CEVA Matrix Technology™: A new alternative for pig medicated premixes

Domps P.*, Zanichelli C., Crambert G.
CEVA Santé Animale, BP 126, 33501, Libourne, France
*corresponding author: pierre.domps@ceva.com

Abstract
Specific problems are posed by medicated premixes: stability of the active ingredient, homogeneity of the medicated premix distribution in the feed and cross-contamination due to dust emission. These problems can have two major consequences: a treatment failure and a risk for human health with selection of resistant strains. CEVA Matrix Technology™, an exclusive CEVA Santé Animale manufacturing process, matches all expectations of an effective and modern medicated premix. CEVA Matrix Technology™ consists of an innovative protective granulation technology. Most non-protected medicated premixes available in the market do not provide good stability and may not reach efficient concentration as the active ingredient is not protected enough. First, the CEVA Matrix Technology™ guarantees that the active ingredient is protected during manufacture (pelleting) and storage of the medicated feed without altering its bioavailability. Secondly, the particle size of CEVA Matrix Technology™ premixes is similar to the feed in which it is to be blended. Therefore the active ingredient is mixed homogeneously into the feed and remains homogeneous even after transportation and storage. This perfect mixability ensures the right active ingredient concentration and dosage in feed every time. Consequently, treatment failure resulting from unequal dosage distribution of the active ingredient in the feed is considerably limited. Thirdly, CEVA Matrix Technology™ guarantees that the premix does not release dust. Therefore, it reduces risks such as cross contamination between two medicated feed batches in mills and inhalation of antimicrobial by users. It protects the workforce and reduces the risk of selecting resistant strains. This article validates all these points by comparing a tiamulin medicated premix manufactured with the CEVA Matrix Technology™ and some non-protected tiamulin.

Introduction
CEVA Matrix Technology™, an innovative protective granulation technology, brings a solution to the specific problems posed by medicated premixes: stability of the active ingredient, homogeneity of the medicated premix distribution in the feed and cross-contamination due to dust emission. The objectives of this study are to compare stability, homogeneity and dust emission of a tiamulin premix (Tiamvet®) manufactured with Matrix Technology™ to others.

Materials and methods
Stability of the active ingredient:
An HPLC method was developed and validated for determination of tiamulin in creep and pelleted feed. The equipment used for the validation was an HPLC system Shimadzu LC-10 AD VP, with a diode array detector. Through a reverse phase column and a mixture of the appropriate solvent, it is possible to separate the substance from the other components present in the feed and make the quantitative determination by comparing the peak area of the sample with the peak area of a reference solution with a known content of Tiamulin hydrogen fumarate. The chromatographic conditions are listed below:

- Column: Hypersil ODS, 250 x 4 mm, 5 µm.
- Mobile phase: (MeOH/ACN/1% ammonium carbonate) (50/30/20) (V/V/V)
  Control pH at 8.9 ± 0.1
- Flow rate: 1.0 ml/min
- U.V. detection: 250 nm
- Injected volume: 20 µl

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Granulometry:
In order to evaluate the "in feed homogeneity" the particle size of three different medicated premixes was measured. The equipment used was an Octagon test sieve shaker.

The method is described below:
- Weigh about 100 g of the product under test and transfer above a series of nine sieves with different aperture sizes. Start sieving with Octagon test sieve shaker.
- Operative condition:
  Accommodate the selected sieves (n° 9) of 200 mm diameter and the receiver on the centre of shaker location and stack them on the top of the receiver.
Place the clamp plate on the top of the sieve located the two holes over an hexagonal rods. Tighten with two handles firmly.
Start shaker vibration for 10 minutes.

Results:
After the test, collect and weigh the amount settled on each sieve and calculated the % of the total deposited amount.

Dust emission
The total powders are determined through dust meter Heubach of specific type II for the fine powder tenor (fraction deposited on the filter less than 10 µm) in granular powders.
- Principle of the method
  The test simulates the conditions that are taken place in the course of the production of feeds (weighing, mixing, transport, handling) and represents an objective method for the measurement of fine powders in granular powders. The product (100 g) is placed in the stress room that turns at 30 r.p.m. and it is stirred from a set of rotary shovels. In the same room, air is introduced, generated from a calibrated vacuum pump (standard flow 20 litre/minute for 5 minutes) and the produced powders are spread along the system. The particles of greater dimensions are separated to level of the first elbow and the subsequent rooms of separation, while those finer (under to the 10 µm) are deposited on the terminal filter in glass fibre (Ø 50 mm).
- Calculation
  The total powders are calculated according to the following formula:
  \[ \text{mg/filter} = \text{weight of the filter in mg (after test)} - \text{weight of the filter in mg (time zero)} \]
  The formula expresses the mg/filter for 100 g of product.

Results and Discussion
Stability study
The two products performed differently in pelleted feed (Figure 1). After three months of storage, active ingredient concentration for the tiamulin without Matrix Technology™ is 60 % of the initial
active ingredient concentration. With the protection of the Matrix Technology™, the active ingredient concentration remains stable even after three months of storage (95% of the initial value).

Homogeneity study
In order to ensure a good homogenisation, the main criterion is the granulometry of medicated premixes. Actually, the simplest solution to ensure effective homogenisation of the active ingredient in the feed and to avoid demixing is to use a medicated premix whose particles are the same size as those of the swine feed. A previous study, conducted by CEVA Santé Animale on fifteen batches of swine feed from seven different countries has shown that more than 70% of the swine feed consists of grains whose size is higher than 300 µm with an average grain size of 700 to 900 µm. On the three tiamulin premixes tested, the tiamulin premix with Matrix Technology™ is the only one with a huge percentage of grains whose size is higher than 300 µm (Table 1).

<table>
<thead>
<tr>
<th>Grain size (µm)</th>
<th>&lt; 45</th>
<th>45-63</th>
<th>63-90</th>
<th>90-100</th>
<th>100-150</th>
<th>150-300</th>
<th>&gt; 300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiamvet®</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>99%</td>
</tr>
<tr>
<td>Product A</td>
<td>10%</td>
<td>36.4%</td>
<td>22.1%</td>
<td>13.4%</td>
<td>5.6%</td>
<td>8.4%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Product B</td>
<td>0.3%</td>
<td>4.5%</td>
<td>6%</td>
<td>10.9%</td>
<td>19.5%</td>
<td>46%</td>
<td>12.8%</td>
</tr>
</tbody>
</table>

Table 1 Granulometry of three tiamulin premixes

A second granulometry study with higher grain size tested has been done on the tiamulin premix with Matrix Technology™. The results show that the grain size of a tiamulin premix with Matrix Technology™ is consistent with the specific granulometry of swine feed (Figure 2). We can therefore conclude that this medicated premix will have a good homogenisation in swine feed.

Swine feed average grain size

![Figure 2 Granulometry of a tiamulin premix with Matrix Technology™](image-url)
Dust emission study

The dust emission of the three tiamulin premixes is radically different (Figure 3). The tiamulin premix with Matrix Technology™ emits 0.1 mg of dust for 100 g of product, making it a medicated premix with a very low level of dust emission. The two other products tested emit respectively 4326 and 9276 more dust, making them a medicated premix with a very high level of dust emission and with the inherent risks of cross-contamination and of inhalation of active ingredient by the operators.

![Dust emission graph](image)

**Figure 3** Dust emission of three tiamulin premixes

Conclusion

CEVA Matrix Technology™ is a global solution to answer all the problems posed by medicated premixes:
- very good stability of the active ingredient during manufacture (pelletting) and storage of the medicated feed (without altering the bioavailability)
- particle size similar to the feed in which it is to be blended allowing a perfect mixability
- very low dust level emission (< 2 mg / 100 g of product)

Consequently, CEVA Matrix Technology™ enables to:
- avoid treatment failure due to incorrect active ingredient concentration
- limit the risk of selecting resistant strains due to low active ingredient concentration
- protect the workforce (no dust emission)
- avoid cross-contamination of batches