Development of Directly Compressible Granules using Calcium Carbonate for Drug Delivery

Chandana Priya E.[1], Kalashanti R. Pyngrope[2], Mukul Kishorkuma K.[3], Guru Gowtham Sri Harsha S.[4],*Shwetha K.[5], Deveshwaran R.[6] and Bharath S.[7]

*Corresponding Author E-mail: shwetha.ps.ph@msruas.ac.in

Contributors:

[1,2,3,4] Post Graduate Students,
[5]Assistant Professor,
[6]Associate Professor, Head DDDC
[7] Head and Professor,
Department of Pharmaceutics, Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, Gnanagangothri Campus, New BEL Road, M S R Nagar, Bangalore
Karnataka, India - 560 054

Abstract

Objective: The present work emphasises on development of Directly Compressible (DC) calcium carbonate based pharmaceutical excipients to aid in faster the manufacturing process. **Methodology:** DC granules were prepared using different ratios of Calcium Carbonate (CC) and diluents such as dextrose and mannitol in varying ratio 60:40, 70:30, 80:20 and 90:10 without and with Poly Vinyl Pyrolidone (PVP) as binder in concentration of 0.5 and 5%. Prepared granules were evaluated for pre-compression parameters. Domperidone, an anti-emetics agent was chosen as a model drug. Domperidone was blended with these directly compressible excipients and compressed into tablets. Prepared tablets were subjected for weight variation studies, hardness, friability and assay, *in-vitro* disintegration and *in-vitro* dissolution studies. **Results:** Prepared formulations showed better flow properties when compared to Calcium Carbonate alone. Tablets were subjected to post compression evaluations and the results shown were acceptable. The formulations showed 80% drug release within 30mins. **Conclusion:** Thus DC granules for direct compression method was formulated successfully which can be used for routine production with lesser manufacturing unit operation process, cost and time.

Key Words: *Calcium Carbonate, Dextrose, Directly Compressible Granules, Pharmaceutical Aid*

1. INTRODUCTION

Tablets are the most commonly used dosage form and 70% of the total medicines are dispensed in the form of tablet due to their ease of administration, transportation, stability, low production cost and patient compliance. They can be prepared either by granulation technique or direct compression technique.[1&2]

Direct compression technique involves compressing of tablets directly from powdered materials without changing the physical nature of materials. This method is suitable for crystalline chemicals which are having good compressible and flow properties.

Most of the pharmaceutical manufacturers are opting for direct compression technique because it involves less processing steps, basic validation, elimination of heat and moisture, economy, and improved the drug stability when compared to granulation technique[3]. The present work emphasizes on development of Directly Compressible (DC) calcium carbonate based pharmaceutical excipients to aid in faster the manufacturing process.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Domperiodone was procured from yarrow chem. Products, Mumbai. Calcium carbonate was procured from Central Drug House Pvt. Ltd. Mumbai. Dextrose and mannitol was procured from Rankem laboratory reagent, Delhi. All other chemicals and reagents used were of analytical grade unless otherwise indicated.

2.2 Preparation of Directly Compressible (DC) Granules

DC calcium carbonate granules were prepared by wet granulation technique using varying

concentrations of diluents such as dextrose and mannitol. PVP 0.5% and 5% concentrations and distilled water were used as binder/granulating agent in the preparation. Calcium carbonate to diluents was taken in varying ratio such as 60:40, 70:30, 80:20 and 90:10. Formulation table of directly compressible calcium carbonate granules are shown in Table 1.

Table 1. Formulation of granules using calcium carbonate and dextrose

Formulation Code	Calcium Carbonate (%)	Dextrose (%)	Binder
FD1	60	40	Water
FD2	70	30	
FD3	80	20	
FD4	90	10	
FD5	60	40	0.5% PVP
FD6	70	30	
FD7	80	20	
FD8	90	10	
FD9	60	40	5% PVP
FD10	70	30	
FD11	80	20	
FD12	90	10	

Calcium carbonate and selected diluent were weighted in varying ratios and mixed. Powder blend was granulated using chosen binder. The wet mass was passed through sieve no.12 and the granules were dried at 45°C for 30 - 40 minutes until they completely dried. The dried granules were subjected to dry screening by passing through sieve number 16. Resized granules were evaluated for their preformulation characteristics.

2.3 Granular Analysis of Pharmaceutical Excipients

2.3.1 Bulk Density (g/cc)

The apparent bulk density was determined by three tap method, in which weighed quantity of sample blend was transferred into 100ml graduated cylinder and the cylinder was dropped onto a hard wooden surface 3times from a height of 2.5cm at an interval of 2sec. Then the bulk density was determined using following formula

$$Bulk\ density = \frac{Weight\ of\ sample\ blend}{Bulk\ volume}$$

2.3.2 Tapped Density (g/cc)

The weighed quantity of sample blend was taken in a graduated cylinder and the cylinder was allowed to tap for 100times onto a hard wooden surface from a height of 2.5cm. Then the tapped density was determined using following formula

$$Tapped\ density = \frac{Weight\ of\ sample\ blend}{Tapped\ volume}$$

2.3.3 Carr's Index or Compressibility (%)

Carr's index is directly related to flow rate, cohesiveness and particle size and was calculated using following equation

$$Carr's\ Index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density}$$

2.3.4 Hausner's Ratio

It is the ratio of tapped density to bulk density. Hausner' ratio gives relationship between interparticle friction and was calculated using following equation

$$Hausner's\ Ratio = \frac{Tapped\ density}{Bulk\ density}$$

2.3.5 Angle of Repose (θ)

Static angle of repose of the granules were determined by the fixed funnel method. The accurately weighed granules were taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose were calculated using the following equation

$$Tan\ \theta = \frac{h}{r}$$

$$\theta = \tan^{-1}\frac{h}{r}$$

Where 'h' is the height of the cone
'r' is the radius of the cone

2.4 Characterization of Pharmaceutical Excipients

2.4.1 Determination of Melting Point

One end of a capillary tube was closed by holding at the end of the bunsen flame and was rotated continuously until it was sealed. The drug was powdered in a mortar. The compound was introduced by thrusting the open end of the tube into a small heap of the powered drug and tapping the sealed end of the tube. The capillary tube was attached to the lower end of the thermometer so that its lower end was in direct contact and in the same level with the bulb of the thermometer. Heat was supplied in a controlledway so that the temperature does not rise more than two degrees Celsius and alter one degree Celsius perminute until the substance melts. When the sample was completely melted, temperature was noted down. Average of triplicate readings was recorded. The observed melting point was compared with the melting point given in the literature.

2.4.2 Fourier Transform Infrared (FTIR) Spectroscopy

Fourier Transform Infrared Spectroscopy (FT-IR) was used to identify the chemical structure of all excipientsand their compatibility. The FTIR spectra were measured with a (FTIR 8400 S, Shimadzu) in the region of 4000–400 cm^{-1}.

2.4.3 Phase Solubility Studies

Phase Solubility studies was conducted by measuring the amount of drug dissolved in distilled water using UV spectrophotometer.

2.4.4 Standard Calibration Curve of Domperidone

From the standard solution (50µg/ml) aliquots of 1, 2, 3, 4, 5 & 6 ml were withdrawn and further diluted to 10ml with 0.1N HCl to obtain a concentration range of 5 to 30µg/ml. The absorbance of the solution was measured at 284 nm using double beam UV-Visible spectrophotometer (UV-1700, Shimadzu, Japan). The readings were performed in triplicate to validate the calibration curve.

2.5 Formulation of Domperidone Tablets

All the prepared granules were subjected to preformulation studies. Based on the preformulation evaluations some of the formulations were selected to punch into tablets. Known quantity of drug and granules were taken and blended slightly. The directly compressible excipients were used in the proportion of 55% in the tablet. The tablet weight was fixed as 200 mg of which 20mg was drug and 180mg was excipients. This blend was mixed well and compressed in a Rimek tablet machine using 6mm punch die. Formulation of Domperidone tablets are shown in the Table 2.

Table 2. Formulation of Domperidone tablets

Selected formulations ↓	Domperidone (mg)	Granules (mg)	Final tablet weight (mg)
FD1	20	180	200
FD8	20	180	200
FD12	20	180	200

2.6 Evaluation of Post Compression Studies

2.6.1 Weight Variation Test

To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared

with average value to find the deviation in weight. Then the percentage of weight variation of each tablet was determined by using following formula:

$$\%\ weight\ variation = \left(\frac{Avg.wt - Individual\ wt}{Avg.wt}\right) X100$$

2.6.2 Hardness (Kg/cm^2)

It was determined using the Pfizer hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm2. Following which constant force was applied by rotating the knob until the tablet was fractured

2.6.3 Friability (%)

The friability of tablets was determined using Friabilator. Ten tablets were initially weighed (W_1) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 min, or alternatively was run up to 100 revolutions. The tablets were weighed again (W_2) and the % friability was calculated using given formula. A loss of less than 1% in weight is generally considered acceptable

$$\%\ friability = \left(\frac{W1 - W2}{W1}\right) X100$$

Where,

W_1= initial weight of 10 tablets

W_2= Weight of 10 tablets after 100 revolutions

2.6.4 *In Vitro* Disintegration Time (min)

The disintegration for all formulations was carried out using tablet disintegration test apparatus. Three tablets were placed separately in each tube of disintegration test apparatus and discs were placed on them. The water was maintained at a temperature of 37°C ± 2°C and time taken for each tablet to break up into small particles and pass out through the mesh was noted

2.6.5 Tablet Assay

Ten tablets were accurately weighed and finely powdered. A weight equivalent to 200mg of powder ($CaCo_3$ + Drug, $CaCo_3$ + Dextrose + Drug) was transferred to a 100ml volumetric flask for dissolve using 0.1N HCl. In that 20mg of powder was dissolved in 20ml of 0.1N HCl and the solution was filtered. From this, 5ml of solution was transferred to 100ml volumetric flask and the volume was made up with 0.1N HCl. The drug content was determined spectrophotometrically at 284nm

2.6.6 *In Vitro* Dissolution Studies

In vitro dissolution studies were performed for all the tablet formulations by using United States Pharmacopeia Dissolution Apparatus Type-II, using 900ml of 0.1 N HCl at 50rpm and temperature was maintained at 37 ± 0.5 °C. Samples (5ml) were withdrawn at pre determined intervals over 15 min using a pipette and 5 mL of fresh dissolution medium was replaced after each sampling in order to maintain sink condition The collected samples were analyzed by UV spectrophotometer at 284 nm

3. RESULTS AND DISCUSSION

3.1 Preparation of Directly Compressible (DC) Granules

DC calcium carbonate granules were prepared by a method as described in section 2.2 and subjected to granular analysis. The results are shown in Table 3.

3.2 Granular Analysis of Pharmaceutical Excipients

3.2.1 Bulk Density (g/cc):

The bulk densities of all the formulations were ranged between 0.66-0.83 g/cc and indicate that it has good compressibility property.

3.2.2 Tapped Density (g/cc)

The tapped densities of all the formulations were ranged between 0.66-1.0 g/cc and indicate to have good compressibility property.

3.2.3 Carr's Index or Compressibility (%)

The Carr's Compressibility index value was between the ranged between 5-17.77%. The value below 15% indicates good flow property and values above 25% indicates poor flow ability.

Table 3. Pre-formulation Analysis of calcium carbonate and dextrose granules

Formulation code	Granular Analysis				
	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner's ratio (%)	Angle of repose (°)
FD1	0.74	0.83	10.84	1.12	19.67
FD2	0.66	0.71	7.04	1.07	20.38
FD3	0.76	0.86	11.62	1.13	21.57
FD4	0.76	0.83	8.43	1.09	22.99
FD5	0.66	0.76	13.15	1.15	18.07
FD6	0.76	0.83	8.43	1.09	16.45
FD7	0.86	1	14	1.16	20.90
FD8	0.74	0.90	17.77	1.21	19.36
FD9	0.62	0.66	7.04	1.06	23.28
FD10	0.60	0.66	6.57	1.1	20.55
FD11	0.71	0.74	5	1.04	22.63
FD12	0.83	0.83	11.11	1	18.74

3.2.4 Hausner's Ratio

The values greater than 1.25 indicates poor flow (33% Carr index) and values less than 1.25 indicates good flow properties (20% Carr index). If it is between 1.25-1.5 addition of any glidant normally improves the flow property. In this study the Hausner's ratio values were found to be less than 1.25 hence, indicating that all the granules are having good flow property.

3.2.5 Angle of Repose (θ)

The angle of repose was found to be between 18.07-23.28°. Thereby, confirming that the prepared granules are showing good flow property

3.3 Formulation of Domperidone Tablets

Based on the preformulation evaluations some of the formulations were selected to punch into tablets. Punched tablets were subjected to post compression analysis

3.4 Characterization of Pharmaceutical Excipients

3.4.1 Determination of Melting Point

From the obtained data, it can be concluded that experimental results complies with the IP standards and reference data given in the literature. Thus, indicating the drug and excipients are of standard quality.

3.4.2 Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR study was performed (Figure 1) in order to find out the compatibility between the drug and excipients such as Calcium carbonate, Dextrose. FTIR values were interpreted. According to the values obtained, it has been found that all the selected ingredients are compatible with each other.

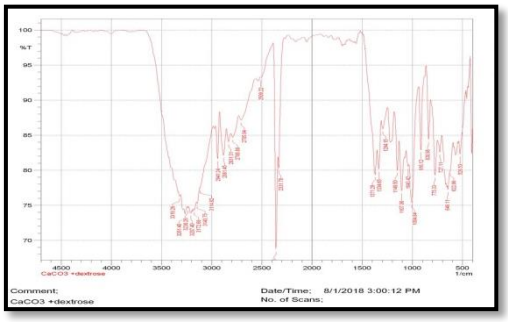

Figure 1: FTIR studies (Drug+Calcium carbonate+dextrose)

3.4.3 Phase Solubility Studies

Phase Solubility studies was conducted by measuring the amount of drug dissolved in distilled water using UV spectrophotometer and their values are mention in the Table 4.

Table 4. Determination of Phase Solubility studies

Sample	Absorbance			Avg. Absorbance	Solubility (µg/ml)
	Trial 1	Trial 2	Trial 3		
Drug	0.235	0.239	0.236	0.237	8.63
FD1 + Drug	0.332	0.334	0.329	0.454	16.55
FD8 + Drug	0.546	0.451	0.454	0.332	12.10
FD12 + Drug	0.301	0.305	0.302	0.303	11.04

3.5 Evaluation of Post Compression Studies

3.5.1 Weight Variation Test

The weight of all tablet formulation ranged between 190-220 mg. As the weight of tablet was 200mg, the obtained weight variation range was ±6.53%which is within the acceptable weight variation range. Hence, it indicated that the tablets are within the pharmacopoeial limits.

3.5.2 Hardness (Kg/Cm^2)

The hardness of all formulations was determined and was found to be in the range of 0.08-4.12 kg/cm-1 indicating that the structural integrity of the tablets are acceptable for handling and exposure to storage and transportation condition.

3.5.3 Friability (%)

The percentage friability of all the formulation was found to be not more than 1%, which is within the pharmacopeial limit of <1%. The results of friability indicated that the tablets were mechanically stable

3.5.4 *In Vitro* Disintegration Time (Min)

The disintegration for selected formulations was carried out using tablet disintegration test apparatus and all tablets were disintegrated within 15mins complying with pharmacopoeial limits

3.5.5 Tablet Assay

Drug content uniformity of the formulation was determined according to the procedure described in 4.7. Drug content was analyzed by UV-Visible spectrophotometer. The percentage drug content was between 97.30% – 99.67%.as shown in Table 5

Table 5. Post-Compression Analysis

Post compression Analysis	Formulation code		
	FD1	FD8	FD12
Weight Variation (mg)	211	217	219
Friability (%)	0.44	1.33	0.84
Hardness (Kg/Cm2)	3.08	0.4	0.08
Disintegration Time (mins.)	14	10	8
Percentage Drug content (%)	97.3	98.58	97.81

3.5.6 *In Vitro* Dissolution Studies

In-vitro dissolution studies was performed selected formulation by using USP Dissolution apparatus – type II, rotating paddle method with 900 ml of distilled water at 50 rpm. The dissolution studies were carried out for 70mins. The results of *In-vitro* drug release data are given below.

Table 6. *In vitro* dissolution studies

Time (Mins.)	Percentage drug release		
	FD1	FD8	FD12
0	0.00	0.00	0.00
10	65.59	41.66	43.25
20	75.67	58.34	55.50
30	80.59	63.31	67.40
40	86.41	71.29	74.64
50	90.16	79.00	77.22
60	95.72	85.84	82.77
70	100.02	94.63	87.89

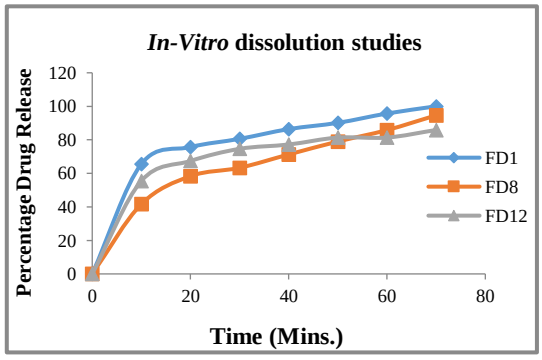

Fig.2 *In vitro* dissolution studies

The drug formulation containing the calcium carbonate and dextrose combination was found to produces pronounced enhancement in the dissolution rate. According to release studies, FD1 formulation shows the faster rate of dissolution when compared to others.

4. CONCLUSION

The main objective of the proposed work was to formulate pharmaceutical excipients which can be used for direct compression of tablets. In the proposed investigation, DC granules were prepared by wet granulation technique using different combinations of calcium carbonate and dextrose in ratios 60:40, 70:30, 80:20 and 90:10 using poly vinyl pyrolidone as binder in concentration of 0.5 and 5% and distilled water as binding agent. Preformulation studies such as FT-IR studies, melting point studies were conducted to analyze the compatibility and melting point determination of all the excipients. DC granules were evaluated for pre-compression parameters and all the formulations showed better flow properties when compared with calcium carbonate alone

Based on pre-compression evaluation results selected ratios of granules - FD1, FD8, FD12 were punched into tablets. Defined amount of the drug was blended with the granules and 200mg tablets were punched using single punch tablet machine. Formulated tablets were evaluated for post compression parameters and results were found to be satisfactory. The drug content of each of the formulations was carried out and was found to be in the range between 97.30% – 99.67%. These formulations were evaluated for *In vitro* disintegration studies and results showed disintegration within 15 min. that comply with the IP specifications. These formulations were also evaluated for *In vitro* the dissolution study and FD1 showed more than 90% of the drug was released in 60mins. The overall study concludes that FD1 formulation was found to be better DC granules based on all evaluation parameters and can be used as directly compressible excipients thereby minimizing the manufacturing processes and cost involved in the production.

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