DRUG DEVELOPMENT COMMUNICATIONS, 1(5), 471-477 (1974-1975)



# TISSUE IRRITATION EVALUATION OF POTENTIAL PARENTERAL VEHICLES

Stanley L. Hem[x], David R. Bright[xx]

Gilbert S. Banker[x] and John P. Pogue[xxo]

[x]Industrial and Physical Pharmacy Department
School of Pharmacy and Pharmacal Sciences
Purdue University
West Lafayette, IN

[xx]Animal Science Department
Commercial Solvents Corp.
Terre Haute, IN

## ABSTRACT

Twenty-three potential nonaqueous parenteral vehicles were evaluated for tissue irritation in chicken pectoral muscle. Benzyl benzoate, 1,3-butylene glycol, ethyl oleate, glyceryl triacetate, sesame oil and sesame oil:benzyl benzoate (1:1) were found to cause minimal tissue irritation.

## INTRODUCTION

The vehicle for a parenteral dosage form must be nontoxic, nonirritating, nonsensitizing, pharmacologically inert and not adversely affect the action of the medicament (1). As an aid in evaluating potential solvents for parenteral products, Reese has suggested a screening procedure (2) which evaluates physical properties, miscibility, stability, toxicity and solvent activity. Carleton (3)

suggests a number of solvents which have been used as solvents for experimental cancer drugs. Groves (4) in a recent text reviews the properties of a number of actual and potential parenteral vehicles. Turco and King (5) limit their discussion of parenteral vehicles to water and various oils.

At present, only a limited number of vehicles are available for use in parenteral dosage forms. In an attempt to determine if additional vehicles are suitable, a study of the tissue irritation properties of 23 nonaqueous vehicles was determined in chicken pectoral muscle.

## METHODS

Table I lists the grade, when specified, and supplier of the vehicles tested.

Tissue irritation evaluation was conducted by injecting 0.5 ml of vehicle ½" deep in the right and left pectoral muscle of 7-8 week old male Hubbard Crossbred broilers weighing 3-4 lb. Six chickens were used for each vehicle. The injection site was the anterior 1/3 of the pectoral muscle. Feathers were pulled and a 1" square was outlined on the skin with waterproof ink. A 20 gauge disposable needle was used for injection.

Two chickens were sacrificed with carbon dioxide and necropsied for gross anatomical lesions at the injection site at 1, 3 and 7 days post injection.

The four injection sites were evaluated for tissue irritation using the following scale:

1 - no visible tissue damage or discoloration

2 - inflammation of tissue involving less than 2.0 $cm^2$

TABLE I

VEHICLES TESTED

| Vehicle | Grade | Supplier |
|---|---|---|
| Benzyl benzoate | U.S.P. | 17 |
| Butyl lactate | —— | 5 |
| 1,3-Butylene glycol | —— | 4 |
| Castor oil | U.S.P. | 3 |
| Diethyl carbonate | —— | 8 |
| Dimethylacetamide | —— | 6 |
| Ethyl acetate | —— | 16 |
| Ethyl formate | —— | 10 |
| Ethyl oleate | —— | 1 |
| Glycerol monoricinoleate | —— | 12 |
| Glyceryl triacetate | Food | 2 |
| Isoamyl formate | —— | 10 |
| Octyl alcohol | —— | 15 |
| Polyoxyethylene oleyl ether | —— | 12 |
| n-Propyl alcohol | Reagent | 14 |
| Propylene carbonate | —— | 13 |
| Propylene glycol dipelargonate | —— | 7 |
| Sesame oil | —— | 9 |
| Sorbitan monoisostearate | —— | 7 |
| Sorbitan POE (polyoxyethylene) trioleate | —— | 7 |
| Sorbitan trioleate | —— | 13 |
| Wheat germ oil | Cold pressed | 11 |

[1]Aceto Chemical Co., Inc., Flushing, NY

[2]Armak Chemicals Division, Chicago, IL

[3]Barre Drug Co., Inc., Baltimore, MD

[4]Celenese Chemical Co., New York, NY

[5]Commercial Solvents Corp., New York, NY

[6]E.I. DuPont De Nemours & Co., Wilmington, DE

[7]Emery Industries, Inc., Cincinnati, OH

[8]FMC Corp., Industrial Chemical Division, New York, NY

[9]Fisher Scientific Company, Pittsburgh, PA

[10]Fritzsche Dodge & Olcott Inc., New York, NY

[11]General Mills Chemicals, Inc., Minneapolis, MN

[12]Glyco Chemicals, Inc., Greenwich, CT

[13]ICI America Inc., Atlas Chemicals Division, Wilmington, DE

[14]Jefferson Chemical Co., Inc., Houston, TX

[15]Mallinckrodt Chemical Works, St. Louis, MO

[16] Matheson Coleman & Bell, Norwood, OH

[17]Chas. Pfizer & Co., Inc., Chemical Division, New York, NY

3 - inflammation of tissue involving 2.1 to 8.0 $cm^2$

4 - inflammation of tissue involving greater than 8.1 $cm^2$

5 - necrosis

(+) vehicle visible in tissue

(0) vehicle not visible in tissue

## RESULTS AND DISCUSSION

Examination of the results of the tissue irritation test contained in Table II indicate that benzyl benzoate, 1,3-butylene glycol, ethyl oleate, glyceryl triacetate, sesame oil and sesame oil:benzyl benzoate (1:1) cause very little irritation initially and are totally free of irritation by the 7th day after injection. In addition, these vehicles were well absorbed as no vehicle was observed in the tissue.

Vehicles causing necrosis were: ethyl formate, isoamyl formate, octyl alcohol, polyoxyethylene oleyl ether, n-propyl alcohol, propylene carbonate and sorbitan trioleate.

Butyl lactate, castor oil and glyceryl monoricinoleate were not absorbed and caused moderate irritation.

The injectability of the lease irritating vehicles were examined by withdrawing 5 ml of vehicle from a stoppered vial and expelling the sample into a beaker. A 10 ml plastic disposable syringe with a 20g, 1½" disposable needle was used. As noted in Table III, all the vehicles except benzyl benzoate, sesame oil:benzyl benzoate (1:1) and glyceryl triacetate were difficult to inject or reacted with disposable plunger tips.

TABLE II

EVALUATION OF TISSUE IRRITATION[a]

| | 1 Day | | | | 3 Days | | | | 7 Days | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Chicken #1 | | Chicken #2 | | Chicken #3 | | Chicken #4 | | Chicken #5 | | Chicken #6 | |
| Vehicle | Left | Right | Left | Right | Left | Right | Left | Right | Left | Right | Left | Right |
| Benzyl benzoate | 2(0) | 1(0) | 2(0) | 2(0) | 2(0) | 2(0) | 1(0) | 2(0) | 1(0) | 1(0) | 1(0) | 1(0) |
| Butyl lactate | 3(+) | 3(+) | 5(+) | 4(+) | 2(+) | 2(+) | 4(+) | 4(+) | 4(+) | 4(+) | 2(+) | 2(+) |
| 1,3-Butylene glycol | 3(0) | 3(0) | 3(0) | 3(0) | 1(0) | 1(0) | 1(0) | 1(0) | 1(0) | 1(0) | 1(0) | 1(0) |
| Castor oil | 2(+) | 1(+) | 3(+) | 3(+) | 3(+) | 3(+) | 3(+) | 3(+) | 3(+) | 3(+) | 4(+) | 4(+) |
| Diethyl carbonate | 3(0) | 3(0) | 3(0) | 3(0) | 5(0) | 1(0) | 1(+) | 1(0) | 5(0) | 5(0) | 1(0) | 1(0) |
| Dimethyl acetamide | 2(0) | 2(0) | 3(0) | 3(0) | 5(0) | 5(0) | 4(0) | 4(0) | 3(0) | 3(0) | 2(0) | 2(0) |
| Ethyl acetate | 3(+) | 5(+) | 5(+) | 3(+) | 3(0) | 2(+) | 3(0) | 3(0) | 2(0) | 4(0) | 3(0) | 5(0) |
| Ethyl formate | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) |
| Ethyl oleate | 2(0) | 2(0) | 3(0) | 2(0) | 1(0) | 1(0) | 1(0) | 1(0) | 1(0) | 1(0) | 1(0) | 1(0) |
| Glycerol monoricinoleate | 1(+) | 5(+) | 1(+) | 1(+) | 3(+) | 3(+) | 1(+) | 1(+) | 3(+) | 3(+) | 1(+) | 5(+) |
| Glyceryl triacetate | 3(0) | 3(0) | 3(0) | 2(0) | 1(0) | 2(0) | 1(0) | 2(0) | 1(0) | 1(0) | 5(0) | 1(0) |
| Isoamyl formate | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) |
| Octyl alcohol | 4(+) | 4(+) | 4(+) | 4(+) | 5(0) | 5(+) | 5(0) | 5(0) | 5(+) | 5(+) | 5(0) | 5(0) |
| Polyoxyethylene oleyl ether | 4(0) | 4(0) | 4(0) | 4(0) | 5(0) | 5(0) | 4(0) | 4(0) | 5(0) | 5(0) | 5(0) | 5(0) |
| n-Propyl alcohol | 3(+) | 3(+) | 3(+) | 3(+) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) |
| Propylene carbonate | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) | 5(0) |
| Propylene glycol dipelargonate | 5(0) | 3(0) | 3(0) | 1(0) | 3(+) | 1(0) | 3(+) | 3(+) | 1(+) | 1(+) | 1(0) | 1(0) |
| Sesame oil | 2(0) | 2(0) | 2(0) | 1(0) | 3(0) | 1(0) | 1(0) | 1(+) | 1(0) | 1(0) | 1(0) | 1(0) |
| Sesame oil: benzyl benzoate (1:1) | 2(0) | 1(0) | 3(0) | 3(0) | 1(+) | 1(0) | 2(0) | 1(0) | 1(0) | 1(0) | 1(0) | 1(0) |
| Sorbitan monoisostearate | 3(+) | 3(+) | 4(+) | 4(+) | 3(+) | 3(+) | 3(+) | 3(+) | 1(0) | 1(0) | 1(0) | 3(0) |
| Sorbitan POE trioleate | 4(0) | 4(0) | 3(0) | 3(0) | 2(0) | 2(0) | 5(0) | 5(0) | 3(0) | 3(0) | 3(0) | 3(0) |
| Sorbitan trioleate | 2(0) | 2(0) | 3(0) | 2(+) | 5(0) | 5(0) | 4(0) | 5(0) | 5(0) | 5(0) | 3(0) | 3(0) |
| Wheat germ oil | 3(+) | 2(+) | 2(+) | 2(+) | 2(0) | 2(0) | 2(+) | 2(0) | 3(0) | 3(0) | 3(0) | 3(+) |

[a] See methods for evaluation scale

TABLE III

INJECTABILITY OF SELECTED VEHICLES

| Vehicle | Observations |
|---|---|
| Benzyl benzoate | good injectability |
| 1,3-Butylene glycol | syringe fills slowly with a 20 gauge needle |
| Ethyl oleate | causes rubber plunger in disposable syringes to bind |
| Glyceryl triacetate | good injectability |
| Propylene glycol dipelargonate | good injectability |
| Sesame oil | difficult to inject |
| Sesame oil: benzyl benzoate(1:1) | good injectability |
| Sorbitan monoisostearate | very difficult to inject |

The relatively high freezing point of benzyl benzoate (Table IV) would make it difficult to use as a vehicle. However, mixtures of benzyl benzoate with sesame oil overcome this problem and appear to be excellent vehicles. Mixtures of benzyl benzoate and oils are used as vehicles in parenteral dosage forms of drugs such as estradiol valerate and dimercaprol (6).

TABLE IV

PHYSICOCHEMICAL PROPERTIES OF BENZYL BENZOATE AND GLYCERYL TRIACETATE[a]

| | Benzyl Benzoate | Glyceryl Triacetate |
|---|---|---|
| Molecular weight | 212.24 | 218.21 |
| Specific gravity | 1.116-1.120 | 1.160 |
| Boiling point | 323-4°C | 258°C |
| Freezing point | 18°C | -78°C |
| Flash point | 298°F | 305°F |
| Free acid | <0.1% benzoic acid | <0.005% as acetic acid |

[a] Data taken from manufacturer's specifications

The lack of tissue irritation, good absorption and favorable physicochemical properties of glyceryl triacetate recommend it as a potential vehicle for parenteral dosage forms.

## ACKNOWLEDGMENTS

o Present address: Norwich Pharmacal Co., Norwich, NY. The authors wish to acknowledge the advice of Dr. Ross G. Brown throughout this study.

## REFERENCES

1. A.J. Spiegel and M.M. Noseworthy, J. Pharm. Sci., 52, 917 (1963).
2. D.R. Reese, Bull. Parenteral Drug Assoc., 16 (5), 11 (1962).
3. F.J. Carleton, Bull. Parenteral Drug Assoc., 21 (4), 142 (1967).
4. M.J. Groves, Parenteral Products, William Heinemann Medical Books Ltd., London, 1973, pp. 19-24.
5. S. Turco and R.E. King, Sterile Dosage Forms, Lea & Febiger, Philadelphia, 1974, pp. 13-18.
6. Physicians' Desk Reference, 28th Edition, Medical Economics Co., Oradell, NJ, 1974, p. 797, 1396.