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A Review on Analytical Methods for the Determination of Glecaprevir in Pharmaceutical Formulation

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ABSTRACT

Glecaprevir is a hepatitis C virus (HCV) nonstructural (NS) protein 3/4A protease inhibitor. It is being developed as a treatment of chronic hepatitis C infection in co-formulation with Pibrentasvir (HCV NS5A inhibitor). Together they demonstrated potent antiviral activity against major HCV genotypes and high barriers to resistance *in vitro.* This review article represents the various analytical methods which have been reported for estimation of Glecaprevir in pharmaceutical formulation. The Chromatographic methods like, RP-HPLC and UPLC were reported. The spectrophotometric techniques like Ultra-Visible Spectrophotometric and Double beam spectrophotometric methods also reported.

INTRODUCTION

Glecaprevir[1-5] is a direct acting antiviral agent and Hepatitis C virus (HCV) NS3/4A protease inhibitor that targets the viral RNA replication. In combination with Pibrentasvir, it is a useful therapy for patients who experienced therapeutic failure from other NS3/4A protease inhibitors. It demonstrates a high genetic barrier against resistance mutations of the virus. In cell cultures, the emergence of amino acid substitutions at NS3 resistance-associated positions A156 or D/Q168 in HCV genotype 1a, 2a or 3a replicons led to reduced susceptibility to glecaprevir. The combinations of amino acid substitutions at NS3 position Y65H and D/Q168 also results in greater reductions in susceptibility, and NS3 Q80R in genotype 3a patients also leads to its resistance.

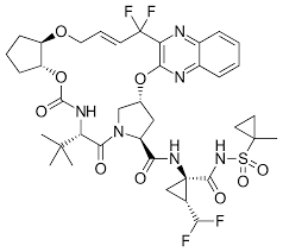

Figure - 1: Structure of Glecaprevir

Mechanism of action:

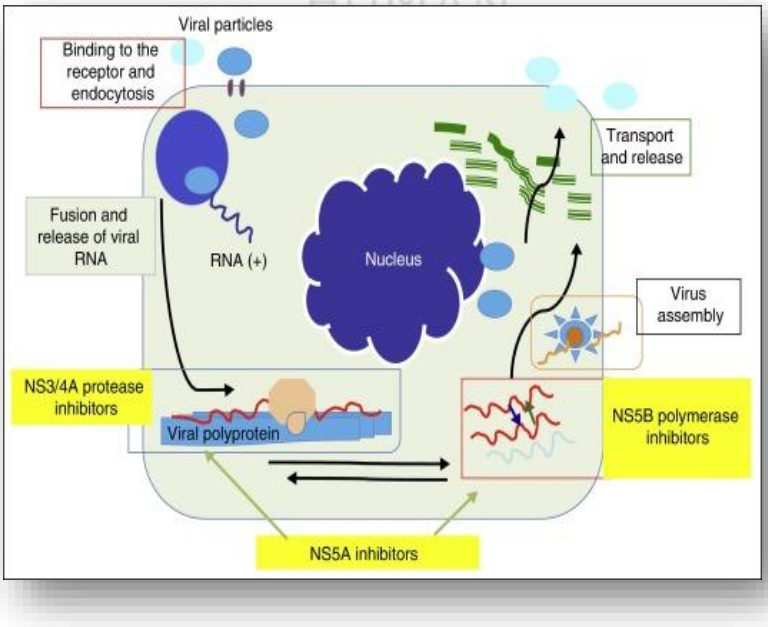

Figure - 2: Mechanism of action of Glecaprevir

Glecaprevir is an inhibitor of the HCV NS3/4A protease, which is a viral enzyme necessary for the proteolytic cleavage of the HCV encoded polyprotein into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins. These multifunctional proteins, including NS3, are essential for viral replication. The N-terminal of NS3 protein confers serine protease activity, while The C-terminus of NS3 encodes a DExH/D-box RNA helicase which hydrolyzes NTP as an energy source to unwind double-stranded RNA in a 3′ to 5′ direction during replication of viral genomic RNA. NS4A is a cofactor for NS3 that directs the localization of NS3 and modulates its enzymatic activities. Glecaprevir disrupts the intracellular processes of the viral life cycle through inhibiting the NS3/4A protease activity of cleaving downstream junctions of HCV polypeptide and proteolytic processing of mature structural proteins.

ANALYTIAL METHOD:

A.COMPENDIAL METHOD:

Monograph of Glecaprevir is not official in any pharmacopoeia.

B. REPORTED METHOD:

Chromatography Method:

Most of the reported methods for determination of Glecaprevir in pharmaceutical formulations are HPLC method. The HPTLC and RP- HPLC methods are also used widely to determine the assay of Glecaprevir. The summaries of reported methods are tabulated below.

SUMMARY OF CHROMATOGRAPHY METHOD OF GLECAPREVIR

TITLE	METHOD	MOBILE PHASE	STATIONARY PHASE	WAVE LENGTH
A New Force Indicating RP-HPLC Method Development and Validation for the Simultaneous Estimation of Pibrentasvir and Glecaprevir in Bulk and its Tablet Dosage Form[6]	RP-HPLC	Mixture of 0.5 mM Ortho phosphoric acid buffer: Acetonitrile in the ratio of 75:25 v/v	water's C_{18} column capacitate 250X4.6 mm	225nm
Stability Indicating RP-HPLC Method for the Simultaneous Estimation of Glecaprevir and Pibrentasvir in Drug Product[7]	RP-HPLC	0.1%v/v Trifluoroacetic acid in water: Methanol: Acetonitrile (30:60:10).	C_8 column (Hypersil BDS-C8 100*4.6, 3.5um)	225nm
Simultaneous Assay of Two Antiviral Agents, Pibrentasvir and Glecaprevir, Using Stability Indicating RP-HPLC Method in Bulk and Tablets[8]	RP-HPLC	Mixture of potassium dihydrogen phosphage (0.1 M; pH 4.0) and methanol in a ratio 55:45 (v/v).	Sunsil C_{18} column (250 mm × 4.6 mm; 5 µm particle size)	226nm
Development of validated stability indicating RP-HPLC method for the estimation of glecaprevir and pibrentasvir in bulk and pharmaceutical dosage form[9]	RP-HPLC	Buffer (pH 4.8) and acetonitrile in the ratio of 60:40 v/v	Denali C_{18} column (150 mm × 4.6 mm, 5 µm	260nm
Method Development and Validation of Glecaprevir and Pibrentasvir In Pure and Pharmaceutical Dosage Forms By RP-HPLC Method[10]	RP-HPLC	Mixture of buffer: methanol in the ratio of 30:70 v/v	Xterra C_{18} column (4.6 x 150mm, 5 (m) column	244nm
Development and Validation of Stability Indicating RP-HPLC Method for Simultaneous determination of Glecaprevir and Pibrentasvir in Its Bulk and Their Pharmaceutical Dosage Forms[11]	RP-HPLC	Methanol: Phosphate buffer	P^H 4.5(20:80 v/v). Kromosil C_{18} Column (250mm x 4.6mm) 5µg	254 nm
Stability indicating RP-HPLC method development and validation for the simultaneous estimation of Pibrentasvir and Glecaprevir in bulk and pharmaceutical dosage form[12]	RP-HPLC	Phosphate buffer (pH 4.0) and Methyl alcohol in the ratio of 30:70 v/v	C_{18} (250 X 4.6 mm),	251nm
Development and validation for the simultaneous estimation of glecaprevir and pibrentasavir in drug product by UPLC[13]	UPLC	Buffer: Acetonitrile (450:550)	C_{18} column (BEH C18 2.1 x 50 mm x 1.7 µm)	260nm

DISCUSSION

The most widely used method for determination of Glecaprevir was RP-HPLC method. Some various chromatographic conditions are presented in the given above table.

CONCLUSION

The sensitivity, specificity and better separation efficacy enable RP-HPLC to be used frequently for Qualitative and Quantitative Determination of Glecaprevir. The presented information is useful for the future study for researcher involved in formulation development and quality control of Glecaprevir.

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