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"Formulation, Development and Evaluation of Calcium with Vitamin D3 Chewable Tablet as Oral Drug Delivery System"

Kedar Sanjay Kunturwar
Student- Dr Ved Prakash Patil pharmacy college, Ch. Sambhaji Nagar, Maharashtra.

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ABSTRACT: The aim of this research is to formulate and evaluate chewable calcium with vitamin D3 tablets for the patients who can't get adequate amount of the vitamin and calcium from their daily diet. Calcium and Vitamin combinations are used to prevent low calcium levels in the body or treat these low levels of calcium in peoples who do not get necessary amount of calcium from their daily routine diet. The ultimate goal of developing these tablets is to create more user-friendly experience to the patients. These tablets will overcome the swallowing difficulties of people with dysphagia, chewable tablets are excellent alternatives to conventional tablets.
Keywords: chewable tablets, Vitamin D3, calcium, wet granulation, direct compression, evaluation.

I. INTRODUCTION:

Tablets Basically chewable tablets are designed to be broken down and chewed between teeth before swallowing. As an alternative to other conventional solid dosage forms chewable tablets plays very important role with respect to convenience of patients**.**The preparation of chewable calcium tablets containing vitamin D3 will be used to treat condition due to low calcium level, like osteoporosis, osteomalacia.It can also be utilized for certain specific patients to ensure the requisite amount of calcium in body (examples such as pregnant women, nursing mothers, for postmenopausal use, persons taking specific medications such as phenytoin, phenobarbital, or prednisone).The main role of calcium in the body has great importance with respect to normal functioning of nerves, cells, muscle, and bone. Whenever there is a lack of calcium in the blood, the body will cover the calcium blood levels by taking the same from bones which in turn causes weakening of bones.Vitamin D addition in such formulation further helps body for absorbing available calcium and phosphorus. Strong bones can be built and further maintained by correct and requisites amount of vitamin D, calcium and phosphorus. Benefit of chewable tablet is that it reduces risk of esophagitis when a conventional tablet comes in contact with esophagus and dissolves the contents while remaining in contact with the esophagus lining. Chewable tablet can be used as another alternative avoid this problem.

Pre-formulation studies: Excipient compatibility is an important part of understanding the role of inactive ingredients in product quality. The selection of excipients for the compatibility study should be based on the mechanistic understanding of the drug substance and its impurities, excipients and their impurities, degradation pathway and potential processing conditions for the drug product manufacture to avoid endorsement of specific products.

Excipient-drug substance compatibility was assessed through analysis of binary mixtures of excipient and drug substance at a 1:1 ratio in the solid state.

Common excipients functioning as filler, Disintegrants, and lubricant were evaluated in this excipient compatibility study.

Samples were stored at 25 °C/60 % RH and 40 °C/75 % RH in both open and closed containers (Glass vials) for 1 month.

II. MATERIAL AND METHOD:

SR. No.	Ingredients Names
1.	Calcium Carbonate

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2.	Tribasic Calcium Phosphate
3.	Calcium Fluoride
4.	Magnesium Hydroxide
5.	Cholecalciferol (coated)
6.	Powdered Sugar
7.	Purified Talc
8.	Maize Starch
9.	Calcium Stearate
10.	Sunset Yellow CINo. 15985
11.	Carmellose Sodium
12.	Americanicecreamsoda
13.	Sodium Carboxymethylcellulose
14.	Dextroseanhy drous
15.	Mannitol
16.	Aspartame
17.	Trusil Orange ASV
18.	Magnesiumstearate
19.	Calciumstearate

Table no1: ingredients name

Sr. No	Ingredients	**Trial (X)**
1	Calcium Carbonate	380.0
2	Tribasic Calcium Phosphate	75.00
3	Calcium Fluoride	0.50
4	Magnesium Hydroxide	52.50
5	Vitamin D_3 (Coated)	0.625
6	Maize Starch	170.8
7	Purified Talc	5
8	Magnesium Stearate	8
9	Aspartame	15
10	Dextrose Anhydrous	382
11	Mannitol	50
12	Flavour Trusil Orange	10
13	Sunset Yellow FCF	0.550
14	Purified Water	q.s.
Average weight mg/tab		1150

Table no 2: trial quantity of ingredients

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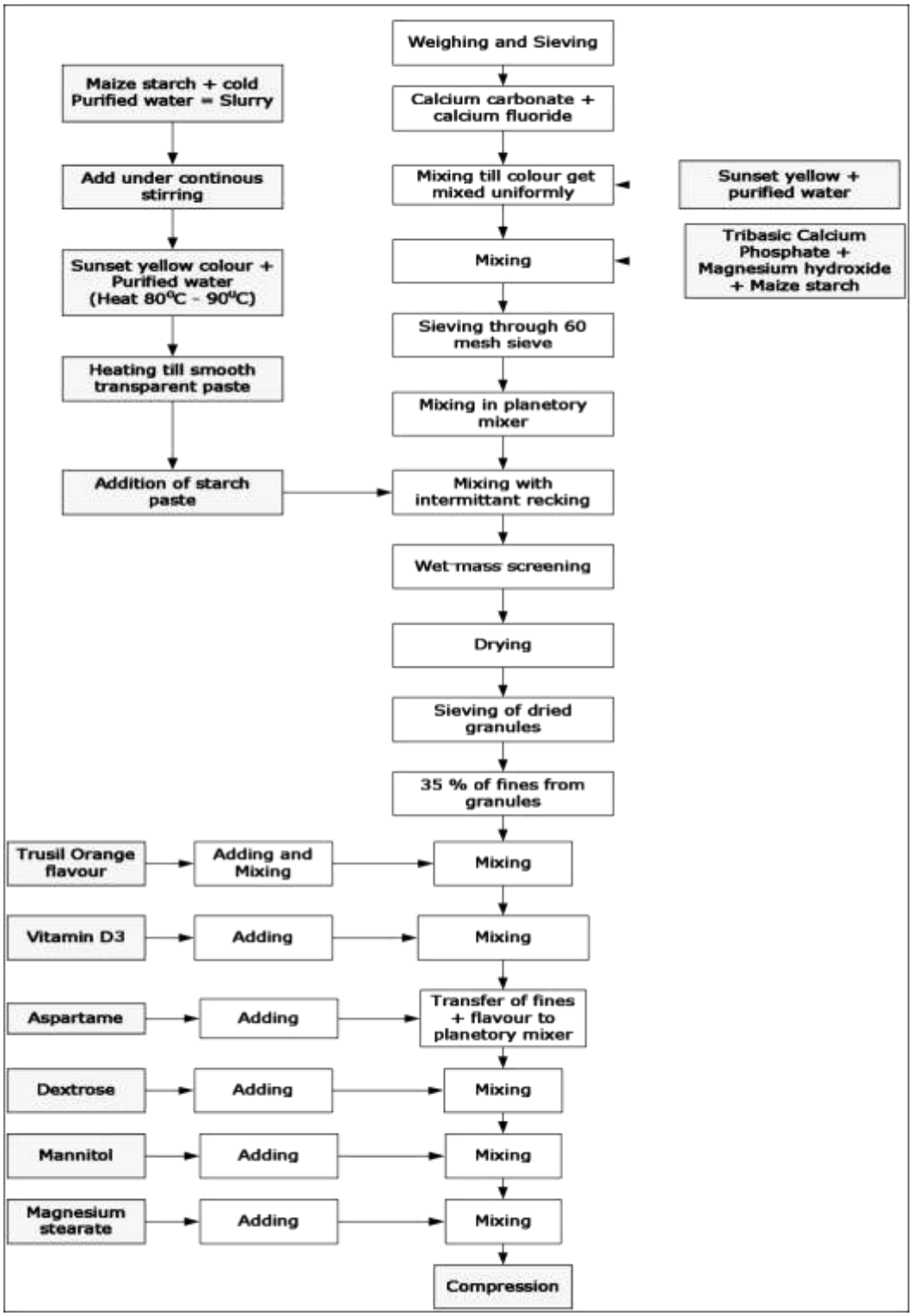
Flowchart of Simplified form of manufacturing process:



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Evaluation parameters:

Angle of repose: Resting angle is a powder element associated with friction between particles or resistance to movement between particles. Angle of rest test results depends entirely on the method used. The test difficulty arises from the significant separation of the compound and the compound or aeration of the powder when forming a cone.

Bulk density and tapped density: Bulk Quantity is not the internal material of an object. It can changes depending on how the property is managed. The quantity of flour simply indicates the amount, usually the weight or weight of the flour by the set volume.

Uniformity of weight:20 Tablets from all the batches were collected randomly during compression and weight of individual tablet was carried out. Limit: Weight of all individual tablets should be in the limit of Average wt ± 7.5%. Average weight was carried out by calculating the total wt. of 20 tablets (individually weighed) and dividing this value by20.

Friability test: Friability of tablets is determined using Fraibilator. Tablets under the combined effect of abrasion and shock in the Fraibilator at 25 rpm and then place the tablets at a height of six inches at each revolt, A sample of pre-measured tablets were placed in the Friabilator and experienced 100 changes. The tablets are dusted off using a soft tissue fabric and re-weighed.

Hardness test: The mechanical strength of pharmaceutical tablets is generally determined by measuring the force required to cause the tables to fail or break in a plane parallel to the applied force. This force is called as tablet hardness.

Chewable difficulty index: The mechanical strength or the tensile strength is a fundamental property of a sample and is independent of the shape, size and measurement method.

$\sigma f = K\sigma d$

Dissolution test: Dissolution/Purification is used to measure the emission rate of an active substance from a solid measuring form under controlled conditions.

Table no 3: acceptance criteria for dissolution

Stage	Numberused	Acceptancecriteria
S1	6	EachunitisnotlessthanQ*+5%S
S2	6	Averageof12units(S1+S2)isequaltoorgreater than Q*andnounitislessthanQ*-15%
S3	12	Average of 24 units (S1+S2+S3) is equal to or greaterthan Q*andnotmorethan2unitsarelessthanQ*-15

Q*=amount of dissolved active ingredient

VITAMIN D3 ESTIMATION (By H.P.L.C.):

Standard preparation:

1.Standard Vitamin D3solution:

Weigh accurately about 50 mg of coated Vitamin D3 standard (having a potency of about 500 IU/mg) into a 100 ml volumetric flask. Sonicate 75 ml of menthol for 5 min. Filter through Whatman no. 41 to remove insoluble coating material and use the filtrate for standard injection.

2.Sample preparation:

Crush and finely powder 10 tablets. Transfer accurately about 5 tablet weight of finely crushed powder to a 250 ml stoppered conical flask. Then extract with 70 ml ether by placing in an ultrasonic bath for 5 minutes. Pass the ether layer through Whatman no. 41 filter paper, collecting the filtrate in a 250 ml conical flask. Repeat the procedure for two more times and evaporate the combined ether extracts on a water-bath (temperature not exceeding 70º C) to about 20 ml volume. Evaporate to complete dryness using nitrogen purge. Reconstitute by addition of 10 ml methanol to the flask and filter through a small cone of Whatman no. 41. Collect the filtrate in a 10 ml stoppered test tube for injection of sample.Inject separately 20 microliter each of standard and sample preparation and note the area corresponding to Vitamin D_3

HPLC conditions:

Column: Phenomenex RP 18, 30 cms X 4.6 mm i.d.

Mobile Phase: Acetonitrile : Methanol : Water [75 : 20 : 5] % v/v

Wavelength: 267 nm

Flow rate: 1.5 ml / min.

Injection volume: 20 micro litre Calculation:

Vitamin D3IU/tablet =Aspl X Cstd X W X % potency / Astd X Cspl X 100

Where,

Aspl&Astd are the area of Vitamin D3 in sample and standard respectively.

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Cspl&Cstd are the concentration of Vitamin D3 in sample and standard respectively W is the average weight of tablet.

III. RESULT AND DISCUSSION:

Various parameters are calculated in the preparation procedure of the tablets like bulk density, tapped density, carr's index, hausner's ratio, angle of repose. These values are calculated by the trials process and all the values are found to be within the limits.

Evaluation result of powder blend

1. Bulk Density (g/ml): 0.72
2. Tapped Density (g/cc): 0.83
3. Carr's Index (%): 11.50
4. Hausner's Ratio: 1.17
5. Angle of Repose: 30.43

Table no 4: Evaluation of tablet

Sr. No.	Tests	Specifications	Results Batch(X)
1	Appearance	LightOrangecoloreduncoated tabletsplainonbothsides	Complies
2	Flavour	Mild&PleasantOrangeflavor	Complies
3	Averageweight	1.130–1.180g	1.150g
4	Uniformityofweight	ComplieswithI.P.	Complies
5	LossonDrying	Nmt1.5%w/w	1.36%w/w
6	Hardness	NLT8.00kg/cm^2	11kg/cm^2
7	Thickness	3.4–3.8mm (3.6±0.2mm)	3.65mm
8	Friability	NMT1.5000%w/w	0.497%w/w
9	Calciumcontent	175.00mg/tab–185.00mg/tab	176.23mg/tab
10	Magnesiumcontent	20.00mg/tab–25.00mg/tab	21.98mg/tab
11	Cholecalciferol content-VitaminD3	350.00IU/tab–375IU/tab	370.89IU/tab
12	Identificationfor sunsetyellow	Positive	Complies

Granulation is basically a size enlargement process in which smaller particles are converted into agglomerates which are physically stronger and larger in size.Granulation is broadly classified as Wet granulation and Dry granulation. The actual effectiveness of granulation processes depends on the following properties

- Particle size of the drug and excipients
- Type of binder (less or more)
- Wet massing time (less or more)
- Amount of shear applied

Drying time (hydrate formation and polymorphism)

Wet granulation

In wet granulation process binder is used in the form of liquid which gives an agglomerate form to the powder mixture

Important steps

- Mixing of the drugs and excipients Preparation of binder solution
- Mixing of binder solution with powder mixture to form wet mass
- Coarse screening of wet mass using a suitable sieve
- Drying of moist granules

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- Screening of dried granules through suitable sieve
- Mixing of dried granules with disintegrants, glidant, lubricants, color, and flavor

Limitations

- Disadvantages include cost, labor, time, equipment, energy and space requirements
- Loss of material during various stages of manufacturing.
- Stability concern for moisture sensitive drugs
- Multiple processing steps and complexity make validation and controls difficult Binder used in the form of liquid requires to be adjusted properly for corrective wetting of powder mass, as over-wetting of powder mass will provide the harder granules and under-wetting will provide too soft granules which are friable. Aqueous solutions will always have the advantage for safety as compared to solvent-based systems but these may not be completely suitable for drugs which are prone to hydrolysis.

IV. CONCLUSION:

Different formulations for calcium with Vitamin D3 were developed using different strategies of optimize the binder concentration which will give desired hardness and further acceptable physical parameters.Compression force was also challenged during trial batches manufacturing.Trial Batch B1 with optimized quantity of Binder (Maize Starch) and with Dextrose and Mannitol as diluents was successful with respect to desired hardness of the tablets on given set of punches design.The scale up batch was taken similar to Batch B1 and the same was subjected to stability studies. The stability analysis was performed for accelerated conditions of temperature and humidity and also at real time conditions. The results for Physical and chemical parameters were well within the requirements of set specifications.The selected excipients were also compatible within the final formulation with respect to stability and also physical parameters of the final tablets. The final formulation was also compared with market samples for Mouth feel, Chew ability Index and other physical aspects. This Final formulation was found to be more appealing with respect to taste, mouth feel and chewability index.The final formulation was also satisfactory with respect to simplified manufacturing process which will have impact on cost also.

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