Microencapsulation and Dissolution Parameters of Undecenovanillylamide: A Potential Coyote Deterrent

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Abstract □ The microencapsulation and dissolution of undecenovanillylamide (I), a potential coyote-aversive agent for use on sheep, were studied. While I has been shown to protect sheep, its short duration of action makes it economically unfeasible. Compound I microcapsules were prepared, and optimum conditions for encapsulation *via* complex coacervation were determined. Microcapsules that were hardened for 0.5, 1, and 2 hr, as well as I powder, were characterized according to their dissolution. Longer hardening times resulted in slower release, with all encapsulated I forms being released slower than the powder. The dissolution t_{50} for unencapsulated powder was less than 3 min; for microcapsules hardened for 30 min, the dissolution t_{50} was 7.3 min; for those hardened 60 min, the t_{50} was 17.7 min; and for those hardened 120 min, the t_{50} was 28 min. The encapsulated I would have a longer field life and, therefore, might be a viable economic and ecologic answer to coyote protection for sheep.

Keyphrases □ Undecenovanillylamide—coyote deterrent, microencapsulation, dissolution □ Coyote deterrents—undecenovanillylamide, microencapsulation, dissolution □ Microencapsulation—coyote deterrent, undecenovanillylamide, dissolution □ Dissolution—coyote deterrent, undecenovanillylamide, microencapsulation

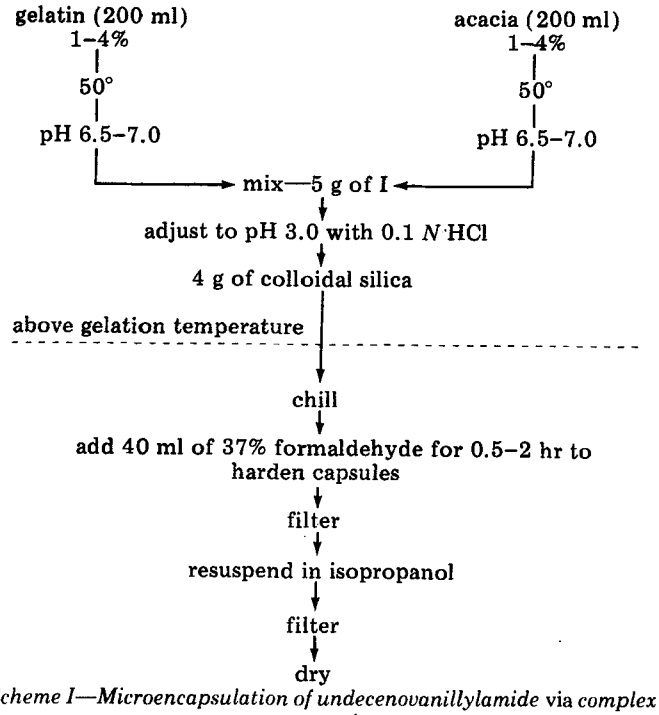
Predator control has been a continual problem for Rocky Mountain area ranchers. This problem is compounded when the predator attacks sheep since almost all survival instinct has been bred out of the sheep to facilitate herding. While destruction of the coyote has been attempted, it is not an acceptable alternative to nondestructive control.

Recently, a chemical solution to this problem has shown promise[1]. Undecenovanillylamide (I) was shown to be an effective coyote deterrent when used as a spray or dip on sheep. Undecenovanillylamide, a pungent, hot-tasting chemical, is applied as a suspension in water or as a dilute isopropanol solution. When a sheep is attacked, the coyote usually discontinues the attack after taking a superficial bite; theoretically, a conditioning response has occurred. There are apparently no problems for the sheep except that I is useful for only 2 or 3 weeks and is not water resistant. The possibility of I encapsulation by complex coacervation was considered as a means of extending the effective I life (ideally for a summer season) and of decreasing the susceptibility of I to weather conditions.

Each possible encapsulation system has particular problems and specific microencapsulation requirements. Optimum encapsulation procedures for one chemical may be useless for a seemingly similar system. While many encapsulation methods exist, microencapsulation *via* complex coacervation was most applicable for I since the acacia–gelatin mixture imparts a stickiness to the microcapsules so that they adhere better to the wool.

EXPERIMENTAL

Microcapsule Preparation—All chemicals were used as supplied by the manufacturer. The basic procedure was previously reported (1); Scheme I shows the encapsulation procedure for I. The drug was passed through a No. 200 sieve before encapsulation. By varying the percent gelatin–acacia and the hardening time, microcapsules with different release rates were recovered.



Scheme I—Microencapsulation of undecenovanillylamide via complex coacervation.

Dissolution Studies—The dissolution rate of pure I powder and microcapsules containing I was determined. The dissolution method was the flask method. A 500-ml round-bottom flask with a hole cut to allow stirrer insertion was filled with 300 ml of pH 6.5 buffer. A water bath maintained at 30° kept the dissolution medium at a constant temperature throughout dissolution. A flat, three-blade metal propeller with 2.5-cm blades was centered in the flask and immersed in the dissolution fluid to 35 mm. A constant-speed motor was calibrated to provide a 120-rpm stirring rate.

For all determinations, a known weight of I powder or microcapsules was added down the side of the flask. Samples of the dissolution fluid, 2 ml, were withdrawn at selected times with a pipet fitted with a glass wool

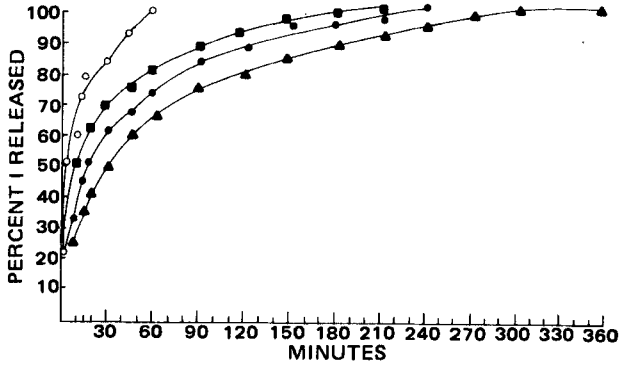


Figure 1—*Dissolution versus time profiles for undecenovanillylamide powder and microcapsules hardened for various times. Key:* ○, *powder;* ■, *microcapsules hardened for 0.5 hr;* ●, *microcapsules hardened for 1 hr; and* ▲, *microcapsules hardened for 2 hr.*

[1] R. J. McColloch and A. Palmieri, University of Wyoming, Laramie, Wyo., unpublished results.

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Table I—*In Vitro* Dissolution t_{50} *versus* Hardening Time for Undecenovanillylamide Microcapsules [a]

Hardening Time, min	*In Vitro* Dissolution t_{50}, min
Unencapsulated	<3
30	7.3
60	17.7
120	28.0

[a] $r = 0.98149$.

plug to ensure that undissolved drug was not included. An equivalent volume of fresh buffer and the glass wool plug were added to the flask after each withdrawal. The samples were then assayed spectrophotometrically at 280 nm after appropriate dilution with pH 6.5 buffer. Each determination was done at least in triplicate.

RESULTS AND DISCUSSION

Since encapsulation *via* complex coacervation occurs best at low colloid concentrations and when acacia and gelatin are employed in a 1:1 ratio (2), 1–4% concentrations were studied. There were no beneficial aspects at the higher concentration, so the 1% colloid concentrations were used to produce the least cohesive powder. The colloidal silica was added to aid in production and did, in fact, lead to easier microcapsule recovery as a dry, noncohesive powder.

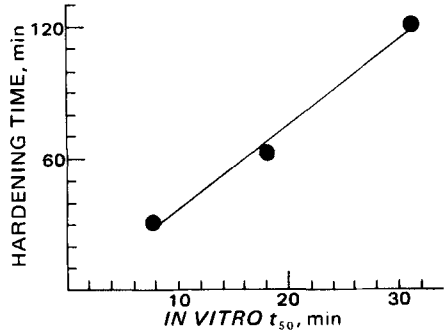

Figure 2—*Hardening time* versus in vitro t_{50} *for undecenovanillylamide microcapsules.*

The resuspension of the product in isopropanol for dehydration was successful with only 30% isopropanol. Lower concentrations did not result in a free-flowing powder, and higher concentrations destroyed the shell wall integrity.

Figure 1 shows the percent release *versus* time data for the various dosage forms studied. Each determination is the average of at least six dissolution profiles. Dissolution results for the powder and encapsulated forms of I indicate that the microencapsulated forms exhibited slower dissolution. The capsules hardened for 0.5 hr featured rapid initial release. This initial release may result from the soft shell and the large amount of unencapsulated I. The profiles in Fig. 1 are in rank order with hardening times; there was a definite delayed, sustained release for encapsulated I.

To explain the drug dissolution from the microcapsules, the release of the active ingredient through leaching or diffusion may be examined. For such release to occur, the dissolution medium must penetrate the wall to the nucleus, dissolve I, and then permeate out through the shell wall. Any of these processes may be rate limiting.

The effect of increased hardening times on the release profile is readily apparent. Since the dissolution t_{50} indicates the central tendency of the data, that point was chosen to compare release (Table I). There was a direct linear correlation ($r = 0.98149$) between microcapsule hardening time and the dissolution t_{50} values (Fig. 2).

REFERENCES

(1) A. Palmieri, *Drug Dev. Ind. Pharm.*, **3**, 309 (1977).

(2) L. A. Luzzi and R. J. Gerraughty, *J. Pharm. Sci.*, **56**, 634 (1967).

ACKNOWLEDGMENTS

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Convenient Synthesis of *N*-Alkoxymethylbarbituric Acids and *N*-Alkoxymethylhydantoins

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Received April 4, 1979, from the *Department of Pharmacology, Division of Clinical Pharmacology, School of Medicine, University of Colorado Medical Center, Denver, CO 80262.* Accepted for publication June 15, 1979.

Abstract □ A simple one-step method for the *N*-alkoxymethylation of barbituric acids and hydantoins is presented. The compounds are *N*-methoxymethylated or *N*-ethoxymethylated using phosphorus pentoxide and dimethoxymethane or diethoxymethane, respectively, in a chlorinated solvent. 1-Methoxymethyl-3-ethyl-5-phenylhydantoin showed significant anticonvulsant activity in the subcutaneous pentylenetetrazol test, while 1,3-bis(methoxymethyl)-5-ethyl-5-(*p*-tolyl)barbituric acid was inactive.

Keyphrases □ *N*-Alkoxymethylbarbituric acids—syntheses, anticonvulsant activity, structure-activity relationships □ *N*-Alkoxymethylhydantoins—syntheses, anticonvulsant activity, structure-activity relationships □ Anticonvulsants—*N*-alkoxymethylbarbituric acids and *N*-alkoxymethylhydantoins, syntheses, structure-activity relationships

N-Alkoxymethyl derivatives of barbituric acids and of hydantoins were recently synthesized, and several derivatives were shown to possess significant anticonvulsant activity in animal tests (1–4). One, 1,3-bis(methoxymethyl)phenobarbital (I), was studied in epileptic patients with promising results (5).

BACKGROUND

The original preparation of the *N*-alkoxymethyl derivatives involved alkylation of the barbituric acid or hydantoin alkali salt with chloromethyl methyl ether (II) (1–4). Since the latter reagent is a potent carcinogen (6–8), its use is highly restricted (9). Therefore, alternatives for the preparation of I have been sought, and two appeared in the patent literature. One method (10) is based on the preparation of 1,3-bis(chloromethyl)phenobarbital from phenobarbital, formaldehyde, acetyl chloride, hydrochloric acid, and a Lewis acid. These conditions are likely (11, 12) to result in the formation of bis(chloromethyl)ether (III), another, even more potent, carcinogen (8). 1,3-Bis(chloromethyl)phenobarbital was converted to I using sodium methoxide in methanol (10). The second

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