Development of a sustained released dosage form for phenylephrine hydrochloride using Solid Lipid Pellets

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PURPOSE

The purpose of this work was to demonstrate proof-of-concept for a stable sustained release dosage form containing phenylephrine hydrochloride (PE HCl) using Capsugel's Solid Lipid Pellets (SLP) technology.

Phenylephrine is the most common over-the-counter decongestant used in the United States. PE HCl is highly water-soluble and therefore the development of a sustained release dosage form is challenging, Moreover, PE HCl exhibits low and variable oral bioavailability due to extensive monoamine oxidase mediated metabolism in the gut and liver.

More specifically the objective was to produce spherical pellets (100–1000 µm) providing a sustained release in-vitro dissolution profile over at least 12 hours and showing acceptable physical and chemical stability on prolonged storage over 18 months.

METHODS

SLP were produced via a solvent-free and surfactant-free patented dispersion process by injecting a lipid matrix composed of a hard fat and a glyceryl ester into a gelled aqueous phase (Figure 1) to form Solid Lipid Pellets upon cooling.

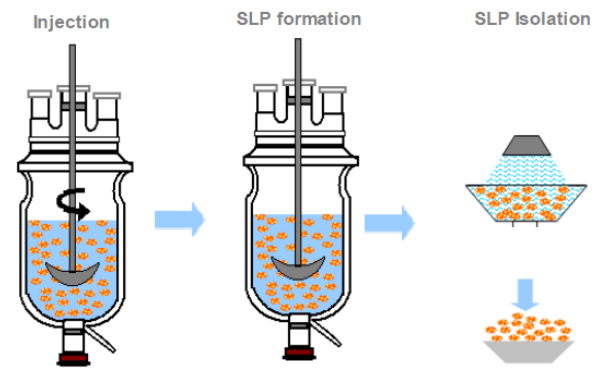

Figure 1: SLP Manufacturing Process

Manufactured SLP were subsequently filled into size 0 capsules to achieve a PE HCl dose of 45 mg per capsule.

Capsules were then packaged in HDPP bottles for physical and chemical stability follow-up under ICH conditions (i.e. 25ºC/60% RH) over 18 months.

Analytical testing methodology adapted to the SLP was developed and testing was performed at predefined time points.

The physical stability of SLP was evaluated through macroscopic and microscopic examinations.

The assay and related substances were determined by Liquid Chromatography. The dissolution profile was established at each defined time point in a pH 7.0 phosphate buffer using USP apparatus II Dissolution tests in a pH 1.2 medium were also performed to evaluate the stability of PE HCl embedded in the SLP against oxidation and acidic degradation

RESULTS

Manufactured micro-pellets were spherical in nature with a regular smooth surface (Figure 2).

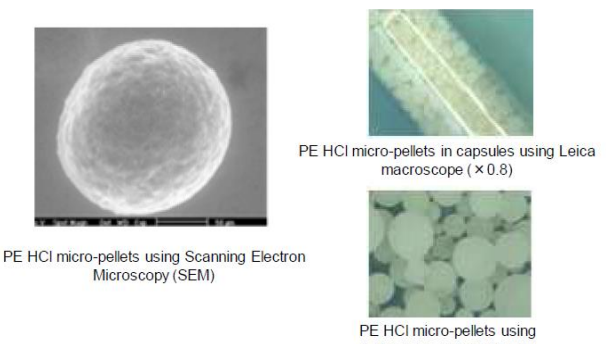

Figure 2: Aspect of PE HCl through microscopic and macroscopic examinations

After 18 months of storage at 25ºC/60% RH, the pellets in the capsules remained physically intact and non-aggregated.

Moreover, an excellent chemical stability profile, i.e. 95-105% of the PE HCl label content and total related substances less than 0.05% of area, was obtained and maintained over the 18 months storage.

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Test	Result	T0	T1	T3	T6	T9	T18
Appearance	Non aggregated with pellets in clear capsules	Complies	Complies	Complies	Complies	Complies	Complies
Assay	Mean (mg/capsule)	45.8	44.0	44.6	44.3	43.5	44.1
	Mean (% label claim)	101.8	97.8	99.1	98.3	96.6	98.0
Related substances	Total (% area)	< 0.05	< 0.05	< 0.05	< 0.05	0.05	< 0.05

Table 1: Physical and chemical stability results of SLP over 18 months storage at 25ºC/60% RH.

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In-vitro dissolution tests in a phosphate buffer confirmed the potential of using SLP to obtain sustained release of PE HCl over at least 12 hours (Figure 3).

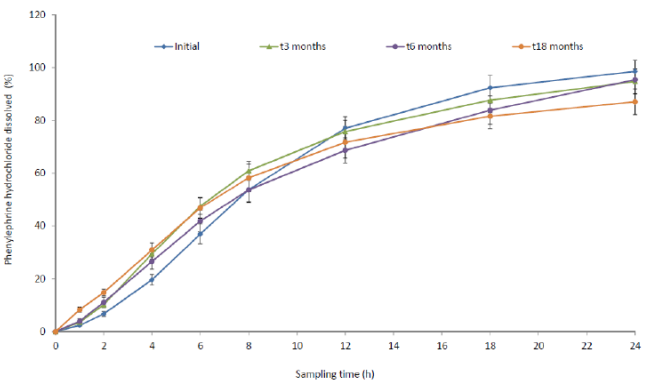

Figure 3: Dissolution profiles of SLP after storage at 25ºC/60% RH

The dissolution tests in acidic medium showed that the SLP provided protection against PE HCl oxidation and acidic degradation in a gastric environment (data not shown).

CONCLUSIONS

The phenylephrine hydrochloride (PE HCl) solid lipid pellets demonstrated a sustained release in-vitro dissolution profile over more than 12 hours and were physically and chemically stabile over 18 months storage at 25ºC/60% RH.

According to these results, we can conclude that the Solid Lipid Pellets technology can be successfully used to develop stable *in-vitro* sustained release dosage forms for highly water soluble compounds.

In a next phase *in-vivo* studies are targeted to be performed to confirm these promising *in-vitro* results.

REFERENCES

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2. Non ionizable hydrophobic galenical system. Patent US 2012/0086595 A1

ACKNOWLEDGEMENTS

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