction between Gliclazide as a secondary amine and lactose as a reduced carbohydrate (an excipient) in a tablet environment was predicted using PCA on the data matrix of the infrared spectra of binary mixtures of Gliclazide and lactose. The produced impurity resulted from the interaction was identified and quantified using HPLC. The reaction was considered as an example of a solid-state reaction in tablets and a mathematical model was proposed for describing the reaction in the tablet. Also, the effect of some excipients was investigated on the rate of the reaction.

Experimental Section

Material

Acetonitrile, Methanol, Triethylamine, and Trifluoroacetic acid were purchased from Merck company. Gliclazide, Gliclazide Impurity F reference standard, and Gliclazide reference standard were purchased from Shandong Keyuan Pharmaceutical Co. Ltd. (China), Mannitol from Microlex, Anhydrous Dibasic Calcium Phosphate from Tabriz Petrochemical Co. (Iran), HPMC (Benecel K100 LV Pharm), and HPMC (Benecel K4M Pharm) from Ashland (Belgium), Trisodium Citrate Dihydrate from Behansar Co., Colloidal Anhydrous Silica (Aerosil 200) from Evonik Industries (Germany), Lactose Monohydrate from DFE Pharma, Microcrystalline Cellulose (Avicel PH 102) from DFE Pharma, Croscarmellose Sodium from Roquette, Povidone from Rahavard Tamin Co. (Iran), Corn Starch from Ebneh Masouyeh (Iran), and Magnesium Stearate from Behansar Co. (Iran) were provided.

Analytical Procedure

FTIR spectrometer IRPrestige-21 was used to record IR spectra of binary mixtures of Gliclazide and lactose with different weight ratios.

High-performance liquid chromatography (HPLC) (Alliance, Waters) was used for the identification of the Millard reaction. Mobile phase and solutions were prepared according to the following.

- **Mobile Phase**
  Water: Acetonitrile: Triethylamine: Trifluoroacetic acid (220: 180: 0.4: 0.4)

- **Chromatographic System**
  The liquid chromatograph is equipped with a UV-visible detector at 235 nm and a 4.0 mm × 25 cm analytical column that contains 4 µm packing C8, the column temperature is maintained at ambient temperature. The flow rate is about 0.9 ml per minute.

- **Impurity F Stock Solution**
  4.0 mg Gliclazide Impurity F RS accurately weighed and was transferred to a 25 ml volumetric flask. 12.5 ml of acetonitrile was added, dissolved by sonication, and diluted with water up to volume and mixed. The obtained solution has a known concentration of about 160 µg of Gliclazide Impurity F RS per ml.

- **Gliclazide Stock Solution**
  5.0 mg of Gliclazide RS accurately weighed and was transferred to a 50 ml volumetric flask. 25 ml of acetonitrile was added, dissolved by sonication, and diluted with water up to volume and mixed. The obtained solution has a known concentration of about 100 µg of Gliclazide per ml.

- **System Suitability Solution**
  0.5 ml of Impurity F Stock Solution and 1.0 ml of Gliclazide Stock Solution were transferred to a 10 ml volumetric flask and diluted with Acetonitrile: Water (45:55 v/v) up to volume and mixed.

- **Impurity F Standard Solution**
  0.5 ml of Impurity F stock Solution was transferred to a 50 ml volumetric flask diluted with Acetonitrile: Water (45:55 v/v) up to volume and mixed. The obtained solution has a known concentration of about 1.6 µg of Gliclazide Impurity F RS per ml.

- **Test Solution**
  Not fewer than 20 tablets were powdered and weighed accurately. The powdered tablets equivalent to about 200 mg of Gliclazide (Tablet Powder: 866.0 mg) were transferred to a 100 ml volumetric flask, and 50 ml acetonitrile was added and shaken on a shaker for 60 minutes. Then the solution was filtered with filter paper and 5.0 ml of the filtrate was transferred to a 25 ml volumetric flask diluted with Acetonitrile: Water (1:2 v/v) up to volume and mixed.

- **Standard Test Solution**
  0.5 ml of the test solution was transferred to a 250 ml volumetric flask diluted with Acetonitrile: Water (45:55 v/v) up to volume and mixed.

- **Procedure**
  Equal volumes (20 µl) of filtered system suitability, Impurity F standard solution, test solution, and standard test solution were injected into the chromatograph, separately and the responses were measured.

- **Note**
  The resolution factor between peaks of impurity F and Gliclazide must not be less than 1.8.

- **Calculation**
  The quantity, in percent of impurity F and other secondary impurities, was calculated by the below formula:

$$Result\ (\%) = \frac{r_U}{r_s} \times 0.2$$

In which, r_U is impurity F and or other secondary impurity peak area obtained from the test solution and r_S is impurity F peak area obtained from the Impurity F standard solution and or Gliclazide peak area obtained from the standard test solution [27].

Formulation

The ready-to-press powder of tablets was prepared by the wet granulation method. The first mixture is kneaded with the binder solution. The wet mass is dried in a hot-air chamber at 50 °C, protected from light. The next step is passing the dried produced mass through the oscillating granulator with a 24-mesh size screen. In the following step, the dry granular mass is mixed with the excipients of the external phase after passing through the 40-mesh screen for 20 minutes. Then, magnesium stearate after passing through an 80-mesh screen is added and mixed for an additional 5 minutes. After that, the powder was compressed using a mini rotary press machine (Kambert Machinery Co. PVT. LTD. India) with a 7 mm diameter concave punch for modified-release gliclazide 30 mg tablets and 9 mm diameter concave punch for modified-release gliclazide 60 mg tablets [28].

Results

Interaction Between Gliclazide and Lactose Using Infrared Spectra

Factor analysis methods such as principal component analysis (PCA) are a solution to determine compatibility. The results of FA can be seen on a two-dimensional score plot. The localization of both ingredients and their blends on the FA plot demonstrates compatibility or incompatibility.

If the API with mixtures at the most amount and the 1:1 blend form a separate cluster and the other cluster comprises of excipient with blends with its most amount; this indicates that compatibility between ingredients is obvious [29]. Binary mixtures of Gliclazide and Lactose with different weight ratios were manufactured. The infrared spectrum of each mixture was recorded by FT-IR spectrophotometer. These spectra are shown in Figure 1.

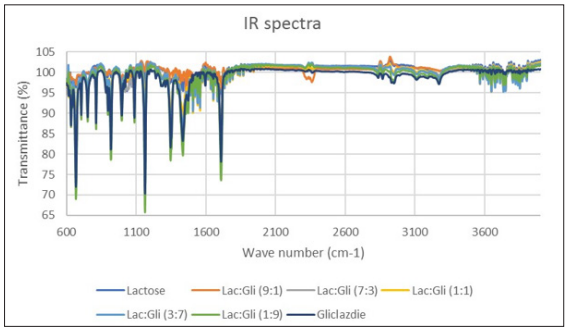


Figure 1: Infrared Spectrum (IR) of Gliclazide in the Presence of Lactose with Different Weight Ratios

Analysis of Maillard impurity by HPLC

Table 1 shows the amount of the Maillard impurity in the tablet at the stability months for Gliclazide modified-release 60 mg tablet (formula 1) with glass packaging containers. Table 2 and 3 show the results of assay and impurity of gliclazide modified-release 30 mg and 60 mg tablets (formula 2) at accelerated stability condition with PVC-Alu and Alu-Alu packaging containers.

Table 1: The Amount of the Maillard Impurity at Accelerated Stability Condition for Gliclazide Modified-Release 60 mg Tablet (Formula 1) with Glass Packaging Containers

	Room temperature	1 month	2 months	3 months	5 months
Impurity quantity (%)	0.18%	0.19%	0.29%	0.40%	0.80%

Table 2: Results of Assay and Impurity of Gliclazide Modified-Release 30 mg Tablet (Formula 2) at Accelerated Stability Condition with PVC-Alu and Alu-Alu Packaging Containers

	Assay (mg/Tab	Related Substances
Gliclazide 30 modified-release tablet	30.0 (28.50 - 31.50) (95.0%-105%)	1) Imp. F: Max. 0.4% 2) Any other secondary peak: Max. 0.2% 3) Sum of any other secondary peaks: Max. 0.4%
Room Temperature	28.80 mg/Tab (96.0%)	1) Not detected 2) Not detected 3) 0.0%
3 months (PVC/Alu)	28.18 mg/Tab (93.93%)	1) Not detected 2) 0.157% 3) 0.157%
6 months (PVC/Alu)	28.80 mg/Tab (96.0%)	1) Not detected 2) 0.45%, 0.07%, 0.10% 3) 0.62%
3 months (Alu/Alu)	28.33 mg/Tab (94.43%)	1) Not detected 2) 0.11% 3) 0.11%
6 months (Alu/Alu)	29.88 mg/Tab (99.60%)	1) Not detected 2) 0.15% 3) 0.15%

Table 3: Results of Assay and Impurity of Gliclazide Modified-Release 60 mg Tablet (Formula 2) at Accelerated Stability Condition with PVC-Alu and Alu-Alu Packaging Containers

	Assay (mg/Tab)	Related Substances
Gliclazide 60 modified-release tablet	60.0 (57.0 - 63.0) (95.0%-105%)	1) Imp. F: Max. 0.4% 2) Any other secondary peak: Max. 0.2% 3) Sum of any other secondary peaks: Max. 0.4%
Room Temperature	66.47 mg/Tab (110.78%)	1) Not detected 2) Not detected 3) 0.0%
3 months (PVC/Alu)	66.47 mg/Tab (110.78%)	1) Not detected 2) 0.116%, 0.055% 3) 0.171%
6 months (PVC/Alu)	66.26 mg/Tab (110.43%)	1) Not detected 2) 0.4%, 0.056, 0.12% 3) 0.58%
3 months (Alu/Alu)	60.83 mg/Tab (101.38%)	1) Not detected 2) 0.10% 3) 0.10%
6 months (Alu/Alu)	62.28 mg/Tab (103.80%)	1) Not detected 2) 0.18% 3) 0.18%

Discussion

Principle Component Analysis on IR Spectra

After applying PCA on the data matrix obtained from IR spectra, the score plot in Fig. 2 shows that the weight ratio of 7:3 of Lactose to Gliclazide put in the cluster of Gliclazide with mixtures at the most amount of Gliclazide (Gliclazide and Gliclazide: lactose (9:1)). Therefore, there is an interaction between Gliclazide and the excipient. This interaction shows the possible Maillard reaction between Gliclazide and the excipient. When we analyzed the impurities of the manufactured tablet according to the British Pharmacopeia monograph for Gliclazide Preparations, the impurity produced from the Maillard reaction was observed in the HPLC chromatogram. Details are included in section 4.2. This is a useful application of PCA in pharmaceutics to predict the appearance of impurities before formulation of drugs. According to Lapkin et al. studies, for prediction of reaction impurities, the knowledge of molecule structure and functional groups is necessary and also it is a theoretical method but PCA is based on experimental data and is simpler and faster than data mining approach [30].

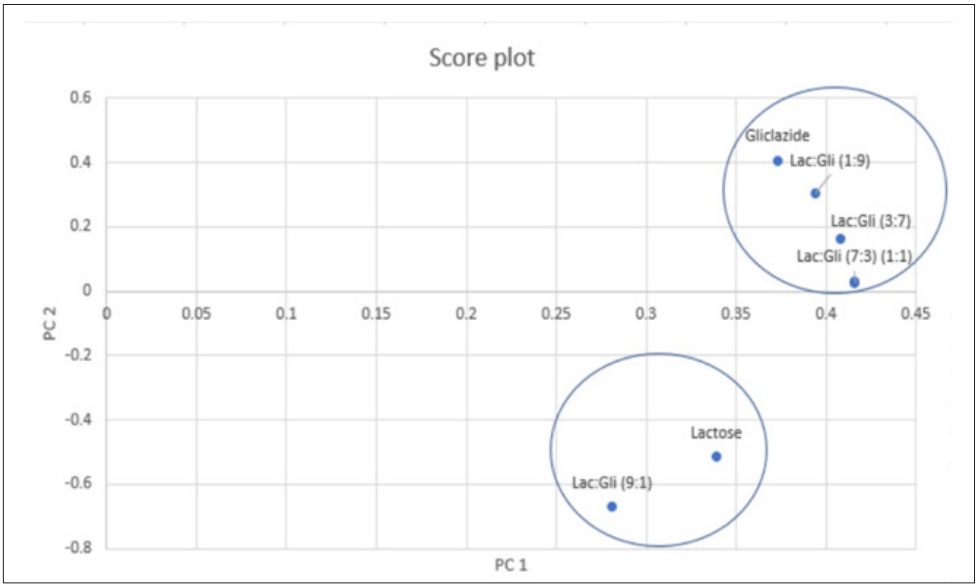
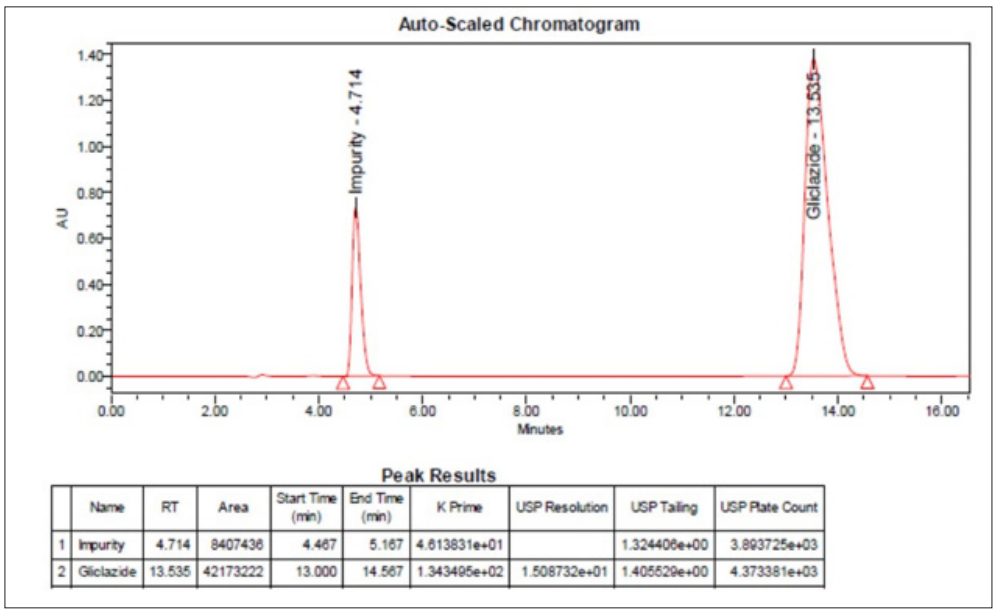


Figure 2: Score plot of the matrix of IR spectra of binary mixtures of Gliclazide and Lactose with different weight ratios

Formulation Survey

As seen in Figure 3 when 70.0 mg of Gliclazide was heated in 50.0 mL of Acetonitrile, the impurity was observed at 4.71 minutes. This is because of the reaction between the amine group of Gliclazide and the nitrile group of acetonitrile and the formation of the imine group. The existence of this reaction in the solution approves the possibility of the occurrence of this reaction in the solid state of a tablet when the amine group of Gliclazide reacts with the carbonyl group of Lactose. When the formula of a tablet consists of Lactose Monohydrate, Avicel PH 102, Hypromellose K100, Hypromellose K4M, Mg Stearate, and Aerosil 200, the impurity appears

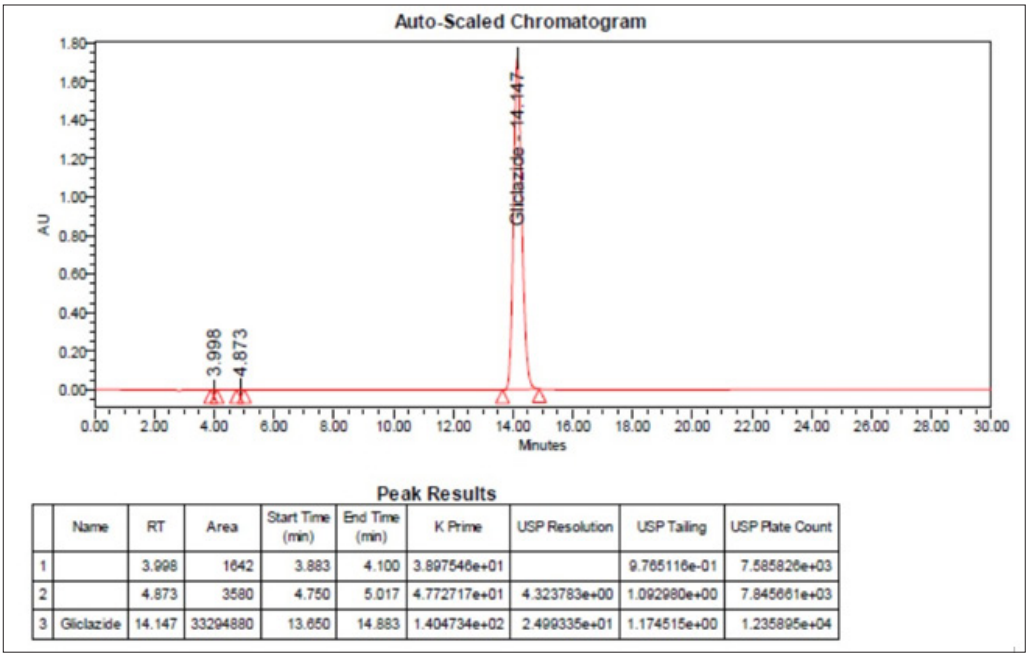
at a retention time of 4.8 min. This impurity is the same as the impurity in the solution. Fig. 4 shows this impurity in the tablet. This impurity is because of the Maillard reaction which occurs between Lactose Monohydrate and Gliclzide as a secondary amine. Table 1 shows the amount of this impurity in the gliclazide 60 mg modified-release tablet at the accelerated stability months with glass packaging containers. Despite our most impenetrable packaging system (glass packaging), this impurity grows fast in the stability condition. It shows the strong reaction between gliclazide and lactose.



Peak Results

	Name	RT	Area	Start Time (min)	End Time (min)	K Prime	USP Resolution	USP Tailing	USP Plate Count
1	Impurity	4.714	8407436	4.467	5.167	4.613831e+01		1.324406e+00	3.893725e+03
2	Gliclazide	13.535	42173222	13.000	14.567	1.343495e+02	1.508732e+01	1.405529e+00	4.373381e+03

Figure 3: The Impurity Produced by the Reaction of Gliclazide and Acetonitrile when the Solution is Heated



Peak Results

	Name	RT	Area	Start Time (min)	End Time (min)	K Prime	USP Resolution	USP Tailing	USP Plate Count
1		3.998	1642	3.883	4.100	3.897546e+01		9.765116e-01	7.585826e+03
2		4.873	3580	4.750	5.017	4.772717e+01	4.323783e+00	1.092980e+00	7.845661e+03
3	Gliclazide	14.147	33294880	13.650	14.883	1.404734e+02	2.499335e+01	1.174515e+00	1.235895e+04

Figure 4: Chromatogram of the Maillard Impurity at 4.8 Minutes in the Tablet

Formulation Change

We changed the formula and substituted Lactose Monohydrate with Mannitol. Avicel PH 102 was removed. Dibasic Calcium Phosphate Anhydrous and Sodium Citrate were added. In this formula, the impurity at the retention time of 4.8 min was not observed at the moment of manufacturing and the amount of the impurity in the Alu-Alu packaging container was in the acceptable range (results in red colors) (≤0.2%) at the stability chamber as seen in Tables 2 and 3 (formula 2). As seen in Fig. 5, Gliclazide is a molecule with secondary amine groups. These amine groups are susceptible to reacting with carbonyl groups of Lactose and formation of imines. The acidic condition is favorable for performing the imine formation reaction and so it is suitable for the Maillard reaction. According to the literature, the pH of microcrystalline cellulose (Avicel PH 102) is in the range of 5.0-7.5 [31]. Therefore, Avicel could facilitate the Maillard reaction. Avicel was removed from the formula and Dibasic Calcium Phosphate Anhydrous was added as an alkaline

excipient to the formula. Sodium Citrate was added to the formula in low amounts as a buffering agent. With all of these changes in the formulation, the Maillard impurity was more than the acceptable range in stability months when the tablets were packaged in PVC-Alu (results in red colors). The results of impurity analysis are good when the tablets are packaged in Alu-Alu blister. Because Alu-Alu blister is more impenetrable than PVC-Alu blister against of heat and humidity.

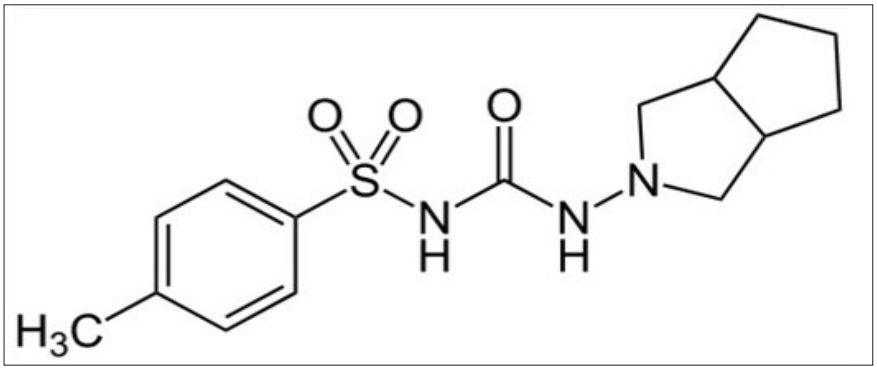


Figure 5: The Molecular Structure of Gliclazide

Immediate-Release Formulation

Surprisingly, in the Gliclazide immediate-release formulations in which we used Lactose Monohydrate, Corn Starch, Povidone, Sodium Citrate Dihydrate, Croscarmellose Sodium, Colloidal Anhydrous Silica and Magnesium Stearate as excipients, the impurity at the retention time of 4.8 min was seen but was below than 0.2% at 6th month accelerated stability condition even in PVC-Alu packaging. Despite the existence of Gliclazide and Lactose Monohydrate together in the formulation, the results of the impurity analysis were good. We believe that hydroxypropylmethylcellulose (Hypromellose) is responsible for the intense appearance of the impurity for the modified-release gliclazide tablet formulations at the accelerated stability studies. Maybe it is because of the hygroscopicity nature of Hypromellose which causes the tablet to absorb more water from the environment of the stability chamber. Water absorption increases the molecular mobility of pharmaceutical solids, maybe clarifying the improved chemical reactivity of these materials in the presence of water [32]. This can be due to the plasticization that comes about when water is retained [33]. Therefore, it will facilitate conditions for performing the Millard reaction.

Kinetic Studies

Solid-state kinetics evolved from homogenous kinetic principles. However, applications of these kinetic principles are different because of the differences between solids, solutions, and gases. For example, particle size, interface advance, diffusion, and geometric shape are variables unique to heterogeneous reactions and have no equivalent in homogenous reactions [5].

The rate of a solid-state reaction can be generally described by the equation 1.

$$\text{Eq (1)} \quad \frac{d\propto}{dt} = Ae^{\frac{-Ea}{RT}} f(\propto)$$

where A is the preexponential (frequency) factor, Ea is the activation energy, T is the absolute temperature, R is the gas constant, f (∝) is the reaction model, and ∝ is the conversion fraction [5].

The conversion fraction ranges from 0 to 1 and is a measure of reaction progress as a function of time or temperature. By plotting the produced impurity amount (%) against time from table 1 and fitting the best exponential equation to data using excel software (Fig. 6), f (∝) is obtained as equation 2.

$$f(\propto)=0.1584e^{0.3145t} \qquad (2)$$

By substitution of Eq (2) into Eq (1) and integration of the substitute, the equation 3 will be obtained.

$$\propto=0.5ke^{0.3145t} \qquad (3)$$

∝ is the rate of the reaction, *k* is the rate constant which is equal to $Ae^{\frac{-Ea}{RT}}$ and t is time in month. This is an empirical equation that describes the reaction of Gliclazide with Lactose in the tablet.

Rodionova et al. used MCR-ALS for estimation of kinetic model of diclofenac degradation in tablets [34]. They used Infrared spectrum of diclofenac during its natural aging. IR spectral changes of API in long times will be enough to investigate the kinetic of the reaction but in short times, the spectral changes of API will be low to use this method for kinetic studies. Therefore, we concentrated on analyzing the reaction product by HPLC to investigate the rate of production of the product (the impurity) instead of reactants for kinetic modeling and kinetic studies. Another advantage of HPLC is that we have no spectral overlapping of degradation products, intermediates and other excipients and the accuracy of estimations is high.

According to the equation, rate of the reaction is dependent to time and temperature directly. As seen in tables 2 and 3, in stability chamber in the presence of heat and humidity, we observe the reaction progress and therefore more production of Maillard impurity with time (red data). In the presence of HPMC the rate of the reaction increases. According to Petri et al. work, The HPMC with the highest hydroxypropyl groups presented the fastest swelling rate [35]. Therefore, HPMC can absorb water to swell. Consequently, the mobility of gliclazide and lactose will increase in this micro semi-solid environment. So, by increasing the Arrhenius constant (A) in the rate equation which is the number of collisions per unit of time, the reaction rate will increase.

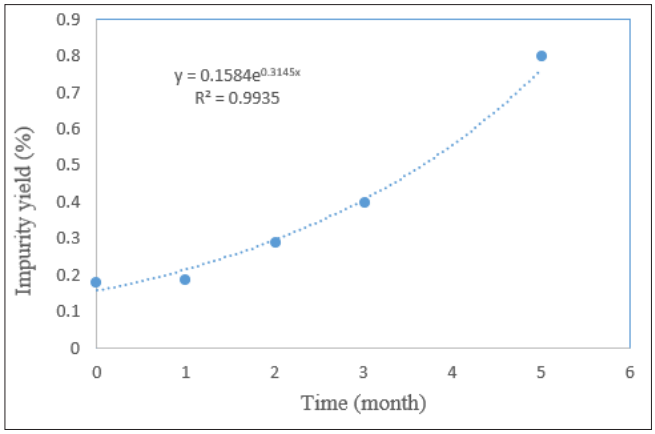


Figure 6: Plot of the Impurity amount (%) Versus Time

Conclusion

In this study, a reaction between an API and an excipient in a tablet environment was considered as a model for the solid-state reactions. The reaction was predicted by the use of Principal Component Analysis (PCA) on the data of binary mixtures of Gliclazide and Lactose with different weight ratios as an API and excipient, respectively. A kinetic model was proposed for this kind of reaction in the solid state. The Maillard reaction was investigated for different formulas in the accelerated stability conditions. By substitution of Lactose with Mannitol, Avicel PH 102 with Dibasic Calcium Phosphate Anhydrous, and the addition of Sodium Citrate, the impurity was in the accepted range in Alu-Alu packaging. The impurity was more than the accepted range in PVC-Alu packaging because of the penetrability of PVC-Alu packaging for moisture and heat. In an immediate-release formula in which Gliclazide, Lactose, Avicel PH 102, Povidone, and Sodium Citrate were present, the impurity was in the accepted range even in our most penetrable packaging system (PVC-Alu) against heat and moisture. Maybe it is because of the hygroscopicity of Hydroxypropylmethylcellulose present in the modified-release Gliclazide formulas.

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Declaration of Interest

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