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Automatic injector apparatus for studying the injectability of parenteral formulations for animal health

J.R. Zingerman, D.G. Pope, P.K. Wilkinson and L. Perfetto

Merck Sharp and Dohme Research Laboratories, Rahway, NJ 07065 (U.S.A.)

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Summary

In order to formulate suitable multidose injectable products for *animal health pharmaceutical* use, a knowledge of the automatic *injector syringeability* characteristics of *parenteral* formulations at wide field use temperature is desirable. The automatic injector pistol grip pressure, the limit for suitable repeat injections in the field, the relationship to injection time, and the correlation to *viscosity* for the multidose injectable formulations used, are the topics of this study. A *Phillips MK II* injector gun equipped with a 16-gauge needle and set at a 10-ml delivery volume, was used.

Introduction

Multidose injectable products being developed for veterinary use must possess suitable viscosity characteristics to allow acceptable syringeability over wide range of field use temperatures. Syringeability must be evaluated to test acceptability under adverse conditions, for example, using a multidose injector gun at temperatures as low as five degrees centigrade.

Multidose injector guns or automatic syringes are commonplace in the veterinary field. They allow time-efficient treatment of large numbers of animals. They usually consist of a syringe barrel designed with a convenient gun handle with automatic feed from a bulk formulation reservoir carried around the neck of the veterinarian or as a harness backpack (Pope, 1983).

Field temperature conditions vary considerably. Herd dosing is commonly done in winter in extreme northern climates. Some warming of the injectable formulation can be effected, but, to allow use under these cold conditions, acceptable syringeability should be targeted for at least a 5°C use temperature.

In order to develop formulations meeting the acceptable syringeability requirements, methodology was developed for quantitating syringeability and the limits for acceptability were defined. To achieve this end, an automatic multidose injector gun test apparatus which allowed collection of information related to the following was used.

(a) *The compatibility of the formulations with the injector gun*. Components of the formulation could cause binding due to swelling of the plunger with prolonged contact during use.

Correspondence: J.R. Zingerman, Merck Sharp & Dohme Research Laboratories, P.O. Box 2000, Rahway, NJ 07065, U.S.A.

Prolonged contact during use could also result in disintegration or dissolution of the plunger and seals, thus resulting in gun leakage. Other methods for determining compatibility of the formulation with the multidose gun could be used, such as soaking of the component parts in the formulation; however, the automatic test apparatus allows dynamic testing of all the components under stress.

(b) *Injector gun grip pressures required to eject solutions at defined temperatures.* The typical adult male hand grip strength is of the order of 90–116 pounds per square inch for a single "grip to exhaustion". For repetitive tasks, a pressure of 50–70 pounds per square inch[1] is considered a useful range which does not result in fatigue.

(c) *The time required to eject liquid formulations at selected pressures.* To circumvent animal handling difficulties, a 3-s injection time is considered maximal. Any time less than 3 s is a bonus in handler acceptability.

Materials and Methods

Automatic injector gun

The Phillips MK II injector gun (Australia) was selected for the evaluation because of its wide use and reliability. A median volume setting of 10 ml and a 16-gauge needle were used throughout the study. The test solution was maintained at constant temperature externally and fed to the rear of the gun by way of a connector tube. The lubrication method recommended by the manufacturer for the injector was followed and the gun was thoroughly cleaned between test solutions. The gun is shown in Fig. 1.

Automatic injector apparatus

A diagrammatic representation of the automatic testing apparatus is shown in Fig. 2. The system is designed so that the injector gun mounting can be removed and replaced with mountings suitable for different style injector guns. While in operation, air pressure forces the piston against the pistol grip of the injector gun. The piston and injector gun grip have a spring return. The pres-

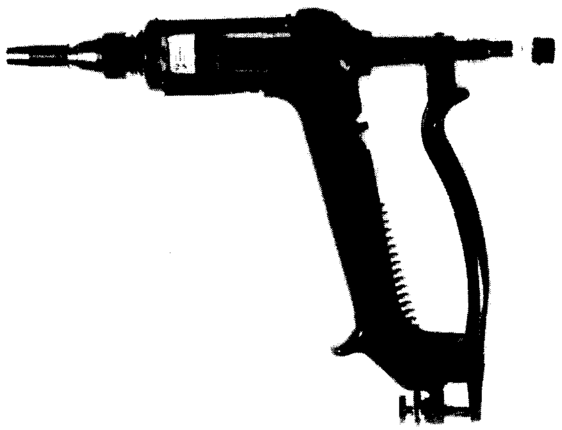

Fig. 1. Phillips MK II injector, N.J. Phillips Pty. Ltd., Dee Why, Australia.

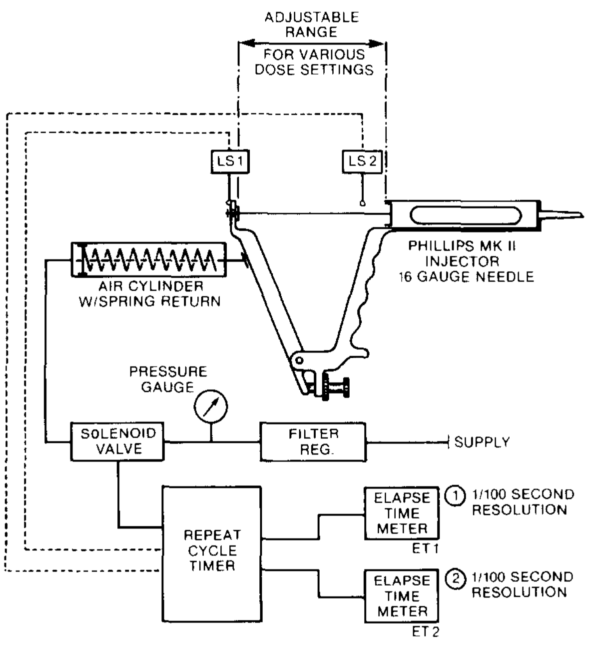

Fig. 2. Description: LS = limit switch; LS1 = starts ET1 and stops ET2; LS2 = starts ET2 and stops ET1; ET1 = measures pump stroke time; ET2 = measures suction stroke time.

[1] The College of Sports Medicine, 1440 Monroe Street, Madison, Wi.

TABLE 1

Ferranti-Shirley viscosities of solutions at 5 °C and 25 °C

Test solution	Viscosity (cps)	
	5 °C	25 °C
1. Aqueous	4	4
2. Aqueous	98	50
3. Organic solvent	133	41
4. Aqueous/Organic solvent	158	53
5. Organic solvent	183	54
6. Aqueous/Organic solvent	208	60
7. Organic solvent	208	61

sure gauge is adjustable in increments of 2.5 psi up to 100 psi. The control box has two timers, ET1 and ET2, which measure the time in 1/100 of a second, and a repeat cycle timer which records the total number of doses (cycles) in the sequential operation of the apparatus. The cycle begins when the pistol grip leaves the LS1 switch and the ejection time registers when the grip touches the LS2 switch. The ET2 registers the total refill time when the pistol grip returns to the LS1 switch.

Test solutions

The evaluation utilized 7 solutions, which were either aqueous or solutions comprising glycerol formal and propylene glycol with varying levels of active ingredient. Based on the data obtained on the Ferranti-Shirley viscometer, the solutions represented a wide wange of viscosity (Table 1), and all of the solutions were Newtonian. The tests were performed on formulations at both 5 °C and 25 °C.

Subjective evaluation

Twelve experienced evaluators were selected to conduct a blinded test on the solutions by repeated injections using the Phillips MK II Injector gun in a 5 °C cold room. The solutions were judged as being: (a) unacceptable, (b) marginally acceptable, and (c) acceptable.

Results and Discussion

Reproducibility of the 7 test solutions with the injector gun was evaluated by performing 200 test injections. At a pre-set pressure, no change in the dose volume, injection time, or refill time was experienced. The precision or repeatability of the ejection times within each pistol grip pressure setting was excellent (i.e. no deviations in the ejection time). As far as prolonged contact of the solutions with the gun parts was concerned, separate studies with the solutions in contact with the gun parts for times in excess of 24 h showed no adverse functionality of the injector gun or corrosion of the internal parts. Whether the 200 test injections were run before or after the 24-h soak, the plunger travel remained smooth and there was no evidence of leakage. All formulations were thus judged satisfactory for evaluation of syringeability in the test apparatus.

For the 7 test solutions, a plot of injection time in seconds against the pressure in psi at 25 °C (Fig. 3) shows that all of the solutions can be successfully injected within a 3-s time period at a mean grip pressure of 60 psi. However, when the formulations were compared at 5 °C (Fig. 4), only solutions 1 and 2 were still satisfactory, with solu-

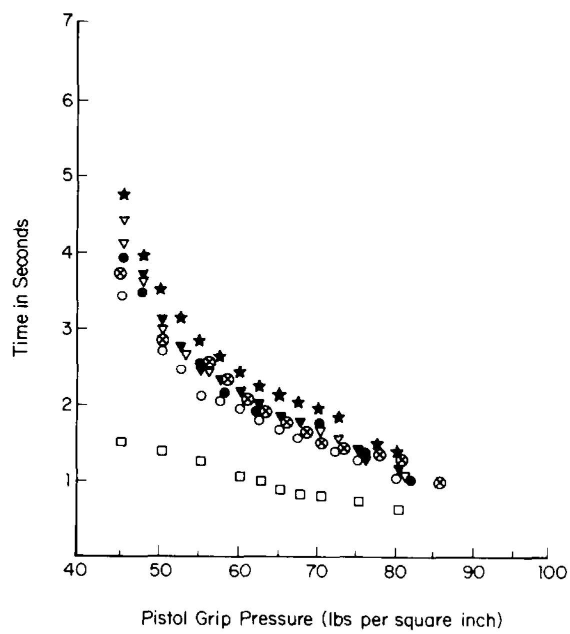

Fig. 3. Automatic ejection time required to eject 10 ml solution at 25 °C through a 16-gauge needle at differing grip pressure. Key: □, Solution 1; ⊗, Solution 2; ○, Solution 3; ●, Solution 4; ▽, Solution 5; ▼, Solution 6; ★, Solution 7.

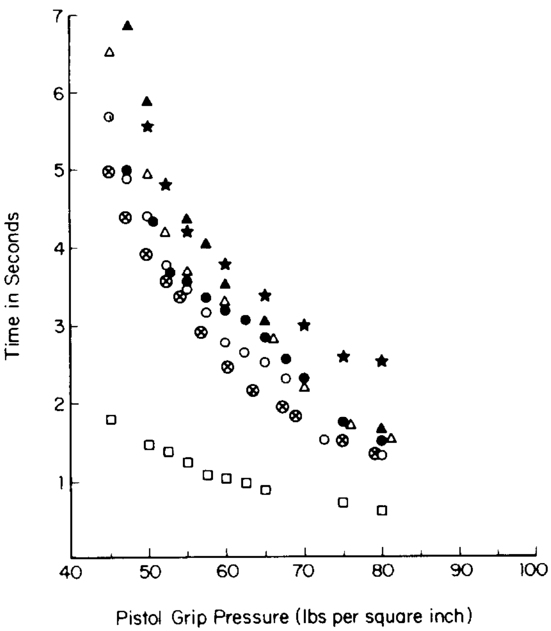

Fig. 4. Automatic ejection time required to eject 10 ml solution at 5 °C through a 16-gauge needle at differing grip pressures. Key: □, Solution 1; ⊗, Solution 2; ○, Solution 3; ●, Solution 4; ▽, Solution 5; ▼, Solution 6; ★, Solution 7.

tion 3 borderline. All others did not meet the 3-s injection time limit for the 60 psi mean grip pressure.

Subjective evaluation of the seven solutions supported the ejection time data (Table 2). Solution 1 and 2 were considered acceptable, while solution 3 was considered marginally acceptable. Solutions 4–7 were evaluated as unacceptable.

The data shown in Table 1 indicate that the limit for acceptable viscosity at 5 °C is of the order of 100 centipoise (cps). Provided no interaction occurs between the automatic syringe and the formulation to be administered, the 100 cps viscosity at the temperature of delivery is a good target for acceptable syringeability.

In all 7 solutions, the large diameter syringe filling port (1/4 inch) did not markedly affect the syringe refill times. These times ranged from only 0.1 to 0.4 s, even for the low temperature high viscosity system. A refill time under one second is certainly within field use practicality.

Within a defined grip pressure range (45–70 psi), the relationship between ejection time and ejection pressure may be explained by examination of Poiseuille's Law:

$$\frac{dv}{dt} = \frac{K \cdot \Delta P}{\eta} \qquad (1)$$

where dv/dt = time rate of flow (ml/s); K = an instrument constant, a function of the radius and length of the delivery orifice, $\pi r^4/8L$; η = the viscosity of the fluid (poise); ΔP = pressure differential.

TABLE 2

Subjective evaluation of test solutions at 5 °C using Phillips MK II multidose injector

Key: +, acceptable; (+), marginally acceptable; −, unacceptable.

Evaluator	Soln. 1	Soln. 2	Soln. 3	Soln. 4	Soln. 5	Soln. 6	Soln. 7
A	+	+	+	+	+	−	−
B	+	+	+	−	+	−	−
C	+	+	−	−	−	−	−
D	+	+	+	−	+	(+)	−
E	+	+	−	−	−	−	−
F	+	+	(+)	−	−	−	−
G	+	+	−	−	−	−	−
H	+	+	+	−	−	−	−
I	+	+	−	−	−	−	−
J	+	+	−	−	−	−	−
K	+	+	−	−	−	−	−
L	+	+	+	−	−	−	−
Total, Acceptable	12	12	6	1	3	1	0

In the current study, K is a constant for all systems and P equals the ejection pressure. All solutions tested exhibited Newtonian behavior, that is, the shear rate was directly proportional at a given temperature to the shear stress within the range of the study. Since ejection time, t, is inversely proportional to the flow rate, it follows that the ejection time is inversely proportional to the applied ejection pressre ($t \propto 1/P$). A regression analysis of the reciprocal of the pistol grip pressure in dynes/cm^2 (over a range of 45–70 psi) against time in seconds to eject 10 ml of solution was performed for each test solution at the two temperature conditions. The curves for each of the solutions were linear within this pressure range and all the respective correlation coefficients were greater than 0.90. These data are shown in Table 3.

A plot of the reciprocal of the pressure on the pistol grip in dynes/cm^2 against time in seconds to eject 10 ml of solution are shown in Fig. 5 for 3 different standard viscosity fluids.

Below 45 psi and above 70 psi the non-linearity is easily understood because at the very low hand grip pressure there are frictional forces, as well as

TABLE 3

Linear relationship between the reciprocal pistol grip pressure in dynes/cm^2 (x) and the time in seconds to eject 10 ml of test solution through a 16-gauge needle (y)

Test solution	Temperature °C	Regression equation	Correlation coefficient
1	25 °C	y = 6.8×10^6 (x) − 0.59	0.99
	5 °C	y = 7.3×10^6 (x) − 0.68	0.98
2	25 °C	y = 1.28×10^7 (x) + 1.18	0.99
	5 °C	y = 2.25×10^7 (x) + 2.73	0.99
3	25 °C	y = 1.31×10^7 (x) + 1.20	0.97
	5 °C	y = 2.80×10^7 (x) + 3.84	0.98
4	25 °C	y = 1.12×10^7 (x) + 0.74	0.98
	5 °C	y = 2.39×10^7 (x) + 2.68	0.96
5	25 °C	y = 1.58×10^7 (x) + 1.68	0.99
	5 °C	y = 3.18×10^7 (x) + 4.47	0.97
6	25 °C	y = 1.56×10^7 (x) + 1.56	0.98
	5 °C	y = 3.81×10^7 (x) + 5.56	0.95
7	25 °C	y = 1.83×10^7 (x) − 1.97	0.99
	5 °C	y = 2.78×10^7 (x) + 2.86	0.97

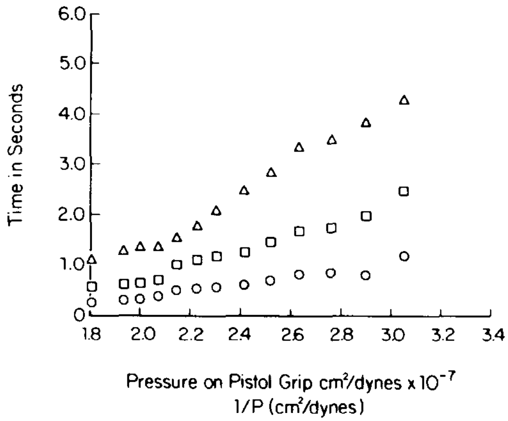

Fig. 5. Automatic ejection time vs reciprocal of the pressure for ejection 10 ml of standard fluid at 25 °C through the automatic injector using a 16-gauge needle. Pressure on pistol grip in cm^2/dynes $\times 10^{-7}$; $1/P$ (cm^2/dynes). Key: △, 98 cps; □, 48 cps; ○, 25 cps.

the pistol grip spring force which must be overcome before any piston movement in the gun is initiated. At the high grip pressure, there are considerable turbulent forces in the syringe barrel coupled with the frictional force of the 16-gauge needle.

Overall the testing apparatus accurately provides a means of screening potential injectable formulations having viscosities up to 100 centipoise. These solutions have injection times below 3 s and require hand grip pressures below 60 lbs./in^2. The automatic testing apparatus is not intended to replace the actual subjective evaluations, but is a means of augmenting the tests to ensure that a successful formulation is selected.

Acknowledgement

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