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Different mathematical processing of absorption, ratio and derivative spectra for quantification of mixtures containing minor component: An application to the analysis of the recently co-formulated antidiabetic drugs; canagliflozin and metformin

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ABSTRACT

In the presented work several spectrophotometric methods were performed for the quantification of canagliflozin (CGZ) and metformin hydrochloride (MTF) simultaneously in their binary mixture. Two of these methods; response correlation (RC) and advanced balance point-spectrum subtraction (ABP-SS) were developed and introduced for the first time in this work, where the latter method (ABP-SS) was performed on both the zero order and the first derivative spectra of the drugs. Besides, two recently established methods; advanced amplitude modulation (AAM) and advanced absorbance subtraction (AAS) were also accomplished. All the proposed methods were validated in accordance to the ICH guidelines, where all methods were proved to be accurate and precise. Additionally, the linearity range, limit of detection and limit of quantification were determined and the selectivity was examined through the analysis of laboratory prepared mixtures and the combined dosage form of the drugs. The proposed methods were capable of determining the two drugs in the ratio present in the pharmaceutical formulation CGZ:MTF (1:17) without the requirement of any preliminary separation, further dilution or standard spiking. The results obtained by the proposed methods were in compliance with the reported chromatographic method when compared statistically, proving the absence of any significant difference in accuracy and precision between the proposed and reported methods.

1. Introduction

Canagliflozin (CGZ); (2*S*, 3*R*, 4*R*, 5*S*, 6*R*)-2-{3-[5-(4-fluoro-phenyl)-thiophen-2-ylmethyl]-4-methyl-phenyl}-6-hydroxymethyltetrahydropyran-3,4,5-triol (Fig. 1) is a glucose lowering agent [1]. CFZ is a member of the gliflozin class or sodium-glucose co-transporter (SGLT2) inhibitors, which are indicated for the treatment of type 2 diabetes mellitus [2]. SGLT2 inhibitors block the reabsorption of glucose causing it to be excreted in the urine [3], they are possibly prescribed as monotherapy or in combination with any of the existing classes of glucose-lowering agents such as metformin [4]. Metformin hydrochloride (MTF); 1,1–Dimethyl biguanide monohydrochloride (Fig. 1) is a biguanide anti-diabetic [5]. It is administered orally for the treatment of type 2 diabetes mellitus where it is the drug of choice for patients suffering from overweight [6]. Biguanides possibly exert their action through delaying the absorption of glucose from the gastrointestinal tract, increasing the insulin sensitivity and glucose uptake into cells, and inhibiting liver glucose production. The main action of MTF lies in increasing the glucose transport across the cell membrane in skeletal muscles [6].

Canagliflozin and metformin hydrochloride are recently co-formulated in Vokanamet® tablets (50 mg CGZ and 850 mg MTF); this formulation is specifically recommended when MTF alone, or in combination with other diabetes medicines, including insulin, do not provide satisfactory control of diabetes.

MTF is official in both the United States Pharmacopoeia (USP) [5] and the British Pharmacopoeia (BP) [7], while as CGZ is a newly released drug in the market, thus, it is not yet official in any pharmacopoeia.

Literature survey has revealed that MTF and CGZ were determined as single components in pharmaceutical formulations as well as in biological fluids by several methods including spectrophotometry, where CGZ as a single component was directly determined at its λ_{max} in the zero order spectrum [1], for MTF; it was determined as a single component either through its reaction with ninhydrin in alkaline medium [8]

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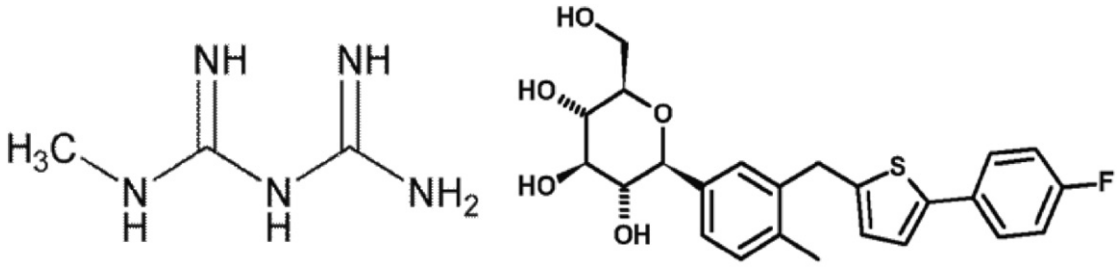

Metformin (MTF) **Canagliflozin (CGZ)**

Fig. 1. The chemical structure of metformin and canagliflozin.

or through the formation of a charge transfer complex with iodine in acetonitrile medium [9]. High performance thin layer chromatography (HPTLC) [10,11], HPLC-UV [12–15], HPLC-fluorescence detection [16], HPLC-MS/MS [17–20] and capillary electrophoresis [21,22] were also utilized. However, the simultaneous determination of MTF and CGZ was performed with the utilization of HPLC-UV [23–25] only. No spectrophotometric methods were reported for the analysis of the proposed drugs in their combination.

In the last few years the mathematical spectrophotometric methods of analysis as well as the chemometric techniques have powerfully emerged and to a pronounced extent have replaced the other chromatographic methods. This could be attributed to their simplicity, less time and solvent consumption, lack of prior extraction or separation steps and of course lower cost. Thus, nowadays the utilization of the spectrophotometric and chemometric methods became vital for the analytical studies which are performed in the quality control laboratories or for the routine analysis of different pharmaceutical products either in the research or industry laboratories. More precisely the spectrophotometric methods are considered advantageous than the chemometric techniques as they do not require purchasing a specific software or a trained person to operate the software.

The quantitative spectrophotometric resolution of the mixtures of two or more compounds having overlapped spectra is an interesting issue for analytical chemists [26–32]. For resolving complex mixtures, the analytical chemist needs new analytical methods or approaches to obtain accurate, precise and reliable results. Therefore, the analytical chemists have focused mainly on the use of a new mathematical technique or the combined use of the mentioned approaches together with traditional analytical techniques to analyze binary mixtures or ternary mixtures after its conversion to binary one by using successive resolution techniques includes successive ratio subtraction and successive derivative subtraction [33]. The diversity of the spectrophotometric methods is considered the most important feature of spectrophotometric analysis, where it gives the analyst a chance to choose the most suitable method for analysis.

The lack of simple mathematical spectrophotometric methods for the simultaneous determination of CGZ and MTF has encouraged the development of four UV-spectrophotometric methods with minimal manipulation steps. Accordingly, the aim of this work is to develop two novel methods namely; response correlation (RC) and advanced balance point-spectrum subtraction (ABP-SS). Moreover, a comparative study between these two methods and another two recently established methods; advanced amplitude modulation (AAM) and advanced absorbance subtraction (AAS) was conducted regarding their ability to resolve overlapped spectra of the binary mixture of CGZ and MTF without any preliminary separation. The proposed methods have showed significant advantages over the reported HPLC-UV methods [23–25] of being rapid, easily applied without any requirements for optimization of conditions such as pH, temperature or flow rate and thus highly economical and time saving. Additionally, these proposed spectrophotometric methods have eliminated the utilization of any harmful chemicals to both health and environment as the main utilized solvent is methanol which is considered less hazardous than the buffers (acetate or phosphate) and solvents (acetonitrile or a mixture of acetonitrile and methanol) that were used in the reported chromatographic methods [23–25]. Thus, our proposed methods could be considered as ecofriendly methods of analysis. Finally, all the developed methods were validated according to the ICH guidelines [34] to decide their appropriateness for the intended use.

1.1. Theory

1.1.1. Response Correlation Method (RC)

This novel method could be applied for a mixture composed of components X and Y whose zero order absorption spectra show partial or complete overlap and intersect in an isoabsorptive point (λ_{iso}) at which both components show the same absorptivities $a_X = a_Y$. The absorbance at this wavelength A_{iso} represent ($A_X + A_Y$) which is retained in the ratio spectra as P_{iso} ($P_X + P_Y$) using pure X as a divisor (X′) (either normalized spectrum of X or a concentration of X). In the application of this method on the binary mixtures two wavelengths (λ_{iso} and λ_2) were chosen one of them is the isoabsorptive point; where component X has equal absorbance at these wavelengths. The absorbance difference ΔA ($A_{iso} - A_2$) between the two chosen wavelengths on the mixture spectra is corresponding to the concentration of component Y only; while the difference for component X equals to zero.

This approach starts with computation of two regression equations using zero order and ratio spectra for different concentrations of pure Y representing the relationship between ($A_{iso} - A_2$) versus A_{iso} Eq. (1) and A_{iso} versus its corresponding P_{iso} Eq. (2).

$$\Delta A = \text{Slope } A_{Y(iso)} + \text{intercept} \quad (1)$$

$$A_{Y(iso)} = \text{Slope } P_{Y(iso)} + \text{intercept} \quad (2)$$

For a mixture of the two component (X) and (Y), recording its zero order absorption spectrum the $A_{Y(iso)}$ corresponding to component Y in the mixture can be calculated using Eq. (1) using the absorbance difference at the selected wavelengths. Then, substituting in Eq. (2) by the obtained $A_{Y(iso)}$ to get the corresponding $P_{Y(iso)}$ of component Y in the mixture.

The amplitude $P_{X(iso)}$ of constant ($\frac{X}{X'}$) in the mixture is calculated via subtracting the recorded amplitude ($P_{M(iso)}$) of the ratio spectrum of the mixture at λ_{iso} ($P_{X(iso)} + P_{Y(iso)}$) and that corresponding to Y in the mixture which is calculated by substitution in Eq. (2) at the same wavelength (λ_{iso}).

$$P_{X(iso)} = P_{M(iso)} - P_{Y(iso)} \quad (3)$$

The zero order absorption spectrum of X for each mixture was obtained by multiplying the calculated amplitude corresponding to X in the mixture $P_{X(iso)}$ by the divisor (X′) (normalized spectrum or concentration of X). While, zero order absorption spectrum of component Y