THE DEVELOPMENT OF LONG-ACTING TERIPARATIDE FORMULATIONS TO TREAT OSTEOPOROSIS

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PURPOSE

The purpose of research investigation is to develop a stable long-acting release Teriparatide formulation for treating parathyroid hormone related calcium and phosphate disorders.

OBJECTIVE(S)

1. To develop a stable formulation of Teriparatide, a parathyroid hormone (PTH) analog.
2. To reduce the frequency of subcutaneous administration of Teriparatide.
3. To develop long-acting release (LAR) formulation of Teriparatide which can deliver approx. 20 micro-gram/day of Teriparatide for 7 days.

METHOD(S)

S.No.	Parameter	Method
1	Assay (%, Teriparatide)	USP <621>, IH
2	Amino acid sequence	USP <621>, IH
3	Peptide content	USP <621>, IH
4	Related substances (RS)	USP <621>, IH
5	Oligomers	USP <621>, IH
6	Molecular weight (Da)	IH
7	pH (units)	USP <791>, IH
8	Osmolality (mOsm/kg)	USP <785>, IH
9	Viscosity (cP)	USP <911, 912>, IH
10	Density (g/ml)	USP <841>, IH
11	Secondary structure (NMR, CD, FTIR)	IH
12	In vitro release studies	IH
13	In vivo release studies	IH
14	Biological activity	IH

Note: USP – United States Pharmacopoeia; IH – In-house

RESULT(S)

1. Teriparatide is a parathyroid hormone analog produced through recombinant DNA technology using E.*coli* strain.
2. Teriparatide has an identical sequence to 34 N-terminal amino acids of the 84 amino acid human PTH.
3. Long-acting release Teriparatide formulations are clear colourless gel formulations.
4. Among polymers-based LAR formulations. Hyaluronic Acid (HA) based one produced a stable & sustained release Teriparatide.

Table 1. Teriparatide Composition (PTF II)

S.No.	Ingredient(s)	Concentration (% w/w)
1	Teriparatide	0.002
2	Hyaluronic acid	5
3	Gelatin	10
4	Phenol	0.5
5	Cysteine	0.1
6	Purified water (Q.S)	Q.S.
7	Acetic acid or sodium hydroxide	Q.S
8	pH (units)	6.5 – 7.3

Note: Q.S. is quantity suffice

Teriparatide Sequence

Fig 1.Amino acid Sequence of Teriparatide

Teriparatide Secondary Structure (Modeling)

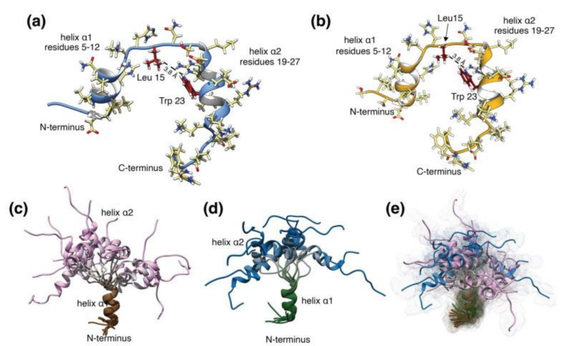


Fig 2.Minimal Energy Structures of Teriparatide from 6 Different Batches

Teriparatide Secondary Structure

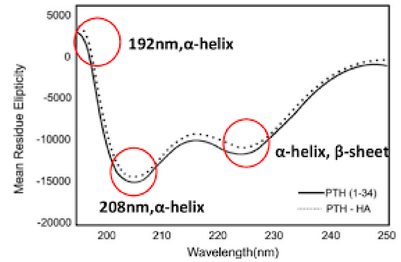


Fig 3.Circular Dichroism of Teriparatide & Teriparatide Formulation

NMR & Chemometric (PCA) Analysis

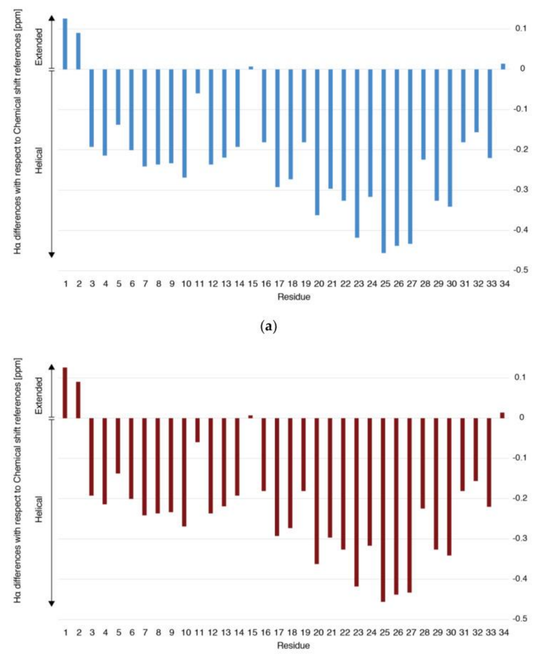
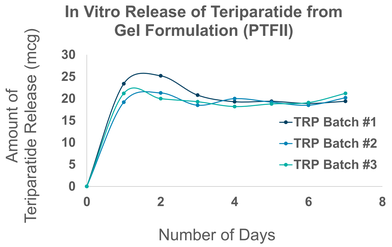


Fig 4.Graphical Representation of Hα Differences with respect to chemical shift index between the a) Reference Teriparatide API and b) Teriparatide after extraction from Gel Formulation

In Vitro Release of Teriparatide



- **Fig 5.** In Vitro Release of Teriparatide into Phosphate Buffer Medium, pH 7.0. Release Studies are a Replicate of Three Formulation Batches. In Vitro Release Studies were Performed in a Medium Maintained @ 37°C.

Table 2. Stability Studies Data (2-8°C- 6M)

S.No.	Parameter	Specification	Result
1	Assay (%, Teriparatide)	90 - 110	98.2
2	Amino acid sequence	Complies	Complies
3	Peptide content (%)	NLT 92.0	93.4
4	Related substances (RS) (%)	NMT 0.20	0.07
5	Oligomers (%)	NMT 0.10	0.02
6	Molecular weight (Da)	4117.8	4118.3
7	pH (units)	6.5 – 7.5	7.05
8	Viscosity (cP)	37 ± 4	35
9	Density (g/ml)	1.15 ± 0.07	1.20
10	Secondary structure (NMR, CD, FTIR)	Complies	Complies
11	Biological activity	Complies	Complies

Note: USP – United States Pharmacopoeia; IH – In-house; NLT – not less than; NMT – not more than

Conclusions

- All the formulations (PTFI-VI) are subjected to real-time stability studies at 2-8 Deg. Cel for 6 months. At the end of 6-months, teriparatide formulations, PTFII exhibited better stability than other formulations.
- The assay value of these formulations is in the range, 95 – 105%. And RS are NMT 0.5%. .
- The CD and FTIR spectral studies showed similar secondary structure as that of active pharmaceutical ingredient (API). .
- The in vitro release data of formulations indicated that teriparatide is released at a rate 18-21 mcg per day. Also, showed similar biological activity compared to Forteo (innovator).

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