A Review on Estimation of Octreotide Acetate In Bulk And Pharmaceutical Dosage Form

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Abstract- *The purpose of this survey to focus on extensive update of different analytical methods for determination of octreotide acetate which is used in the treatment of acromegaly and carcinoid tumor.It is somatostatin analogue and binds to the somatostatin receptor subtypes II and V, inhibiting GH secretion. Somatostatin suppresses the serum GH level and normalizes circulating IGF-I slevels. The review entails about analytical procedures like RP-HPLC, HPLC,LC/MS, capillary zone electrophoresis, two dimensional HPLC-CE methods taken from the literature. This review provides detailed information of development and validation for octreotide acetate in bulk and in pharmaceutical preparations.*

Keywords- octreotide acetate, Analytical methods, Acromegaly, carcinoid tumor.

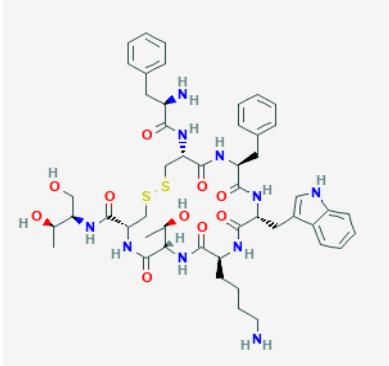
I. DFINITION OF OCTREOTIDE ACETATE

Octreotide is a synthetic long-acting cyclic octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide is a more potent inhibitor of growth hormone, glucagon, and insulin than somatostatin. Similar to somatostatin, this agent also suppresses the luteinizing hormone response to gonadotropin releasing hormone, decreases splanchnic blood flow, and inhibits the release of serotonin, gastrin, vasoactive intestinal peptide (VIP), secretin, motilin, pancreatic polypeptide, and thyroid stimulating hormone.[1]

II. APPROVAL OF OCTREOTIDE ACETATE FOR INJECTABLE SUSPENSION

In November, 1998 FDA approved octreotide acetate [2]

III. DRUG PROFILE: [3,4]

Name	Octreotide acetate
Structure	
IUPAC Name	(4*R*,7*S*,10*S*,13*R*,16*S*,19*R*)-10-(4-aminobutyl)-19-[[(2*R*)-2-amino-3-phenylpropanoyl]amino]-16-benzyl-*N*-[(2*R*,3*R*)-1,3-dihydroxybutan-2-

	yl]-7-[(1*R*)-1-hydroxyethyl]-13-(1*H*-indol-3-ylmethyl)-6,9,12,15,18-pentaoxo-1,2-dithia-5,8,11,14,17-pentazacycloicosane-4-carboxamide
Molecular formula	$C_{51}H_{70}N_{10}O_{12}S_2$
Molecular weight	1019.2 g/mol
Physical state	Solid
Solubility	soluble in water (water soluble), soluble in methanol, slightly soluble in Acetic acid, DMSO
Melting point	153°C to 156°C
Storage	2-8°C
Category	Growth inhibitor hormone
Pharmacokinetic study	Absorption:Volume of distribution is found to be 0.27 l/kg and plasma protein binding is 65 %. and metabolism is reported Not Established. Renal Excretion accounts for 32 % and plasma half- life is 85 min (I/V), 101 min (S/C). Administration with fatty meals does not alter AUC but decreases level of Cmax by 32%.
Uses	For treatment of acromegaly and reduction of side effect from cancer chemotherapy. Octapeptide analogue of somatostatin. A gastric anti-secretory agent. Symptom associated with metastatic carcinoid tumor (flushing and diarrhoea). And vasoactive intestinal peptide (VIP) secreting adenomas (watery diarrhoea). In many cases it reduces or normalizes growth hormone and/or IGF-1 (somatostatin C) level in patient with acromegaly. Non-approved uses: AIDS- associated diarrhoea, oesophageal varices, and pituitary tumors
Side effects	Hypoglycaemia, hepatic dysfunction, acute pancreatitis, which are responsible for the discontinuation of Octreotide (Acetate) therapy. Symptomatic adverse reactions these include flatulence, loose stools, anorexia, abdominal pain, local pain, local reaction, nausea, vomiting, tingling, steatorrhea, tenderness, bloating, stinging.
Dosage & Administration	500ug/1mL –intravenous or subcutaneous

IV. REPORTED ANALYTICAL METHODS

<table>
<tr><th>Sr. No</th><th>Title</th><th>Method</th><th>Description</th></tr>
<tr><td>1.</td><td>[5]USP-40</td><td>HPLC</td><td>Column: 4.6-mm* 25-cm; 4-µmPackingL87
Mobile Phase:Solution A: 0.02% (v/v) of trifluoracetic acid inwater
Solution B: Acetonitrile
Flow rate: 1.0 ml/min
Injection volume: 10µl
Wavelength: 220nm
Column temperature: 40°C Rt:16.5 min
<table>
<tr><th>Time(min)</th><th>Solution A</th><th>Solution B</th></tr>
<tr><td>0</td><td>90</td><td>10</td></tr>
<tr><td>25</td><td>65</td><td>35</td></tr>
<tr><td>30</td><td>10</td><td>90</td></tr>
<tr><td>35</td><td>10</td><td>90</td></tr>
<tr><td>40</td><td>90</td><td>10</td></tr>
<tr><td>45</td><td>90</td><td>10</td></tr>
</table>
Gradient programme:</td></tr>
<tr><td>2.</td><td>[6]Octreotide acetate</td><td>HPLC</td><td>Chromatographic conditions:
Column: ZORBEX 300SB-C8 column (2.1 mm* 150mm, 5µm)
Mobile phase: 0.1% TFA WATER
0.1% TFA Acetonitrile (50:50)
Flow rate: 0.25 ml/min
Injection volume: 20 µL
Wavelength: 210nm
Column temperature: 40°C</td></tr>
</table>

3.	[7]Octreotide acetate and its related substances	HPLC	**Chromatographic conditions:** **Column:** Lichrospher - C18 column (200nm* 4.6 mm, 5 µm) **Mobile phase:** **Mobile phase A:** 0.1%trifluoroacetic in water **Mobile phase B**: 0.1% trifluoroacetic in Acetonitrile **Flow rate**: 1.5ml/min **Wavelength**: 215nm Mobile phase was increased from 20% to 40% in twenty minutes.
4.	[8]Impurities in octreotide acetate and its injection	LC- MS	**Chromatographic conditions:** **Column:** Hypersil C18 (4.6 mm* 250mm, 5 µm) **Mobile phase A:** tetramethylammonium hydroxide solution (20ml of 10%) tetramethylammonium hydroxide solution and 880 ml water were added, pH was adjusted to 5.4 with 10% phosphoric acid)- Acetonitrile (900:100) **Mobile phase B**: tetramethylammonium hydroxide solution (20 ml of 10% tetramethylammonium hydroxide solution and water 380 ml were added, pH was adjusted to 5.4 with 10% phosphoric acid)- Acetonitrile (400:600) **Flow rate**: 1.0ml/min **Wavelength:** 210nm
5.	[9]LC determination of Octreotide acetate in compound formulations of sandostatin and	HPLC	**Chromatographic conditions:** **Column:** Lichrospher RP Select B column (125nm* 4 mm, 5 µm) **Mobile phase:** Acetonitrile- phosphate buffer (pH 7.4,20 mM, 5 µm) **Flow rate**: 1.0ml/min

	diamorphine hydrochloride		**Wavelength**: 210nm
6.	[10]The compatibility and stability of octreotide acetate in the presence of diamorphine hydrochloride in polypropylene syringes.	HPLC	**Chromatographic conditions:** **Column:** Lichrospher RP Select B column (125nm* 4 mm, 5 µm) **Mobile phase:** Acetonitrile- phosphate buffer (pH 7.4,20 mM, 50:50) **Flow rate**: 1.0ml/min **Wavelength**: 210nm
7.	[11]Reversible blocking of Amino Groups of octreotide for the inhibition of Formation of Acylated peptide Impurities in poly (Lactide-co-Glycolide) Delivery system	RP-HPLC &LC-MS	**Chromatographic conditions:** **Column:** C18(250*4.6mm*5 micrometer) Dionex **Mobile phase:** Acetonitrile in Water containing 0.1% v/v Trifluoroactetic acid with linear gradient from 30% to 50% for 20 minutes. **Flow rate**: 1ml/min **Wavelength:** 215nm The mass spectrometer is operated in the positive ion mode using the following: Conditions: drying gas (N) flow of 10 ml/min, drying gas at 350°C, nebulizer pressure of 45 psi, and capillary voltage is 100V. Ions were detected by scan mode and mass range is Set from m/z 400 to 1400.
8.	[12]Stability of Octreotide acetate in aqueous solution and PLGA films.	RP- HPLC	**Chromatographic conditions:** **Column:** Prosphere C18 (250*4.6mm*5 micrometer) with Prosphere C18 (250*4.6mm*5 micrometer) **Mobile phase A:** 0.1% TFA in water **Mobile phase B:** 0.1% TFA in Acetonitrile Linear gradient from 80:20 to 65:35 of mobile

			phase A: B **Wavelength**: 215nm **Flow rate**: 1ml/min **Injection volume:** 40µl **Run time: 30 minutes**
9.	[13]Prediction of the stability of Octreotide in a mixed infusion	HPLC	**Chromatographic conditions:** **Column:** C18 (150* 4.6 mm, 5µm), type MG **Mobile phase:** 1% Trifluroacetic acid: Acetonitrile (75:25) **Flow rate**: 1.5ml/min **Wavelength**: 215nm **Injection volume:** 200µl **Column temperature:** 40°C
10.	[14]Analysis of Biologically active peptides	Two Dimensional HPLC-CE	**HPLC:** **Column:** Nucleosil 120-5 C18 250*4 mm (Macherey- Nagel) **Mobile phase A:** 25 mM of pH 2 tetramethylammonium hydroxide with 10% acetonitrile. **Mobile phase B:** 25 mM of pH 2 tetramethylammonium hydroxide with 60% acetonitrile. Time(min) Solution A Solution B 0 90 10 15 80 20 45 55 45 50 90 10 55 90 10 **Flow rate**: 2.0ml/min **Wavelength**: 210nm **Injection volume:** 100µl **Column temperature:** 25°C

11.	[15]Stability of Octreotide acetate decreases in a sodium bisulphate concentration dependent manner (compatibility with morphine & metoclopramide injection)	HPLC	**Column:** COSMOSIL C18 (150*4.6 mm) **Mobile phase A:** Water: ACN: 1M tetramethylammoniumhydroxide (440:50:10) **Mobile phase B:** Water: ACN: 1M tetramethylammonium hydroxide (190:300:10) **Mobile phase C:** Water: CAN (50:50) & Adjust pH to 4.5 using two types of phosphate solution (0.17 M sodium dihydrogen phosphate & 0.17 M disodium hydrogen phosphate) Linear gradient elution, mobile phase ratio is change from A:B = 73:27 to 55:45 for 12 minutes & set mobile phase C at 100% from 12 to 17 minutes. **Flow rate**: 1.0ml/min **Wavelength**: 210nm **Injection volume:** 10µl

V. CONCLUSION

The above study presents analytical method for analysis of octreotide acetate in bulk materials and pharmaceutical dosage forms by various method. The various parameters like accuracy, precision, reliability, repeatability, analysis time and sensitivity are performed These methods are adequate to analyse the drugs in single component formulation as well as combination preparation. Literature survey suggested that various RP-HPLC, HPLC, two dimensional HPLC-CE, LC-MS, Capillary zone electrophoresis methods were developed and reported. The published methods were validated for various parameters as per ICH guidelines.

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