



FC-CUBES



The history



The issue ...

It is not easy to administer oral medicines to pets. Many owners try to hide tablets in a piece of meat or cheese to give it to their cat or dog. It rarely works: the animal eats the treat and neglects the tablet!

The solution ...

On the US market Merial is currently selling two different drugs for cats and dogs (*Heartgard and Heartgard Plus*) as “chewable” formulations, characterized by a high percentage of palatable agent and with a texture truly appreciated by the animals.

Looking at the annual turnover achieved by these drugs compared to tablets, it is evident that chewable presentation is highly appreciated by animals and owners alike.

The limit ...

These chewables are obtained by extrusion: a string is produced by the extruder and then cut along the length to obtain single tablets. This method of production is unable to provide a perfectly dosed medicine. Several parameters should be optimized to ensure dosage homogeneity: density throughout the extruded rod must be the same to have equal amount of API for a given length, formation in the matrix should be prevented by having a constant screw compression system, shape should not be modified. In addition, rejected products can not be re-extruded to avoid API degradation.

...finally, even if the chewable presentation is very interesting it has some defects especially from the production point of view (extrusion)



FC-cubes: the idea

Friulchem's idea ... production by compression instead of extrusion

Friulchem identified a different manufacturing method which allows to reach a chewable matrix with all the benefits presented for the drugs already on the market, but without the limit connected to production by extrusion.

Friulchem technology (for which a patent has been submitted) is based on a compression stage, which shows different advantages compared to extrusion:

- a. **Compression allows the manufacture of products with higher fat and palatable material content**, which leads to perfect appetency (total ingestion by animals even on a repeat basis).
- b. **Compression provides full control over the weight** of the chewable cube and hence over **the quantity of API contained in each unit** of the finished-product, thereby guarantees compliance with therapeutic treatment;
- c. By compression **the product could be obtained in different shapes**, from the common square to new "suggestions": heart, bones, fish-shape ...





The applications...

Due to the high palatability showed in the preliminary tests performed, FC-cubes could be used to prepare formulations which can include:

- Nutraceutical products/additives
 - Vitamins
 - Minerals
 - Elements
 - Herbes
 - ...
- Active pharmaceutical ingredients
 - Antibiotics such amoxicillin, amoxicillin+clavulanic acid, cephalixin
 - Anti parasitic as ivermectin, pyrantel+ivermectin, moxidectin
 - Insecticide
 - Cardiotonic as levosimendan

The matrix composition developed in Friulchem is 100% palatable and able to mask also active components which are particularly disliked by the animals.

Friulchem R&D studies the best formulation for each API/nutraceutical component, providing the customer with samples for evaluations, initial palatability tests and stability studies, during the preliminary feasibility stage.



The possibilities ...

Current shapes available:

- Cube (square punches)
- Cylinder (round punches)



Current dimensions available (set of punches)

- 12,5 mm – cylinder diameters or cube side
- 19,5 mm – cylinder diameters or cube side

Height of chewable chunk can be modified and this allows a wide range of weight, from 0,8 g to 8 g (depending from the matrix density), obtainable with these 2 sets of punches.



Stability studies

Friulchem performed the following preliminary stability studies on FC-cubes prototypes containing different APIs: Ivermectine (IVM), Pyrantel Pamoate (PYRP), Praziquantel (PZQ) and Milbemycine (MBO).

✓ BINARY COMPATIBILITY

A binary compatibility study has been performed on a selected list of excipients to predict and determine the stability of PZQ, MBO, IVM and PYRP in the final formulation.

The other excipients were not evaluated since they are already used in other formulations currently on the market and containing the same APIs.

✓ CRASH TEST

Crash test study carried out on 9 different chunk Friulchem cubes formulations containing Praziquantel (PZQ) and Milbemyacin Oxime (MBO), to test APIs stability into the prototypes under stressed conditions, and in comparison with the reference product (Milbemax chunk *Novartis*).

✓ STABILITY STUDIES under VICH conditions

VICH preliminary studies has been initiated on 9 formula prototypes to collect first data about prototypes stability



Protocols (I)

stability study

Heading	Description				
Study conditions	Packaging:	Brown glass bottles			
	Temperature:	70 °C			
	Humidity:	dry atmosphere			
	Time:	14 days			
	Time points:	4			
	Time points interval:	day 0 (T0)	day 4 (T4)	day 7 (T7)	day 14 (T14)
	Analyses per time point:	HPLC assay / qualitative impurities profile			
	Analytical method:	as developed by Friulchem			

binary compatibility

crash test

Heading	Description				
Study conditions	Packaging:	Brown glass bottles			
	Temperature:	50 °C			
	Humidity:	dry atmosphere			
	Time:	21 days			
	Time points:	4			
	Time points interval:	day 0 (T0)	day 7 (T7)	day 14 (T14)	day 21 (T21)
	Analyses per time point:	Cube appearance (size, shape, colour) Hardness Friability PZQ and MBO HPLC assay / qualitative impurities profile at 254 nm and 210 nm			
	Analytical methods:	as developed by Friulchem			
	Reference:	EU: Milbemax ® chunk batch n.36284			
Items tested	1.1 g cubes - 9 different prototypes				



protocols (II)

stability study

VICH stability

Heading	Description				
Study conditions	Packaging: Time	Alu/Alu sachets* T0 15.10.2013			
	Temperature / humidity:	25 °C / 60 %		40 °C / 75 %	
	Time points:	4@25 °C		3@40 °C	
	Time points intervals@25 °C:	month 3 (T90) 15.01.2014	month 6 (T180) 15.04.2014	month 12 (T360) 15.10.2014	month 24 (T720) 15.10.2015
	Time points intervals@40 °C:	month 1.5 (T45) 30.11.2013	month 3 (T90) 15.01.2014	month 6 (T180) 15.04.2014	
	Analysis to be perform at each time point:	See table			
	Analytical methods:	as developed by Friulchem			
Items to be tested	1.1 g cubes for 3 different formulations (F4, F7 and F9)				
Each sample packed will be tested under vacuum to prove the tightness of seal					

Test	Regulatory reference	T0	T1.5	T3	T6	T12	T24
Appearance	VICH 39 page 11	√	√	√	√	√	√
Friability	2.9.7/VICH 39 page 16	√	√	√	√	√	√
Disintegration	2.9.1	√	√	√	√	√	√
Light stress		√	-	-	-	-	-
Loss on drying		√	√	√	√	√	√
Texture analyses (hardness, stickiness)	Internal method	√	√	√	√	√	√
Uniformity of mass - weight	2.9.40	√	average value	average value	average value	average value	average value
Dissolution	EP	√	-	-	√	-	-
Assay and Uniformity of content (HPLC)*	2.9.6/VICH 39 page 11	single assay + average value	average value	average value	average value	average value	average value
Related substances and impurities**	5.10	√	√	√	√	√	√

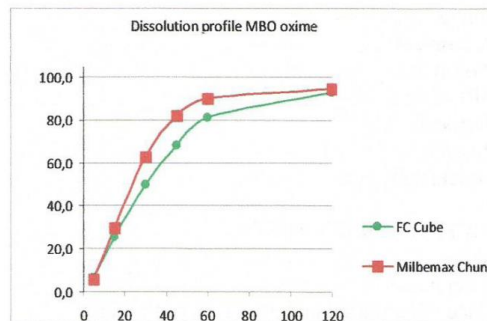
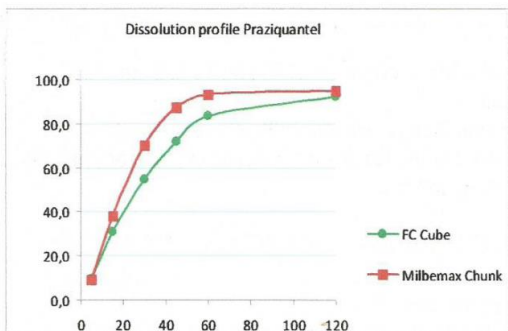


protocol

Dissolution test has been performed on 6 cubes with sampling at 5, 15, 30, 45, 60, 120 minutes (regulatory reference Ph. Eur. 2.9.3, dissolution test for solid dosage forms)

Reference: Milbemax Chunk

results



Dissolution profile Praziquantel		
	FC Cube	Milbemax Chunk
time	%	%
5	9,6	9,1
15	30,9	38,1
30	54,8	70,4
45	71,9	87,4
60	83,7	93,5
120	92,5	95,1

Dissolution profile MBO oxime		
	FC Cube	Milbemax Chunk
time	%	%
5	6,8	5,9
15	25,5	29,8
30	49,9	62,7
45	68,2	82,1
60	81,3	90,1
120	92,7	94,5



friability

results

Test		Formula 1	Formula 2	Formula 3
Friability % p/p*	Mass before	11.1189	11.1578	11.0927
	Mass after	11.0766	11.1170	11.0687
	Δ	0.380	0.366	0.216
Friability % p/p 2d wheel – small drum*	Mass before	10.9212	11.0674	10.9112
	Mass after	10.9081	11.0362	10.8834
	Δ	0.120	0.282	0.255

friability test



uniformity of mass

uniformity's test

n.	Formula 1	Formula 2	Formula 3
	FC	FC	FC
1	1.1153	1.0875	1.0937
2	1.1091	1.1001	1.1013
3	1.1199	1.0956	1.1195
4	1.0808	1.0870	1.0888
5	1.0780	1.1116	1.1194
6	1.1183	1.1103	1.0843
7	1.0897	1.0953	1.0994
8	1.1193	1.0909	1.1108
9	1.0857	1.1142	1.1151
10	1.1164	1.0979	1.1012
11	1.1160	1.1012	1.1013
12	1.0809	1.0841	1.1189
13	1.0849	1.1151	1.0891
14	1.1202	1.1131	1.1013
15	1.0905	1.0949	1.0818
16	1.0831	1.1009	1.1201
17	1.0926	1.1170	1.1198
18	1.0916	1.1103	1.0934
19	1.1150	1.0981	1.0987
20	1.0902	1.1071	1.0813
Average	1.100	1.102	1.102
n. of samples	20	20	20
Minimum	1.078	1.084	1.081
Maximum	1.120	1.117	1.120
CV%	1.5	0.9	1.2

Uniformity of mass – weight (g)

protocol



palatability test on dogs and cats

Assessment of voluntary acceptance

Ref. VICH Guideline on the demonstration of palatability of veterinary medicinal products

For assessing the acceptance of the test product, it could be offered in the following pre-determined order:

1. First, it may be offered in an empty bowl or trough, or on the ground to assess voluntary acceptance during 30 seconds.
2. In case of failure, the product could be offered by hand for an additional 30 seconds, such that the maximum total offering time is one minute.

Failure might be of different types as follows:

1. Delayed uptake although complete consumption (time to be defined in the protocol)
2. Partial intake
3. Regurgitated or spitting out of the product
4. Consumption only when hidden in food/water
5. Forced intake by placing the product into the mouth and making sure the animal swallows
6. Refusal

dogs

dogs



CODE	NAME	SEX	SIZE
1	Stella	F	small
2	Nerina	F	small
3	Max	M	med-big
4	Gaia M	F	med-big
5	Mosé	M	med-big
6	Berni	F	med-big
7	Attila	M	med-big
8	Spillo	M	small
9	Liqui	F	med-big
10	Billy	M	med-big
11	Schizzo	F	med-big
12	Aibell	F	med-big
13	Axel	M	med-big
14	Pepe	M	small
15	Desy	F	small
16	Mailin	F	small

CODE	NAME	SEX	SIZE
17	Mimì	F	med-big
18	Garcia	M	med-big
19	Pablo	M	med-big
20	Nerino	M	med-big
21	Briciola	M	med-big
22	Fulvio	M	med-big
23	Spino	M	med-big
24	Shumi	M	med-big
25	Skipper	M	med-big
26	Maya	F	small
27	Bolla	F	med-big
28	Poldo	M	med-big
29	Athos	M	med-big
30	Minù	F	small
31	Billy 2	M	med-big
32	Lola	F	med-big

CODE	NAME	SEX	SIZE
33	Apollo	M	med-big
34	Rucola	F	med-big
35	Steve	M	med-big
36	Ivan	M	med-big
37	Brenda 2	F	med-big
38	Buddy	M	small
39	Tai	F	small
40	Sasha	F	small
41	Brenda	F	med-big
42	Mallory	F	med-big
43	Botticella	F	med-big
44	Pippo	M	med-big
45	Iulia	F	med-big

product characteristics

dogs' weight < 10kg

shape:	cylinder
size:	1 gr
manufacturing:	manual press

dogs' weight > 10kg

shape:	cylinder
size:	3.5 gr
manufacturing:	manual press



results

palatability test

SMALL ANIMALS (weight < 10Kg)				MEDIUM-BIG ANIMALS (weight > 10Kg)			
	n. of animals tested	voluntary uptake			n. of animals tested	voluntary uptake	
		YES	NO			YES	NO
Formula 9C	3	3	0	Formula 9C	6	6	0
Formula 21 C	4	4	0	Formula 21 C	6	5	1
Formula V2D	5	5	0	Formula V2D	7	7	0
Formula 21 A	2	2	0	Formula 21 A	7	5	2
Formula 21 D	2	2	0	Formula 21 D	7	7	0

Size Small Dogs (1g)																	
		FORMULA 9C			FORMULA 21 C				FORMULA V2D				FORMULA 21A		FORMULA 10D		
		1	2	26	8	38	39	26	14	15	16	30	26	20	40	23	24
Voluntary uptake	YES	In an empty bowl or trough (max 30')		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
		By hand (max 30')															
		Delayed uptake although complete consumption															
		Partial intake															
		Regurgitated or spitting out of the product															
		Consumption only when hidden in food/water															
		Forced intake by placing the product into the mouth and making sure the animal swallows															
		Refusal															

Medium-Large Dogs (3.5gr)																																		
FORMULA 9C					FORMULA 21 C					FORMULA V2D					FORMULA 21A					FORMULA 10D														
6	7	4	3	5	27	9	12	10	27	13	11	19	17	18	28	29	31	27	21	22	41	42	43	44	45	32	25	33	34	35	36	37		
✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
																		✓																
																								no teeth										



cats

CODE	NAME	SEX
1	Mia	F
2	Bruno	M
3	Minù	F
4	Penny	F
5	Felin	M
6	Renato	M
7	Kefi	F
8	Sayid	M
9	Sawyer	M

CODE	NAME	SEX
10	Betty	F
11	Lucilla	F
12	Lilli	F
13	Perla	F
14	Titti	F
15	Terry	F
16	Axl	M
17	Mia2	F
18	Amelia	F

product characteristics

shape:	cylinder
size:	1gr
manufacturing:	manual press



results

	n. of animals tested	voluntary uptake	
		YES	NO
Formula 9C	18	16	2
Formula 21 C	18	14	4

		FORMULA 9C																		FORMULA 21 C																	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Voluntary uptake	YES	In an empty bowl or trough (max 30')	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
		By hand (max 30')																																			
	NO	Delayed uptake although complete consumption																																			
		Partial intake																																		✓	
		Regurgitated or spitting out of the product	✓																		✓																
	NO	Consumption only when hidden in food/water																																			
		Forced intake by placing the product into the mouth and making sure the animal swallows																																			
	Refusal																	✓																✓	✓		