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STUDY OF THE FORMULATION AND PREPARATION OF CHEWABLE TABLETS WITH A CALCIUM COMPLEX ASSOCIATION AND VITAMIN D3

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Abstract. The experimental study objective was the development of chewable tablets with the calcium complex association, the minerals and vitamin D_3 for children, subject to the rules as stipulated by the Romanian Pharmacopoeia X^{th} edition. Generating sources of calcium, used as raw materials in the preparation of these tablets are natural products represented by complex mineral rich in calcium - Lactoval® HiCal (ratio of calcium and phosphorus is 2,2:1, report the same as breast milk) and 30% bovine colostrums [1, 3], making the absorption of calcium should be increased. Also, in order to fix and better absorb calcium in the body was added to make the preparation of these chewable tablets and vitamin D_3.

Was chosen as a method of preparing direct compression. Excipients for direct compression are diluents-binder-disaggregated. They are unitary excipients or co-processed products, multi-processed excipients together to meet those properties: microcrystalline cellulose (Vivapur 102) Ludipress, lactose (Tablettose 80), Kollidon CL Isomalt DC 100. Was also added to a lubricant (magnesium stearate) and sweetener and flavoring to carry out the preparation of tablets and after 30 days as provided Romanian Pharmacopoeia X^{th} and its 2001 supplement, which comprises: organoleptic control, uniformity of weight, strength, disintegration and their friability. Working method chosen and make the appropriate choice leads to tablets in terms of quality standards officinal.

Keywords: *chewable tablets, calcium complex association, vitamin D_3, direct compression method.*

2000 *Mathematics Subject Classification*: 92C99.

1. Introduction

Chewable tablets are solid pharmaceutical dosage forms with the following advantages: an improved bioavailability due to decay in the mouth (an improvement of dissolution); ensure the elimination of the need for available water to swallow the tablet. The administration seeks immediate therapeutic effect, confers an increased level of patient acceptance (especially in pediatrics) by pleasant taste and a commercial presentation through a substitution variant form preparations liquid.

Calcium is the most abundant mineral in the human body. An average human body constitution contains calcium ion 1000-1500g, 99% of which is located in the bones and teeth. Besides the ability to give skeletal mechanical strength, calcium is essential for transmitting nerve impulses and muscle contraction. The calcium is known as the preventive factor in osteoporosis, increase bone density. Milk and milk products constitute one of the main sources of calcium from food, both in childhood and in adolescence, adulthood and old age. Recent studies have shown that immunostimulator effect of vitamin D is higher than that of vitamin C [2]; the likelihood of upper respiratory tract infections is inversely proportional to the concentration of vitamin D in blood.

2. Materials and method

Materials:

Were used Lactoval® HiCal, (DMV International), 30% bovine colostrums, vitamin D_3 type 100 (DSM), Ludipress (BASF AG, Germany), Kollidon CL-crospovidon (BASF AG, Germany), Isomalt DC 100 (BANEO-Palatinit GmbH, Germany), Tablettose 80 - (Meggle, Wasserburg GmbH), Vivapur 102, vegetable magnesium stearate (Faci Spa), maize starch (CHEMaster International Inc.), caramel flavor powder (Vegan, Kosher, gluten free), sweetener. All excipients used were pharmaceutical quality and purity analysis.

The tablets formulation:

In the Table(1) are shown the composition of the studied wording. Mixing for compression was obtained using a cone double homogenizer. In that were loaded materials: that vitamin D_3, and sweetener, caramel flavor, and corn

starch, magnesium stearate, kollidon, vivapur 102, colostrums, isomalt, ludipress and lactoval. Time is set during the mixing: 20-minutes. The mixture was passed through the sieve VI and compressed. Direct compression mixture was made with a rotary tablet TX 30 equipped with 30 pairs of stainless ponsons flat edge, with edges intact, with a diameter of $15mm$.

Were obtained uncoated tablets, uniform appearance, as a disk, compact structure, with smooth, flat and edges intact 15 mm;

- Color - white, mottled with yellow pigment;
- Odor - weak characteristic odor;
- Taste - sweet, refreshing;

After preparation of chewable tablets were determined:

- Uniformity of mass;
- Friability;
- Mechanical strength (diameter, height of tablets);
- Disintegration.

Determinations were performed in accordance with F.R. X., and E. Ph. 5 [4, 5, 6]. All calculations were performed on 20 or 10 (friability test) tablets.

Equipment:

- Balance Mettler - Toledo - for uniformity of mass;
- The apparatus Pharmatest PTF 10/ER for friability test;
- Pharmatest PTB 311E device for mechanical strength (diameter, thickness of tablets);
- Pharmatest PTZ S device for the test of disruption;

Table 1: The compositions of the chewable tablets with calcium and vitamin D3

ACTIVE SUBSTANCES	
Ingredients	Quantity
Lactoval® HiCal	0,8 mg
Colostrum	400 mg
Vitamin D3 type 100 (100.000 UI/g)	100 mg

EXCIPIENTS		
Ingredients	Quantity	Role
Ludipress	100,1mg	binder,diluent,disintegrant
Isomalt DC 100	96,4 mg	sweetener
Tablettose 80	89,31 mg	diluent
Kollidon CL	36,4 mg	binder
Vivapur 102	36,4 mg	diluent
Magnesium stearate	22,75 mg	lubricant
Maize starch	18,2 mg	lubricant, diluent
Caramel flavor	5 mg	flavor
Sweetener	4,64 mg	
TOTAL	910 mg	

3. Results and Discussions

Uniformity of mass:

It weighted 20 tablets uncovered and calculated the average mass. The same tablets are weighted individually. Compared to the average mass calculated, the individual mass may submit a deviation: 18 tablets ±5% and just 2 tablets ±7, 5%.The values of individual, average masses and the percentage deviations calculated are shown in the Table(2) and Figure 1

Conclusion: It is noted that the tablets meet standards officinal regarding individual mass, masses limits of the tablets which can vary are between 0,866-0,957, and has the corresponding percentage deviations range from: -2.19% and 2.64%.

The friability:

A loss of less than 1% is considered acceptable for most products. From the experimental results, show that the formulation studied requirement as regards friability. For studied wording, weight loss is less than 1%.
To test using 10 chewable tablets are dusting with a soft brush. The drum introduced in tablets, previously weighed, to secure the cover and fasten the drum unit. The drum starts to rotate with the rotation speed of 25 *rpm* default operating mode. The determination is made after 100 revolutions, respectively after 4 minutes, the tablets are removed and remove all dust again any tablet is broken away.

Weigh the tablets, then friability calculated using the formula:
Friability = $[(M_i\text{-}M_f)\ /\ M_i]$ x 100 where,
M_i = initial weight of tablets
M_f = final mass of tablets

The test is done once. If results are not satisfactory or if weight loss is less than 1%, repeat the test twice and calculate the average of three determinations.
Results:
$M_i = 893.786\ mg$
$M_f = 890.777\ mg$
Friability = $0.33\% < 1\%$.

Conclusion: It is noted that the friability for 10 chewable tablets is less than 1%, so the tablets meet USP requirements.

The mechanical resistance, the diameter and the thickness of tablets:

To test were using 10 chewable tablets. Each tablet was placed in the device (Pharmatest PTB 311E), after which values were determined for the three parameters (diameter,height and hardness).The tests led to following results and are shown in the Table(3)and Figures(2, 3).

Conclusion: The data in the table above and Figures(2, 3) observed that chewable tablets have values very close in terms of their size (diameter, height)

Table 2: The values of individual, average masses and the percentage deviations of tablets

Crt.No.	**Individual Mass** (g)	**Percentage deviation(%)**
1.	0,909	-0,11
2.	0,896	-1,54
3.	0,892	-1,98
4.	0,921	+0,10
5.	0.902	-0,88
6.	0,934	+2,64
7.	0,916	+0.66
8.	0,911	+0,11
9.	0,923	+1,43
10.	0,899	-1,21
11.	0,893	-1,87
12.	0,917	+0,77
13.	0,925	+1,65
14.	0,913	+0.33
15.	0,890	-2,19
16.	0,899	-1,21
17.	0,901	-0,99
18.	0,887	-2,53
19.	0,920	+1,10
20.	0,894	-1,76
Average	0,8584	

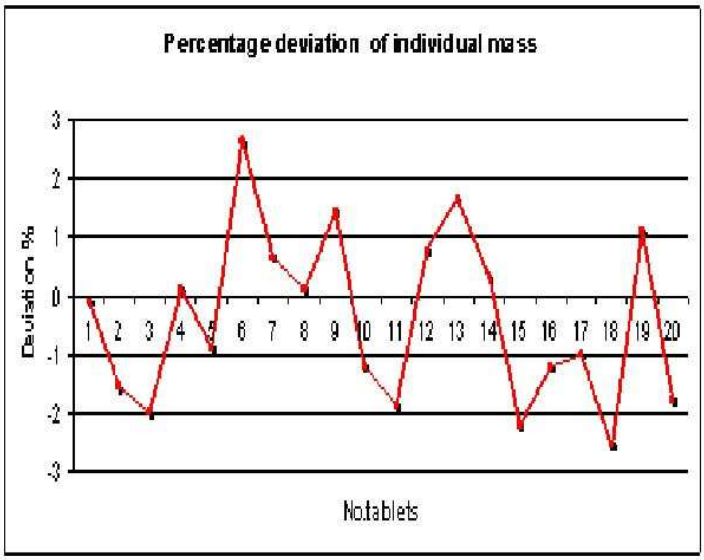

Figure 1: Percentage deviation of invidual mass of tablet

but also in terms of mechanical strength. This is due largely to correct adjustment tablet machine.

The disintegration of chewable tablets:

For chewable tablets disintegration test were used 6 tablets at the same time absolutely the same conditions, so that all samples are inserted into the same water bath maintained at 36-38°C; arm support device with baskets of moving up and down control by a microprocessor running 30 races per minute over a distance of 55 mm.

It is preferable that chewable tablets correspond to the dissolution test for uncoated tablets, which must be disintegration, more than 15 minutes. The following table IV shows disintegration times for the disintegration six chewable tablets under test.

Conclusion:

Chewable calcium tablets correspond officinal disintegration rules for uncoated tablets (disintegration time 8-8, 4 min. <15 min., Figure(4).

Table 3: The diameter (mm), the thickness (mm) and the mechanical resistance (N) of the studied formulation

Crt.No.	**Diameter** (mm)	**Height** (mm)	**Hardness** (N)
1.	15.02	3.94	123.5
2.	14.99	3.98	115.0
3.	14.99	3.95	120.5
4.	15.01	3.93	109.5
5.	14.98	3.97	125.1
6.	14.99	3.95	113.8
7.	15.00	3.94	119.3
8.	14.99	3.97	113.7
9.	14.99	3.93	131.9
10.	14. 8	3.97	120.8
Average	14.99	3.95	119.31

4.Conclusions

Two natural products represented the calcium complex association used for preparation of chewable tablets: a Lactoval® HiCal, rich in minerals, with a high content of calcium, and bovine colostrums. To obtain chewable tablets, direct compression method was used to very good because it eliminates the presence of high temperature and humidity, which are risk factors, using direct compression excipients coprocessor, which ensured the stability of active components. Working method chosen and make the appropriate choice leads to tablets in terms of officinal quality standards.

Following the test of stability is seen that after 30 days the average weight values, individual mass, diameter, thickness, resistance and disintegration increases and decreases relative to the friability tablets made initial determinations. This is due hygroscopicity of some excipients, which may adversely affect the stability of chewable tablets. Therefore, preparation of these tablets should be made under controlled conditions followed by blister or filling their bottles with a desiccant substance.

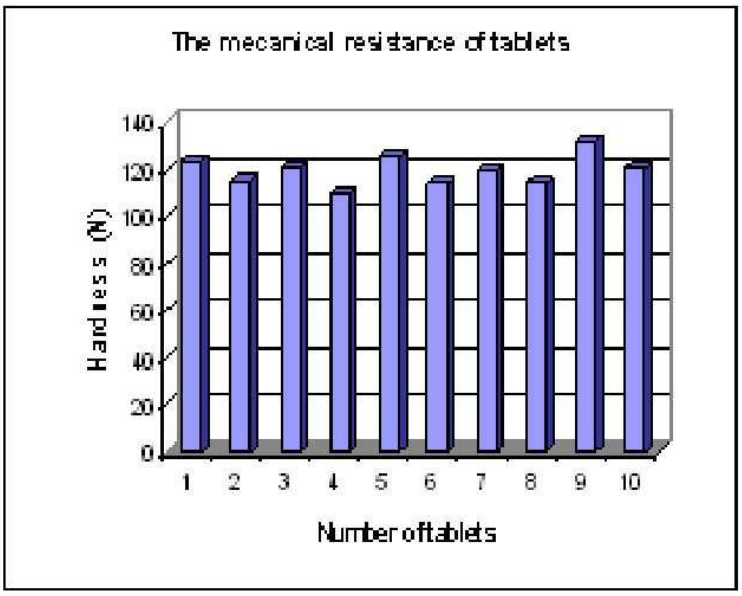

Figure 2: The hardness of tablets (N)

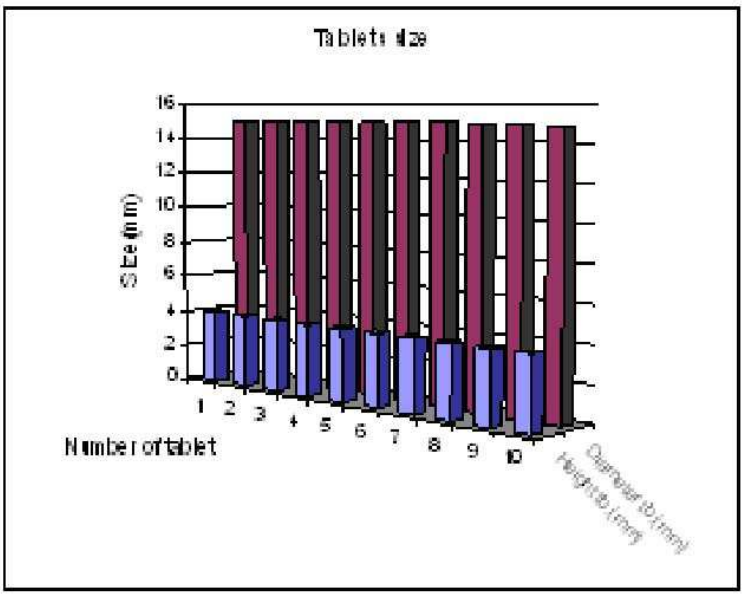

Figure 3: Diameter (mm) and height (mm) of tablets

Table 4: Time of disintegration of chewable tablets

Crt.	**Time of disintegration(min)**	**Time of disintegration(sec)**
1.	8	480
2.	8.32	499,2
3.	8.2	492
4.	8.04	482,4
5.	8.18	490,8
6.	8.4	504

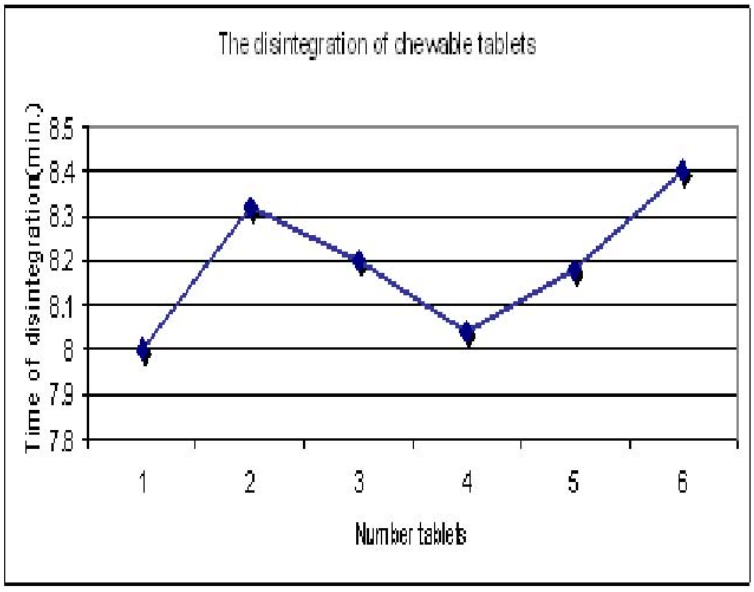

Figure 4: The disintegration time of chewable tablets

Experimental study has shown the possibility to obtain film-based natural products that have an appreciable content of calcium and other trace elements, minerals and vitamin D_3, an important role in returning stability excipients used.

Children having a pleasant taste will more easily accept the chewable tablet flavor and active substances are more easily disposed of pharmaceutical form as the tablets are broken in the mouth and are more easily absorbed and metabolized in the body, with the development of therapeutic, to the tablets are swallowed.

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