International Journal of Pharmaceutics 491 (2015) 91–98

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Dynamic behavior of a spring-powered micronozzle needle-free injector

Aurélie Schoubben[a], Andrea Cavicchi[b], Lanfranco Barberini[c], Alessio Faraon[d], Marco Berti[d], Maurizio Ricci[a], Paolo Blasi[e,*], Lucio Postrioti[b,**]

[a] Dipartimento di Scienze Farmaceutiche, Università degli Studi di Perugia, Perugia, Italy
[b] Dipartimento di Ingegneria, Università degli Studi di Perugia, Perugia, Italy
[c] Dipartimento di Chimica, Biologia e Biotecnologie, Università degli Studi di Perugia, Perugia, Italy
[d] Brovedani Group, San Vito al Tagliamento, Italy
[e] Scuola di Scienze del Farmaco e dei Prodotti della Salute, Università degli Studi di Camerino, Camerino, Italy

ARTICLE INFO

Article history:
Received 21 March 2015
Accepted 25 May 2015
Available online 29 May 2015

Keywords:
Spring-powered needle-free injectors
Jet injectors, micronozzle
Transdermal delivery
Insulin

ABSTRACT

Conventional injection is still the leading method to deliver macromolecular therapeutics. Needle injection is considered a low compliance administration strategy, principally due to pain and needle phobia. This has fostered the research on the development of alternative strategies to circumvent the skin barrier. Among needle-free drug delivery methods, jet injection is an old strategy with great potential not yet completely disclosed. Here, the design, engineering and dynamic behavior of a novel spring-powered micronozzle needle-free injector is presented. Fluid mechanics was first studied in air to calculate jet force and speed as well as injection duration in different conditions. Polyacrylamide gel was used to simulate a soft tissue and to investigate the jet evolution over time of different injected doses. Finally, *ex vivo* characterization was carried out on pig skin. Results evidenced a direct dependence of the force, velocity, and duration with the injection volume. The model material allowed individuating the different steps of jet penetration and to attempt a mechanistic explanation. A different behavior has been recorded in the skin with interesting findings for subcutaneous and/or dermal delivery. Peculiar features with respect to existing jet injectors confers to this device good potentiality for a future clinical application.

1. Introduction

Conventional injection, syringe provided with needle, is at the moment the leading method to deliver macromolecular therapeutics. Transdermal drug delivery offers a number of advantages, especially when biological macromolecules are the therapeutics to be delivered (Prausnitz and Langer, 2008). Needle injection is considered a low compliance administration strategy, particularly when applied to chronic therapies. Pain during administration and needle phobia are the factors limiting its compliance. This has fostered the research on the development of new strategies for transdermal delivery: these include formulation strategies and devices able to circumvent the skin barrier avoiding conventional needles.

Formulation strategies comprise the addition of penetration enhancer (i.e., additives able to reduce the skin barrier proprieties) (Williams and Barry, 2004) or the inclusion of the active pharmaceutical ingredient (API) in a carrier able to cross the skin (Cevc, 2004). Pro-drug approach has been also found useful but API chemical modification is not always feasible (Puglia et al., 2006).

Devices capable to puncture the skin and deliver therapeutics without the use of a conventional needle (e.g., needle-free injectors, micro needles) are a reliable alternative to conventional injections (Arora et al., 2007; van der Maaden et al., 2012; Xiang et al., 2013). Needle-free jet injectors have been conceived to minimize pain and inconvenience in parenteral therapy. Invented more than a century ago, liquid jet injectors were used in clinics for mass immunization only in the 1950s (Mitragotri, 2012).

The basic components of a liquid jet injector are a compressed gas or a spring, a piston, a compartment where the formulation is loaded, and a nozzle. These devices use the gas or the spring as power source to push the piston that impress a pressure to the liquid formulation that, as a reaction, is ejected through the nozzle orifice at high velocity ($v > 100$ m/s). Nozzle orifices have been

* Corresponding author. Tel.: +39 737402289, fax: +39 737637345.
** Corresponding author. Tel.: +39 755853733; fax: +39 755853733.
E-mail addresses: paolo.blasi@unicam.it (P. Blasi), lucio.postrioti@unipg.it (L. Postrioti).

http://dx.doi.org/10.1016/j.ijpharm.2015.05.067
0378-5173/

Nomenclature

API	Active pharmaceutical ingredient
v	Speed at the nozzle exit section
m	Injected mass
Δt	Injection duration
ρ	Density of the solution
A	Nozzle outflow section
F	Force
$P(n)$	Nozzle pressure
Δy	Distance between the nozzle and the target
$\Delta t_{(n\rightarrow t)}$	Time of flight from nozzle to target
L_t	Penetration depth in pig skin
L_m	Distance from the skin surface and the maximum width
Q	Volumetric flow rate
μ	Dynamic viscosity
L	Needle length
D	Needle bore diameter
As	Syringe stopper area
C_d	Discharge coefficient

produced with diameters ranging from 76 to 360 μm but the most used devices had orifice diameter of about 150 μm (Mitragotri, 2013). The liquid jet pierces the *stratum corneum* delivering the established formulation volume subcutaneously. From the engineering point of view, they are easy to produce and relatively cheap because neither electrical power nor electronic parts are required. From the clinical side, they are easy to handle, are applicable virtually to all liquid formulations and may improve their pharmacokinetics (Schramm and Mitragotri, 2002).

Paradoxically, one of the drawbacks that seems to limit the large clinical use of needle-free jet injectors pain but this issue is still controversial (Schneider et al., 1994; Zsigmond, 2002). More critical are the inconsistency of formulation penetration and the pool out of liquid on the skin (Mitragotri, 2012). The latter limits intra- and inter-individual reproducibility of the key pharmacokinetics parameters with obvious issues on formulation bioequivalence. This inconsistency seems to be device related because some of them have shown even better pharmacokinetic and pharmacodynamic parameters than conventional injection (Engwerda et al., 2011; Engwerda et al., 2013).

Most of the mentioned drawbacks are due to the limited number of systematic studies on the key parameters involved in jet formation, skin penetration and drug delivery to tissue as well as the lack of studies aimed at crossing these parameters with clinical data.

One possible solution to the pain generated by the jet could be the use of smaller orifice (i.e., 80 μm) to generate a high-velocity microjet ($v > 100$ m/s). This solution has been proposed and validated for the delivery of nanoliter volumes (Arora et al., 2007). Here we propose a novel device provided with a micro-nozzle for medium volume skin delivery that could cover the gap between microjets and conventional jet injectors.

The design (Fig. 1) and the full characterization of the dynamic behavior of a novel spring-powered needle-free liquid jet injector are reported below.

2. Materials and methods

2.1. Materials

Acrylamide, bis-acrylamide, tetramethylethylenediamine and ammonium persulfate were purchased from Bio-Rad Laboratories (Segrate, Italy) while methylene blue was obtained by Sigma (Milan, Italy).

Porcine skin was kindly provided by the Centro Macellazione Carne (Ponte San Giovanni, Italy).

The needle-free injector mounted with an 80 μm nozzle was produced and provided by Brovedani spa (San Vito al Tagliamento, Italy). All other reagents and products were of the highest grade commercially available and used as received.

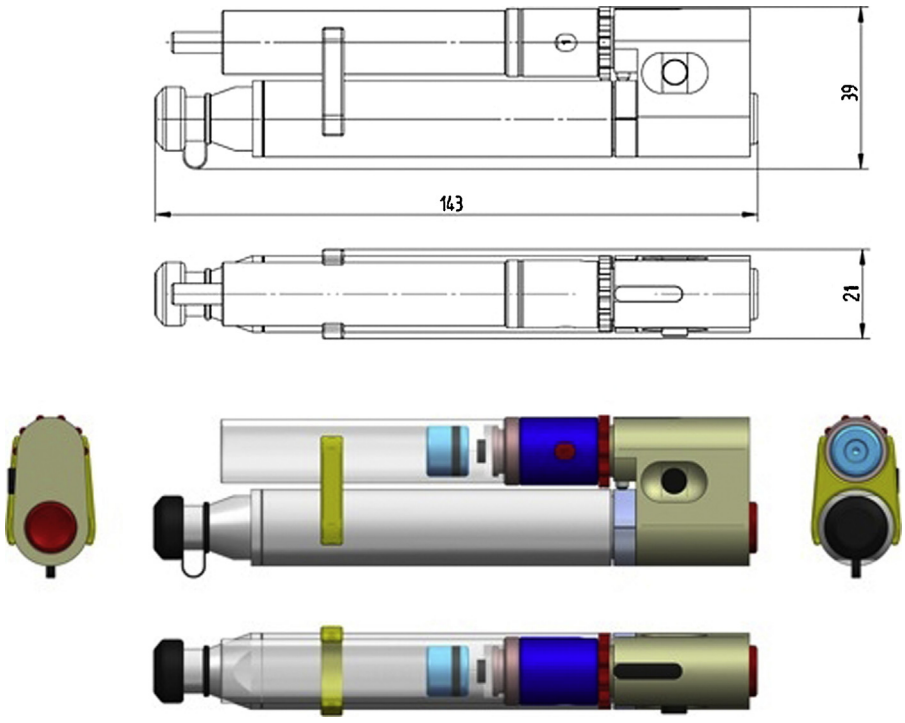

Fig. 1. Design of the Brovedani Nebulizer. Dimensions are given in millimeters.