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SOLUBILIZATION OF A LOW CONCENTRATION SUSPENSION BY LECITHIN

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Lecithin, a suspending agent employed in many intramuscular suspensions, was found to mediate the solubilization of a suspended drug, fluspirilene.

INTRODUCTION

Lecithin, a water dispersable phospholipid with strongly polar groups is known to be surface active (1, 2) and is reported to form sheet-like micelles which can accommodate a variety of organic compounds (3,4). In spite of the fact that it has surface activity and can form micelles, lecithin is not generally considered to be a solubilizer, and its role as a solubilizer in pharmaceutical products has not been reported.

In concentration of 0.2% to 1.5%, lecithin functions as a suspending agent in sterile procaine penicillin G suspension, sterile procaine penicillin G with aluminum stearate suspension and sterile benzathine pencillin G. suspension (5).

Since these suspensions contain from 300 mg to 600 mg of drug per ml , the drug to lecithin ratio is such that solubilization of the

drug by lecithin would be insignificant in terms of the percent of the drug. However, in a low concentration suspension where the quantity of lecithin might equal or exceed the amount of drug, the percent of drug dissolved might be high.

Fluspirilene,[1] 8-(4,4-bis(4-fluorophenyl)butyl)-1-phenl-1,3,8-triazaspiro(4,5)decan-4-one, is a neuroleptic drug intended for intramuscular administration as a suspension. This paper describes the solubilization of fluspirilene in intramuscular injection vehicles and the implication that lecithin is responsible for the solubilization.

EXPERIMENTAL

Suspension Preparation- Ten batches of sterile fluspirilene suspension, 2 mg/ml, were prepared as part of a development project. All suspensions were prepared in pH 7.4 phosphate buffer, by conventional techniques, from commercially available ingredients in grades suitable for parenteral use.

All suspensions were prepared from fluspirilene having a mean particle diameter of from 5.0 to 10.0 microns. Mean particle diameters were determined by a Coulter Counter®, model B[a].

The suspensions were stored at ambient temperature in amber vials with Teflon® lined rubber closures. Table I lists the formulation variables.

Suspended Fluspirilene Assay - The equivalent of 10 mg of fluspirilene, was collected on a 0.45μ MF Millipore® filter. The solid thus collected was transferred to a 50 ml volumetric flask and

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[1]Fluspirilene is marketed by Janssen Pharmaceutica, Beerse Belgium under the trade name of IMAP , a 2 mg/ml suspension which does not contain any lecithin and has been found to be stable for over 3 years at room temperature.

[a]Coulter Electronics, Inc., Hialeah, Fla.

Table I

Fluspirilene (2 mg/ml) Suspension Formulations

batch no.	% ingredients: polysorbate 80	CMC-7 LF[a]	lecithin	parabens[b]	benzyl alcohol	suspended drug: age (mo.)	% suspended: individ.	mean	dissolved drug: age (mo.)	% dissolved: individ.	mean
1	0.1	0	0	0	1.2	20	83.6 92.3	88.0	29	5.5 8.0	6.8
2	1	1	0	0.2	0	18	74.5 69.0	71.8	27	23.3 30.0	26.6
3	1	1	1	0.2	0	18	0.4 0.0	0.2	27	84.5 77.9	81.2
4	1	0	1	0	1.2	18	21.6 18.3	20.0	27	86.0 84.6	85.3
5	1	1	0	0	1.2	18	76.1 79.0	77.6	27	28.1 18.9	23.5
6	0.1	0.1	1	0	1.2	15	38.2 32.1	35.2	24	45.4 47.6	46.5
7	0.01	0.35	1	0	1.2	12	18.9 14.0	16.4	21	84.1 82.0	83.1
8	0.01	0.35	1	0	1.2	12	28.2 26.2	27.2	21	52.0 59.8	55.9
9	0.01	0.35	0.5	0	1.2	12	54.7 53.1	53.9	21	47.0 37.0	42.0

[a] sodium carboxymethylcellulose, Hercules, Inc., Wilmington, DE

[b] 0.18% methylparaben plus 0.02% propylparaben

brought to volume with chloroform. Thirty ml of the resulting solution was extracted with 30 ml of 0.1N NaOH and then extracted with 30 ml of water. A portion of the chloroform solution was diluted 1 to 10 with chloroform and assayed spectrophotometrically at 254nm against a similarily prepared blank. A standard with a final concentration of 0.02 mg/ml in chloroform was also prepared.

Dissolved Fluspirilene Assay- The equivalent of 10 mg of fluspirilene was collected on a 0.45μ MF Millipore® filter. Seven ml of the filtrate were added to 10 ml of 0.1N NaOH. The resulting solution was extracted 3 times with 30 ml of ether. The ether extracts were filtered through cotton and brought to 100 ml with chloroform. The ether-chloroform solution was extracted twice with 35 ml of 0.1N H_2SO_4. The The two H_2SO_4 extracts were combined and extracted twice with 15 ml of ether. The two ether extracts were combined and extracted twice with 10 ml of 0.1N H_2SO_4. These two H_2SO_4 extracts were combined with the previous H_2SO_4 extracts, filtered through cotton and brought to 100 ml with 0.1N H_2SO_4. The final H_2SO_4 solution was assayed spectrophotometrically at 248 nm against a similarly prepared blank. A standard with a final concentration of 0.021 mg/ml in 0.1N H_2SO_4 was also prepared.

Solubility Studies - Six fluspirilene suspensions, 2 mg/ml, were prepared by conventional methods from pH 7.4 buffer containing 0.01% polysorbate 80. Table I lists the formulation variables.

Forty ml of each suspension were rotated in a rotating bottle apparatus immersed in a 45° water bath. Samples were removed for analysis after 144 hours and assayed for suspended fluspirilene.

RESULTS AND DISCUSSION

Two vials from each batch were assayed for suspended fluspirilene. Nine months later, two additional vials from each batch were assayed for dissolved fluspirilene. The results are reported in Table I. The variability in the data for any batch at a specific time is due to vial to vial variation in the amount of drug which dissolved under the static storage conditions. The failure for the percent suspended plus the percent dissolved to total 100 percent is due partially to vial to vial variation but, it is more likely due to the occurrance of solubilization or crystallization from the time the batches were assayed for suspended fluspirilene to the time they were assayed for dissolved fluspirilene.

From Table I, it is noted that the three suspensions without lecithin are the ones which contained most fluspirilene suspended as well as the least fluspirilene dissolved. In addition, batch 9, which differs from batches 7 and 8 in that it contains 0.5% lecithin instead of 1.0%, contained more suspended and less dissolved fluspirilene than the others.

The solubility study results in Table II substantiate the results from the analysis of the sterile development suspensions. The only preparations in which the full quantity of fluspirilene was recovered as suspended particles were those which did not contain lecithin.

The important aspect of this investigation is the realization of the adverse effect lecithin can have on low concentration suspensions. Depending on the drug and how it is formulated, a suspension to solution conversion could accelerate chemical decomposition, affect the absorption of the drug and change the general physical properties of the product.

Table II

Fluspirilene Solubility Study

formula no.	% CMC 7 LF	% lecithin	% benzyl alcohol	% solid drug
A	-	-	-	104
B	0.35	-	-	102
C	-	-	1.2	104
D	0.35	1.0	-	81
E	0.35	-	1.2	102
F	0.35	1.0	1.2	69

CONCLUSION

Lecithin, a suspending agent in low concentration fluspirilene suspensions, was found to act as a solubilizing agent for the drug. Although in most cases only a small quantity of the drug was solubilized, this represented a large percentage of the total amount of fluspirilene present.

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