CASE HISTORIES OF CONTROLLED RELEASE PRODUCTS

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Those of you who are familiar with the Wisconsin Alumni Research Foundation may wonder why a company not engaged in private enterprise is participating in a symposium on the economics and marketing opportunities for controlled release products. WARF has been involved in technology transfer for 50 years and, since 1959, has been actively working with industrial firms on coating and encapsulating solid particles using the patented Wurster Air Suspension Process. This invention was assigned to WARF and is licensed to industry on a non-exclusive basis.

The WARF Coating Laboratory, now affiliated with WARF Institute, has participated in the initial development of many an encapsulated product having controlled release characteristics. Sometimes this beginning and the eventual end of the concept come quickly but eventually a few of them do get to market. We would like to tell you about the development of two encapsulated products differing greatly in their concept and markets.

Warfarin: The active ingredient in a large number of anticoagulant rodenticides. An anticoagulant rodenticide bait requires that the rodent feed on the bait for several consecutive days before it succumbs to internal hemorrhaging.

Those who are familiar with the rodenticide industry are aware of the role the Environmental Protection Agency (EPA) has in regulating rodenticide compounds, formulations, quality and labeling. They are also aware of the consternation that gripped many rodenticide formulators when the EPA's test protocol for acceptability and mortality of commercial rodenticides was announced.

Very briefly, the protocol states that in order to meet the EPA acceptability requirements, the test bait is to be consumed at a level consisting of at least 33% of all the food eaten during the test period and 90% mortality must be obtained within 15 days. The penalty for failure to comply is that the EPA has authority to remove that product from the market. While some rodenticide formulators found that their baits could somehow be made to meet these performance levels, the great majority of commercial rodenticide baits failed miserably, with acceptability levels often below 10%.

Somewhere along the line, it became evident that bait rejection by rats was not necessarily the sole fault of the formulator or a result of poor quality bait ingredients. Although anticoagulant baits almost invariably met the mortality requirements of the EPA, the relatively small amount of test bait consumed in many of these tests indicated that something in the test bait was displeasing to the target rats. The displeasing substance turned out to be the technical anticoagulant itself; in this case the warfarin.

Because the Wisconsin Alumni Research Foundation has a background on anticoagulant rodenticides and a process that encapsulates solid particles, it was hypothesized that the problems of the formulator might well be solved by encapsulating technical warfarin so that any objectionable taste was masked and the compound itself was not released until it reached the digestive system of the animal. The project was not a simple challenge. It was a series of challenges relating to:

a) Formulating a coating to mask taste and keep the active ingredient biologically available to rats and mice.
b) Encapsulating a needle-like crystalline structure.
c) Maintaining small particle size distribution of the encapsulated product.

In other words, the encapsulated product would have to be equally as toxic as the unencapsulated compound.

In August 1972, a program was initiated to encapsulate warfarin. The literature indicated that earlier attempts to encapsulate warfarin were unsuccessful because the warfarin was not biologically available. Coating materials were selected that had the desired release characteristics for the target animals. A coating formulation was applied to commercial powdered technical warfarin. The resulting encapsulated product was tested on rodents in the WARF Institute laboratories against the standard EPA test diet. The bait containing encapsulated warfarin was eaten and the rodents died. This single feasibility study demonstrated that the taste of the warfarin was masked and the acceptability of the bait was greater than 33%. A potential product was born.

The next year was devoted to:

1. Selecting the coating ingredients
2. Studying variations in the coating level
3. Biologically testing every sample
4. Developing product standards
5. Developing analytical procedures
6. Encapsulating technical warfarin from both domestic and foreign sources.

Three moths after the first laboratory tests, a sample of the encapsulated product was used to prepare 1500 lbs. of a commercial bait. This product failed the acceptability test. The poor acceptability of that first product was traced to the corn and oats being used in the commercial bait. The commercial bait test was repeated using different corn and oats with good acceptability.

The successful test on a commercial bait resulted in a decision to scale the process to production capacities. The last few months in 1972 and the early months of 1973 were devoted to problems associated with scaling the process to produce the desired particle sizes on larger Wurster equipment. Each step and every change made on the product was documented with acceptability and biological data. The product kept performing well, so in February 1973 WARF applied to the EPA for a registration on encapsulated warfarin.

The work went well until it became necessary to substitute one ingredient in the coating formulation. This change enabled us to use faster coating rates and increased processing temperatures resulting in higher production rates. However the encapsulated product had poor acceptability. In re-evaluating the coating process, the only variable that we were unsure of was the effect temperature had on the product. Therefore, the temperature of the process was returned to the previously acceptable level. The resultant product was both acceptable and toxic to the rodents. The total lapsed time, up to this point, was nine months.

A significant amount of animal data had been accumulated and additional testing and correlation of data was required in order to answer the many questions asked by the EPA regarding registration, labeling and toxicity of the product. Finally, one year later, February 1974, WARF received registration of the encapsulated product. The product is called Tox-Hid, which is a registered trademark of WARF.

During this time, WARF was working closely with several rodenticide companies and when product registration was approved, it licensed two companies to manufacture the product under WARF patents and know-how.

Tox-Hid was introduced into the commercial market in June 1974, 23 months after the program was started. The additional cost for using encapsulated warfarin, Tox-Hid, in place of warfarin is about 4-5 cents per pound of bait.

Encapsulated Warfarin

Purpose: IMPROVE ACCEPTABILITY OF RODENTICIDES CONTAINING WARFARIN

	Months
Project Start:	August 1972
Feasibility Demonstration:	August 1972 1
First Test in Commercial Bait:	October 1972 3
Repeated Test in Commercial Bait:	November 1972 4
Scale-up to Production:	January 1973 6
Application for New Product Registration:	February 1973 7
Continued Product Development:	April 1973 9
Re-evaluation Product Parameters:	May 1973 10
Acceptance of Registration:	February 1974 19
License of Product:	April 1974 21
First Commercial Sale by Licensees:	June 1974 23

Looking for new ways to improve the productivity of land in the Manitoba province of Canada, the Plant Science Department at the University of Manitoba initiated studies on the coating of seeds, especially rape and spring wheat seeds. In 1965, there was no history of applying coatings to seeds to control germination. It was known that if seeds were planted at just the right time late in the fall of the year, they would survive the winter and germinate in the early spring. However, if the seeds germinated in the fall, the freezing conditions would kill the plants.

The main advantage for planting seeds in the fall is that in many areas moisture prevents the farmer from getting into his field for early spring planting. By having the seed already in place, he can take advantage of both the high moisture and the cool growing conditions, which stimulate good tilloring and root development. This permits the crop to develop earlier, have the advantage of fewer weeds and less rust damage; and permits earlier harvesting which, in some years, would escape early frost.

It was reasoned that if the seeds were given a water resistant coating, they would be protected form the fall weather conditions. But the seed coating had to break away during the winter months to allow the seed to imbibe moisture in the spring.

Initial feasibility studies were started at the University of Manitoba in early 1965. Chemical companies were asked to send samples of polymers systems that had water resistant characteristics for evaluation. These materials were applied to seeds for planting in the fall of 1966. The method of coating the seed proved to be as critical to the program as the selection of

the coatings. The Wurster process was selected because of the uniformity and reproducibility of the coatings applied by this technique.

The most abundant seed used in central Canada is wheat and substantial effort was directed to the coating of wheat seed for fall planting. By 1970, the coated wheat was a technical success but not economically practical. The major problem in developing an economical coating centered around the peculiarities of wheat itself and the sophisticated coating, which was developed. In 1971, the project emphasis shifted from coating wheat to rape. Rape seed was becoming more important as a cash crop and requires planting only six pounds per acre versus sixty pounds for wheat. The rape seed is smaller, more nearly spherical and uniform in size compared to wheat, making it easier to coat. It has been estimated that in the Manitoba province alone 500,000 lbs. of rape seed are planted and about 5 million lbs. are planted in the western provinces.

Laboratory tests were worked out to determine whether the seed was adequately protected by the coating to survive the fall environment. The water absorption characteristics of a large number of polymers were studied. Because the field testing was done only once a year, there was considerable time delay in correlating laboratory and field data. The field tests gave several important clues to the mechanism by which moisture entered the seed for germination and these studies eventually led to a better understanding of the properties required of the barrier coating. In the summer of 1973, a coating material was selected that met all the known parameters and gave successful field trials. During these years of extensive field testing, WARF scaled the Wurster process to meet the volume required.

Ten years after the first research trials were made, the Plant Science Department was successful in finding an industrial partner who was willing to invest and plant production quantities of rape seed in Manitoba. Observations made last fall indicated the seeds were well protected. The yield data on the 1976 crop is not available at this time.

On the supposition that the field trials of last fall meet the 10-40% yield increase of the test plots, what are the economics coated seed offers the farmer? It appears that the farmer might have to pay about $1.00 per pound for coated certified rape seed or $7.00 per acre. By comparison, some farmers are already paying approximately this same amount for herbicides. The average yield is 17 bu/acre at $6-$7/bu. Therefore, it is possible for the farmer to invest a few extra dollars for the coated seed because even a moderate yield increase would pay for the cost of the seed and return a reasonable profit, while providing the added convenience of fall planting.

The cost and demand for agricultural products has risen enough in the past few years to make new and novel approaches economically interesting to growers and farmers.

Bibliography

1. Acceptability and Performance of Encapsulated Warfarin; Pest Control, May 1974.

2. Encapsulation of Solid Particles; Joe Abrams and Thomas Hinkes, September 1974, Controlled Release Pesticide Symposium.

3. Manufacture of Coated Seed with Delayed Germination; Canada Journal of Plant Science, Vol. 47 (July 1967).

4. Plastic Coated Seeds; Crops & Soils Magazine, August-September 1967.

5. Optimism Over Plastic Coated Wheat; The Farmer, March 7, 1970.

U.S. Patent	Title
2,648,609	Method for Applying Coatings to Edible Tablets or the Like
2,799,241	Means for Applying Coatings to Tablets or the Like
3,089,824	Granulating and Coating Process for Uniform Granules
3,117,027	Apparatus for Coating Particles in a Fluidized Bed
3,196,827	Apparatus for the Encapsulation of Discrete Particles
3,207,824	Process for Preparing Agglomerates
3,241,520	Particle Coating Apparatus
3,253,944	Particle Coating Apparatus
3,545,129	Manufacture of Dormant Pelleted Seeds
3,698,133	Seed Having a Multiple Layered Coating and Process for Preparing same
3,803,761	Manufacture of Dormant Pellet Seed