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A Mathematical Model and Experimental Verification of Optimal Nozzle Diameter in Needle-Free Injection

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ABSTRACT

Needle-free injection (NFI), as an alternative drug delivery strategy, owns great potential. It is able to reduce complaints about needle phobia and avoid the occurring of accidental needle stick injuries. The nozzle diameter is inherently important in determining the injection dose, injection depth, and pain associated with NFIs. In this work, needle-free injectors with nozzle diameters of 0.17, 0.20, 0.30, 0.40, and 0.50 mm were studied in the simulation and experiment. This article optimizes the mathematical model for spring-powered NFI by considering the hydraulic loss due to the abrupt change in the nozzle exit area and the friction force between the piston and ampoule. We explore the dispersion pattern in gels with different nozzle diameters. Mice insulin injection was conducted to investigate the pharmacological effect of different injection methods. The experimental results show that there is the best dispersion effect and available injection depth while the nozzle diameter is 0.30 mm, which is in agreement with the result predicted by the mathematical model. Also, there is a satisfactory pharmacological effect on the mice insulin injection under the same injection condition. Undoubtedly, the mathematical model is capable of predicting the suitable nozzle diameter under the given conditions.

Introduction

Needle-free injection (NFI), a novel drug delivery method, aims at penetration and delivery of a high-speed stream of fluid into skin for drug administration. It was initially developed in the 1930s and was as effective as needle injection in the drug delivery. Among alternative strategies, NFI is capable of reducing complaints about needle phobia and avoiding the occurrence of accidental needle stick injuries. Moreover, NFI is an old strategy with great potential not yet completely disclosed and became an important drug delivery method for the administration of insulin, human growth hormone, and vaccines.[1,2] Recently, several other small-molecule and macromolecular drugs, such as anesthetic, steroids, and erythropoietin, have been delivered using the NFIs.[3-5] Although the NFIs have shown obvious advantages over traditional needle injection as having high efficiency and excellent bioavailability, it had not gained wide acceptance from the public, due to complaints about splashback, painful bruising, and bleeding experiences during the injection process of the NFIs. As the nozzle diameter of the NFIs increases, it leads to larger injection depth, which would reach the deeper nerves.[3,6,7] Moreover, the larger nozzle diameter would cause a serious wound, resulting in more bleeding.[2,8] Thus, it is the common method for the NFIs to control the injection dose and injection depth to own better injection efficiency. The nozzle diameter was inherently important in determining the injection dose, injection depth, and pain associated with the NFIs. Therefore, the determination of a nozzle diameter should be taken into necessary consideration in designing NFIs.

Theoretical analysis was a viable approach that is capable of describing the process of injection and predicting the final depth and dosage in one single NFI. To analyze the influencing factors of the NFIs through the theoretical perspective, a theoretical model for spring-powered jet injection was first established by Baker and Sanders.[9] The relationship between impact pressure and nozzle diameters could be obtained under the given conditions. The proposed model was of significance in improving the controllability of the NFIs by controlling different injection parameters, such as the

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Nomenclature

PAG	Polyacrylamide gels
NFI	Needle-free injection
NS	Normal saline
INS	Insulin
A	Impact sensor area
A_0	Nozzle cross section
A_p	Ampoule cross section
b	Rubber piston length
B	Bulk modulus
D	Rubber piston diameter
D_0	Nozzle diameter
D_p	Ampoule diameter
F	Impact force
F_k	Spring force
F_N	Liquid pressure
F_f	Friction force
h_w	Hydraulic loss
k	Spring stiffness
L	Piston distance
m_p	Piston rod mass
P	Average pressure
P_0	Ambient pressure
P_p	Chamber pressure
v	Impact sensor speed
v_p	Piston speed
$x0$	Spring initial compression
ζ	Hydraulic loss coefficient
α_1	Velocity coefficient
α_2	Velocity coefficient
ρ_0	Liquid density

nozzle diameter, the initial velocity, and the piston area. But in the use of the energy balance equation, they determined the Bernoulli equation without considering the hydraulics loss. Also, friction force between the piston and ampoule was ignored when analyzing the force balance of the driving piston. And then, several researchers optimized the theoretical model of the NFIs based on the model by Baker and Sanders. Chen and Zhou[10] presented a physical model focusing on stagnation pressure. Their studies show that the maximum stagnation pressure determines whether the jet can erode and penetrate into the skin. With respect to the controlled-release method for the NFI devices, Taberner et al.[11] implemented the real-time control of a prototype jet injector that utilizes a linear Lorentz-force motor, which was feedback controlled during the time course of an injection. Based on a custom high-stroke linear Lorentz-force motor, Taberner et al.[12] developed a controllable jet injection device and were able to monitor and modulate continuously the speed of the drug jet and regulate precisely the volume of drug delivered during the injection process. These studies furthered the injection efficiency of the NFIs and improved the injection experience. Although significant optimization had been conducted, the model was leaving much to be desired because hydraulic loss and friction force between the piston and ampoule had not been included in the analysis of the injection process yet. Accordingly, an in-depth understanding of the factors that influence the penetration capability and a predictive model to describe the penetration capability are necessary to reliably administer drugs.

The basic design of the NFIs consists of a power source (spring, compressed gas, or linear Lorentz-force motor), drug-loaded compartment, and a nozzle with orifice sizes typically ranging between 0.15 and 0.30 mm.[3] It is reported that nozzle orifices have been produced with diameters ranging from 0.076 to 0.36 mm, but the most used devices had an orifice diameter of about 0.15 mm.[13] Besides, the injection depth increased as the nozzle diameter increased at a constant velocity.[14] In addition, the large dose sizes and nozzle diameters used in these devices likely worsen the reliability problem by causing splashback of the drug from the skin and may be responsible for pain.[15] Although these studies revealed the relationship between the nozzle diameter and the injection depth, injection power, and injection duration, no information exists on the optimal size of the nozzle diameter for assigned receptor in the NFIs on the injection efficiency, which is just the novelty of this work. Furthermore, such understanding may also aid in avoiding interactions with nerve endings that are suggested to be the primary source of pain associated with the NFIs.

Toward these ends, this study focuses on the theoretical model for spring-powered NFI which is able to describe the process of injection and the relevance between impact pressure and nozzle diameter, taking the hydraulic loss and the friction force between the piston and ampoule into consideration. And, the effects of nozzle diameter on dispersion pattern, injection depth on polyacrylamide gels (PAG), and insulin efficacy on mice were also investigated in detail. The experimental platform of impact force was established to validate the impact force predicted by the proposed mathematical model. Penetrations in PAG were conducted to uncover the dispersion pattern of the high-speed liquid in the condition of different nozzle diameters. Also, mice insulin injection experiments were carried out to observe the injection effects of the NFIs with different nozzle diameters. The understanding gained from these investigations would serve as guidelines for selecting the suitable nozzle diameter under the given conditions.

Experimental

Materials

The penetration of PAG has frequently been used in studies on NFIs to simulate the penetration of dermal tissue owing to advantages of a model soft material including transparency, controllable mechanical properties, and controllable dimensions.[6,7,16] In this study, PAGs (10% acrylamide) (provided by Wuhan University, Wuhan, China) were prepared by adding initiators (10% ammonium persulfate and N,N,N′,N′-tetramethylethylenediamine) to a 30% (acr-bis) acrylamide solution of 29:1 acrylamide to bisacrylamide. Approximately 100 mL of acrylamide solution (10% [w/v]) was mixed with 26.6 mL of distilled water and polymerized by the

Table 1
Grouping of Mice Administration Method

Group	Method	Average Weight (g)
1	0.25-mm needle-NS	19.78
2	0.17-mm needle-free-NS	20.27
3	0.25-mm needle-INS	19.69
4	0.17-mm needle-free-INS	21.05
5	0.20-mm needle-free-INS	19.45
6	0.30-mm needle-free-INS	19.19
7	0.40-mm needle-free-INS	20.59
8	0.50-mm needle-free-INS	20.41

The needle size of the needle injector used is 31G (0.25 mm).
NS, normal saline; INS, insulin.