

Stabilizing Excipients for Coated Microneedle Drug Product (BA058-sMTS)

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Abstract

BA058, a novel synthetic analogue of PTHrP (human parathyroid hormone related peptide), was developed to treat osteoporosis and is currently undergoing a Phase 3 clinical trial as an injectable product. The sMTS (solid microstructured transdermal system) is 3M's microneedle-based delivery technology wherein drugs such as BA058 are coated onto the microneedles and inserted into the skin where the drug is rapidly released and delivered into the systemic circulation. BA058-sMTS is currently undergoing a Phase 2 clinical trial. The purpose of this work was to explore the degradation mechanism of BA058 when coated onto sMTS and to identify excipients that may improve the stability of BA058 coated onto microneedles and prolong the shelf life of drug product. BA058 degradation products, aggregated and acetylated impurities, were identified by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF) and monitored by reversed-phase high performance liquid chromatography (RP-HPLC). The BA058 coating formulations were prepared with and without excipients to examine differences in the kinetics of degradation of the peptide. Histidine, identified as the best stabilizing excipient, was successfully formulated with BA058 and coated onto sMTS. The addition of histidine did not adversely effect coating performance and *in vivo* delivery but did improve the product stability.

Experimental methods

Arrays: The sMTS arrays were injection molded from a medical grade polymer and were of a surface area of approximately 1.27cm². The arrays were composed of approximately 316 microneedles with a needle height of ~500 μm and a tip-to-tip needle spacing of ~550 μm.

Coating: Formulations with or without histidine were prepared using PBS as the solvent and then were coated onto arrays. The dip coated microneedles were examined microscopically to assess coating uniformity.

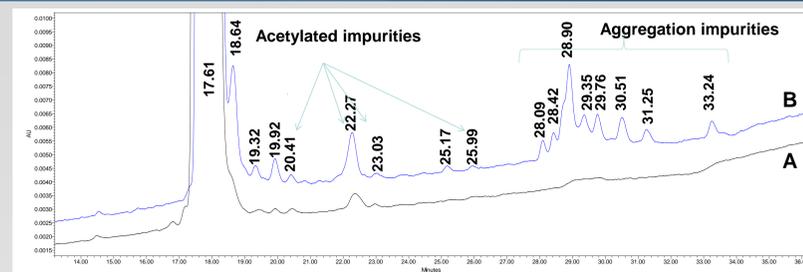
Stability study: The arrays coated with BA058 were packaged into a packaging system consisting of the array inside a plastic tray sealed with Tyvek. Then the packaged BA058-sMTS was individually placed into a 8"X10" foil pouch and heat sealed. The pouches were then stored at three conditions with controlled temperature and humidity (40°C/75%RH, 25°C/60%RH and 4°C/ambient RH) for up to 3 three months. The BA058 purity was analyzed.

Analytical method: Analysis of BA058 content and purity was conducted using HPLC. The BA058 coated arrays were first extracted in a solution of 0.1N acetic acid. A Zorbax 300SB-CB, 5μm particle size, 250X4.6 mm I.D. column maintained in a column oven at 50°C was used for the separation. The mobile phase consisted of two eluents: Eluent A was 0.1% (v/v) TFA in 77:23 water:acetonitrile, eluent B was 0.1% (v/v) TFA in 65:35 water:acetonitrile. The injection volume was 100 μl and the flow rate was 0.9 mL/min. A linear gradient from 100/0 to 40/60 (A/B) was applied over 30 minutes. The total run time was 52 minutes. The UV detection wavelength was 220 nm.

Identification of impurities: The degradation impurities were identified by MALDI-TOF MS. MALDI-TOF MS samples were prepared by mixing 1 μl of BA058 solution with 0.5 μl of MALDI matrix solution. The peptide and matrix solution mixture were applied on a MALDI plate and were allowed to dry in air prior to mass spectrometry analysis. MALDI-TOF-MS analysis was carried out with a Bruker Ultraflex II MALDI-TOF/TOF instrument. The total examined mass range was m/z 120-30000, which was explored in reflector/linear mode.

In Vivo study: Female Yorkshire swine, weighing between 10-45 kg, were anesthetized with isoflurane gas. Arrays were applied to the swine with a spring-loaded applicator that provides an impact velocity of ~8m/s; the arrays remained in contact with the skin for 15 minutes. The patches were removed and a cotton ball moistened with PBS was used to swab the application site. The used arrays were assayed by HPLC to determine the residual drug on the arrays.

Identification of impurities



HPLC chromatograph of freshly coated BA058-sMTS (A) and three months aged BA058-sMTS at 25°C/33%RH (B)
Note: Acetylated impurities and unidentified impurities were co-eluted at retention time 22.27 minute

Table 1 The mass and assigned structure

Observed mass (m/z)	Assigned Structure
3959.1	BA058+H ⁺
3942.6	BA058+H ⁺ -H ₂ O
4001.1	BA058+H ⁺ +AC
4043.2	BA058+H ⁺ +AC+AC
7919.6	(2×BA058+H) ⁺
7962.1	(2×BA058+H) ⁺ +AC
7945.1	(2×BA058+H) ⁺ +AC-H ₂ O
8004.6	(2×BA058+H) ⁺ +AC+AC
7988.1	(2×BA058+H) ⁺ +AC+AC-H ₂ O
11875.2	(3×BA058+H) ⁺
11917.4	(3×BA058+H) ⁺ +AC

AC: acetyl group (CH₃CO-); table contains both monoisotopic/centroid masses

Purity of BA058 under accelerated conditions

Table 2 Purity of BA058 under accelerated conditions

Array/Drug substance	condition	Time (days)	Purity (%)	Soluble aggregates* (%)
BA058 flood coated arrays	40°C/96%RH	0	99.8	0.3
BA058 flood coated arrays	40°C/96%RH	3	99.0	1.0
BA058 flood coated arrays	40°C/96%RH	7	97.9	2.1
BA058 flood coated arrays	40°C/96%RH	14	55.7	44.3
BA058 flood coated arrays	40°C/96%RH	21	28.9	63.9
BA058 drug substance	40°C/96%RH	4	96.7	3.3
BA058 drug substance	40°C/96%RH	7	89.4	10.1
BA058 drug substance	40°C/96%RH	14	74.1	24.2 ^a
BA058 drug substance	40°C/96%RH	21	0	0 ^b
BA058 drug substance	21°C/96%RH	4	99.1	0.4
BA058 drug substance	21°C/96%RH	7	99.0	0.5
BA058 drug substance	21°C/96%RH	14	99.0	1.3
BA058 drug substance	21°C/96%RH	21	98.3	1.2

*% of aggregates was tested by SEC

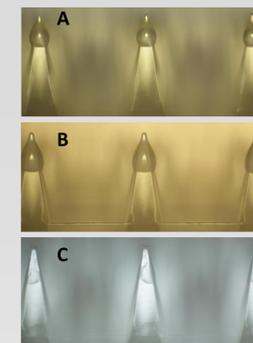
a: part of BA058 lyophilized powder was insoluble;
b: all the BA058 lyophilized powder became insoluble.

BA058 coated arrays

•Various excipients were selected to explore stabilizing effects on BA058 coated arrays. This screening study showed that amino acids, such as histidine stabilize BA058 coated onto microneedles.

Table 3 BA058 coating formulation for sMTS

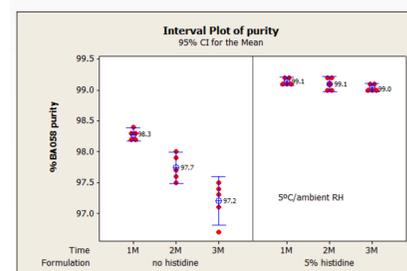
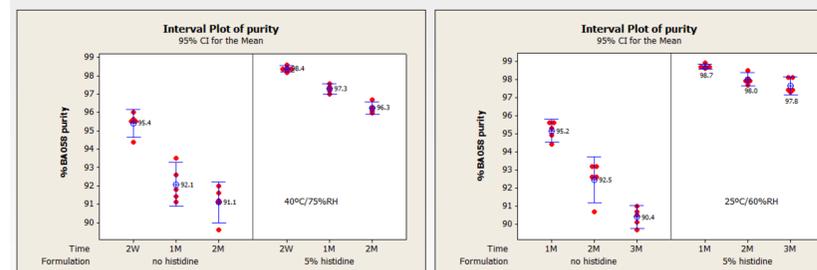
Formulation ID	BA058 (wt%)	Histidine (wt)	PBS (wt%)	Initial content (μg/array)	Initial purity %
A	51	0	49	124±6	98.9
B	49	5	46	134±11	99.5



Microscope imaging of contact coated arrays with Formulation A, no excipient (A), Formulation B, with 5% histidine (B), Formulation C, after 15 minute *in vivo* (C).

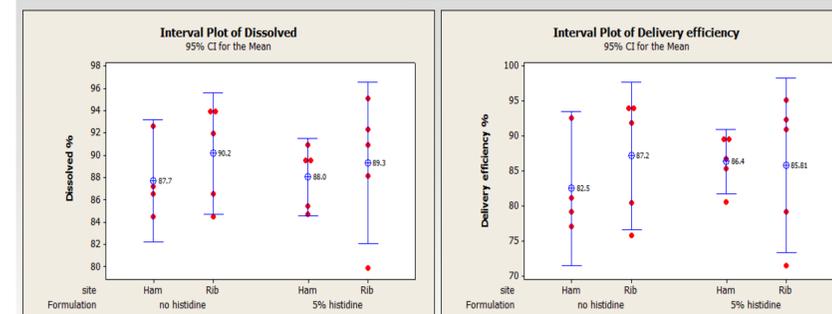
•Adding histidine in the formulation did not adversely affect the coating performance of BA058 onto microneedle arrays;

Purity of BA058-sMTS after storage at 3 conditions



•Histidine significantly improved the stability of BA058-sMTS by inhibiting both aggregation and acetylation

Effects of histidine on the *in vivo* release of BA058-sMTS



% Dissolved of BA058-sMTS coated with different formulations
Patch wear time:15 minutes

% Delivery efficiency of BA058-sMTS coated with different formulations

Dissolved %=(initial content-residual on the array)/initial content×100
Delivery efficiency %=(initial content-residual on the array-skin swab) /initial content×100

- Adding histidine in the formulation has not affected the delivery efficiency of BA058-sMTS;
- Majority of the drug was delivered into the skin instead of on the skin.

Conclusions

The degradation pathways for BA058-sMTS are aggregation and acetylation. An excipient screening study was conducted with formulations with low BA058 concentration and flood coated arrays under accelerated aging conditions. Amino acids such as histidine were identified as potential BA058 stabilizers when the drug is flood coated on arrays. Coating formulations containing histidine were dip coated onto arrays with no significant impact on the coating performance of the formulations due to the inclusion of the excipients. The stability of BA058-sMTS at all three storage conditions studied was increased by adding histidine in the formulation. The purity of BA058-sMTS coated with the formulation containing 5% histidine remained greater than 97.8% for 3 months under 25°C/60%RH storage condition. Adding histidine in the coating formulation had no effect on the *in vivo* release, over 80% delivery efficiency was achieved with 15 minutes patch wear time.

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