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A Review Article on Analytical Method on Sitageliptin and Metformin

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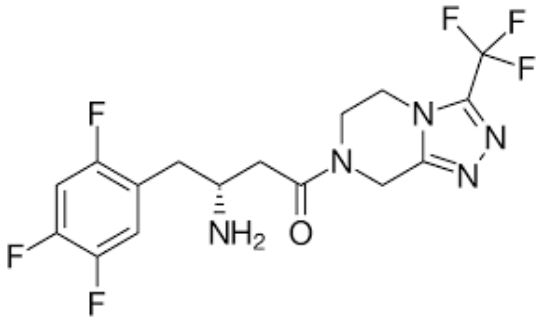
Abstract: *An overview about simultaneous estimation of the combination drugs, metformin and sitagliptin using RP-HPLC method. Reverse phase chromatography is the most commonly used separation technique in HPLC, common reasons being its simplicity, versatility and its ability to handle compounds of a diverse polarity and molecular mass.Good knowledge about different types of mobile phases and their combination are required for highly precise and accurate method development. The retention time and linearity of metformin and sitagliptin are found to be determined underdifferent chromatographic conditions such as column, mobile phase, elution mode, flow rate and wavelength detected using UV detector. In this article, we will be reviewing different developed methods for estimating the given combination drugs by RP-HPLC.*

Keywords: RP-HPLC

I. INTRODUCTION

Sitagliptin (SITA) chemically (3R) -3-amino-1-[3- (trifluoromethyl)-6,8-dihydro-5h-[1,2,4] triazolo [3,4-c] pyrazin-7-yl]-4-(2,4,5-trifluorophenyl) butan1-one (Figure 1), is an oral anti-diabetic agent that blocks DPP-4 activity, used in the treatment of type 2 diabetes.1,2 DPP-4 enzyme breaks down the incretin hormones including glucagon like peptide-1 (GLP-1) and glucose dependent insolinotropic polypeptide (GIP). GLP-1 and GIP are gastrointestinal hormones released in response to a meal. By preventing GLP-1 and GIP inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the pancreas. This drives blood glucose levels towards normal.3,4 The absolute bioavailability of SITA is approximately 87%. The coadministration of high fat meal with SITA has no effect on the pharmacokinetics. It may be administered with or without food.1 Approximately 80% of the SITA excreted unchanged in urine. The fecal route accounts for 13% of elimination.5 Several analytical methods based on UV [10-12], spectroflourimetry[12] , RP-HPLC[13-14], LC-MS/MS[15-17] was reported for the determination of sitagliptin phosphate monohydrate in plasma and urine of humans, rats and dogs.



sitageliptin

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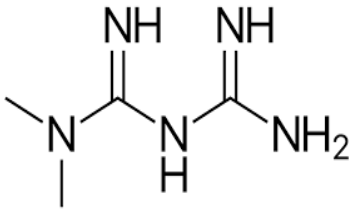
Metformin is widely used for the treatment of DM2. It is a biguanide developed from galegine, a guanidine derivative found in Galega officinalis [6]. Chemically, metformin is a hydrophilic base (Figure 1), however, is usually present in oral dosage forms in its hydrochloride salt form. Metformin HCl has acid dissociation constant values (pKa) of 2.8 and 11.5 and, therefore, exists very large as the hydrophilic cationic species at physiological pH values (>99.9%) [6]. The lipid solubility of the unionized species is low as shown by its low water-oil partition coefficient value (logP=1.43) [7]. This chemical parameter indicates low lipophilicity and, therefore, rapid passive diffusion of metformin trough cell membranes is unlikely [6]. Based on these properties, metformin HCl is defined as class III (low permeability, high solubility) by the Biopharmaceutics Classification System (BCS) [8]. The oral dose of metformin is considered as hydrochloride salt, but all concentrations in biological fluids are expressed as the free base [9]. Metformin is official in IP 2014(21), USP 2012(22) and BP 2009(23) and estimated potentiometrically. Sitagliptin is not official in any Pharmacopoiea. Combination of these both drug is used in the treatment of non –insulin-dependent diabetes mellitus.



metformin

II. DEVELOPED METHODS

Different methods for simultaneous estimation of metformin and sitagliptin from literature review are as follows.

METHOD	CHROMATOGRAPHIC CONDITION	OBSERVATION	REFERENCE
1.	***Column:*** *C18 Monolithic column (100mm× 4.5mm i.d., 5µm) connected with an C18 guard cartridge (4mm×3mm i.d., 5µm).* ***Mobile Phase:*** *MeOH, ACN, 0.01mM KH2 PO4 (pH 3.5±0.5), adjusted with freshly prepared 10% orthophosphoric acid* ***Wavelength:*** *210 nm* ***Injection Volume:*** *20µl.*	*pH 3.5±0.5 balanced with the diluted orthophosphoric acid solution and flow rate of 0.484ml/min and pH 3.946. Peak area ratio of the analyte was utilized for the evaluation of pharmaceutical formulation tests. Total chromatographic analysis time per sample was approximately 4.33 min with metformin and sitagliptin eluting with retention times of 3.3 and 4.4 min respectively.*	***18***
2.	***Column:*** *C18 column (Phenomenex, 250 x 4.6 mm, 5 µm)* ***Mobile Phase:*** *0.02M potassium dihydrogen phosphate (KH2 PO4) and acetonitrile in the ratio of 55:45(v/v) at pH 4.3.* ***Elution Mode:*** *isocratic mode* ***Flow Rate:*** *1 ml/min,* ***Injection Volume:*** *20 µl* ***Run time:*** *10 min* ***Detector:*** *252nm*	*The recoveries of Sitagliptin and Metformin were found to be 100.27 and 100.73% respectively. The validation of method was carried out utilizing ICH-guidelines. The described HPLC method was successfully employed for the analysis of pharmaceutical formulations containing combined dosage form*	***19***
3.	***Column:*** *Phenomenex Luna C18 A 100*	*Sitagliptin Phosphate and*	***20***

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	C18Column (250mm X 4.6 mm i.d.,5µ) ***Mobile Phase:*** *0.02M Potassium dihydrogen phosphate pH (4.0): Acetonitrile* ***Elution Mode:*** *Isocratic* ***Flow Rate:*** *1.0 ml/min* ***Injection Volume:*** *20 µ l* ***Temperature:*** *: 25°C* ***Detector:*** *252 nm*	*Metformin Hydrochloride were eluted at 2.718 and 1.925 min. The detection was carried out at a wavelength 252nm. The method was validated for system suitability, linearity, accuracy, precision and robustness of sample solution. The linear ranges for Metformin Hydrochloride and Sitagliptin Phosphate were 20-120µ g/mL, 2-12µ g/mL respectively with good recoveries i.e. 99.4% to 101.35%.*	
4.	***Column:*** *Zorbax Eclipse XDB C18 (150 mm × 4.6 mm)* ***Mobile Phase:*** *0.01M Phosphate buffer: methanol in a ratio 50:50 % v/v at pH 2.5 adjusted with 0.2 % orthophosphoric acid* ***Flow Rate:*** *0.7 ml/min* ***Injection Volume:*** *10 µL.* ***Temperature:*** *ambient* ***Detector:*** *PDA detection at 267 nm.*	*The assay of Sitagliptin was found to be 99.89 %. The results of the study showed that the proposed RP-HPLC method is simple, rapid, precise, reliable, accurate and economical which is useful for the routine determination of Sitagliptin phosphate in bulk and its pharmaceutical dosage form.*	***24***
5.	***Column:*** *Agilent C8 (250 x 4.6mm x 5µ)* ***Mobile Phase:*** *Methanol: Water (25:75) v/v* ***Elution Mode:*** *Isocratic* ***Flow Rate:*** *1.0* ***Detector****PDA266*	*The retention times were found as 3.227 and 15.760 for Sitagliptin and Simvastatin respectively. Validation parameters like Precision, Accuracy, Robustness and System suitability parameters were determined and examined by applying validated parameters*	***25***
6.	***Column:*** *Hi-Q Sil C18 (250 x 4.6mm x 5µ* ***Mobile Phase:*** *ACN: Methanol: 10 mM PB (65:25:10) v/* ***Flow Rate:*** *1.2* ***Detector:****PDA 250*	-------	***26***
7.	***Column:*** *Phenomenex C18 (250 x 4.6mm x 5µ)* ***Mobile Phase:*** *0.02M KH2PO4:ACN (55:45)v/v* ***Flow Rate:*** *1.0* ***Detector****UV 252*	-------	***27***

III. CONCLUSION

Analytical method development using RPHPLC are allsaid to be highly accurate, specific, simple and cost effective. Fromthe above mentioned methods, method5 shows the least retention time of 1.773 min for metformin and 3.696 min for sitagliptin respectively, where 50% of Methanol and 50% of Potassium dihydrogen orthophosphate buffer were used as mobile phases for elution and peak was observed at 260nm in an UV detector. Following this, method 4 shows second least retention time of 2.35 min for metformin and 3.04 min for sitagliptin where 20% of Methanol and 80% of

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Ortho Phosphoric Acid buffer were used as mobile phases for elution and the peak was observed at 210nm in UV detector. Finally, method 9 showed a retention time of 3.3min for metformin and 4.4 min for sitagliptin where 42.135% of Methanol, 10% of Acetonitrile and 47.865% of Potassium dihydrogen orthophosphate buffer were used as mobile phase for elution and peak observed at 210nm in UV detector. From this review, we can get an overall idea of different combination of mobile phases that can be used for simultaneous estimation of Metformin and Sitagliptin.

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