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Research Article

DESIGN DEVELOPMENT AND FABRICATION OF NOVEL PLATFORM FOR ORODISPERSIBL TABLETS

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ABSTRACT

Evolution of existing drug molecules from a conventional form to novel delivery system can significantly improve its performances in term of patient compliance, safety, and efficacy. These days drug delivery companies are engaged in the development of multiple platform technologies to get competitive advantage extend patent life and increase market share of their products. In the present study an attempt has been made to develop a platform for orodispersible tablet. Fluid bed granulation technique was utilized to prepare granules using various concentrations of fillers, superdisintegrants, wetting agents, solubilizer and sweetener. The prepared blend was evaluated for pre compression parameters such as granule size, loss on drying, bulk density, compressibility index and angle of repose. The prepared batches of tablets was evaluated for the weight variation, mechanical strength, attrition resistance test, friability, fracture resistance test,crusing strength and diameter, disintegration test water absorption test and wetting time. Among the formulation contain mannitol as filler and Crospovidone 15mg/tab as superdisintegrants with low substituted hydroxypropyl cellulose LH 11 4 mg/tablet and sucralose 3 mg/tab as sweetener show best wetting and disintegration time with minimal mechanical properties.

KEYWORDS: *Platform technology, Mannitol; Orodispersible tablets; Fluid bed granulation.*

INTRODUCTION

A solid dosage form that dissolves or disintegrates rapidly in the oral cavity, resulting in a solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form [1]. These are also known as fastdissolving, rapid-dissolve, rapid-melt, mouth-dissolving, and quick-disintegrating tablets. Some of the advantages of oral fast-dispersing dosage forms include administration to patients who have difficulty in swallowing, more rapid drug absorption, patient convenience, and compliance [2-3].

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These dosage forms are particularly helpful for pediatric and geriatric patients who have difficulty in swallowing (dysphagia) and also for traveling patients, for whom water may not be easily or readily accessible [4-5]. The technologies, some of which have been successfully marketed, mainly utilize conventional tableting processes with slight modification, freeze-drying methods, and floss-formation techniques for manufacturing [7- 8].

Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety, and improved patient compliance. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the development of new drug delivery systems [9-10] Today, drug delivery companies are engaged in the development of multiple platform technologies for controlled release, delivery of large molecules, liposome, taste-masking, oral fast dispersing dosage forms,

technology for insoluble drugs, and delivery of drugs through intranasal, pulmonary, transdermals, vaginal, colon and transmucosal routes. Platform technology can work as a common base comprising of polymeric system with release modulator and able to accommodate the drugs with common physicochemical and therapeutic properties with minimal changes. A platform drug delivery system allows a company to use one drug delivery system for several drugs. This builds an internal base of experience, which can shorten development, and scale-up times, improve quality control, and better utilize manufacturing capabilities. The utility of system is directly related to its complexity [11-12]. It the developed platform technology should have properties such as tailored to suit the drug, release pattern, Targeting, Dosing frequency, Improved plasma levels, Low cost, Manufacturing ease, Low risk inactive ingredients, Intellectual property and Life-cycle management.

Fluidised bed granulation is a popular process to produce granules aiming at improving powder flowability, mechanical resistance and physicochemical properties of drugs in the pharmaceutical industry. In fluidised bed granulation, the powder mixtures is fluidised by a flow of air injected upwards through the bottom distributor of the granulator and the binding solution is sprayed using one or more nozzles above the powder bed in the direction opposite to the air flow [13-14].

Using a systematic screening approach allows the assessment and to identify the most promising molecules that match predefined stability criteria, as specified in the target molecule profile. All molecules that match with these criteria would show comparable characteristics and become next-in-class molecules, which can be developed by using a technology platform using a standardized formulation e.g., composition, excipients, and packaging components as well as standardized process equipment and unit operations. Such a systematic approach to use prior knowledge can significantly reduce the development efforts needed to initiate continuous improvement of the product and process understanding with every molecule of the respective class. Finally, an additional benefit is the increased predictability and accuracy of development timelines allowing synchronization of multiple projects more efficiently.

MATERIALS AND METHOD

Materials:

Mannitol (Perlitol SD 200) was procured from Roquette, Signet Chemical Corporation Mumbai India, Dibasic calcium Phosphate was procured from Sudeep pharma ltd, Baroda, India, Lactose Monohydrate was procured from Schreiber Dynamix Dairies ltd India, Crospovidone XL was procured from ISP sales Calvert City UK, Low substituted hydroxypropyl cellulose (LH 11) was procured from ShinEstu, Joetsu- shi, Japan, Citric acid Monohydrate was procured from Amijal Chemicals, Ankleshwar India. Sucralose was procured from JK Sucralose Inc China, Povidone (PVPK 30) was procured from BASF India, Colloidal silicon dioxide was procured from Cabot Sanmar Mumbai India, and Magnesium stearate was procured from Sunshine organic Mumbai India. Materials and Excipients used in preparing tablet were of IP grades.

Method:

Preparation of Dry Mix:

The granules were produced in the (UFBM-1/05Umang fluid bed Multiple 1 Umang Pharamtech, Germany). The compositions were: Mannitol (Perlitol SD 200 mesh, Crospovidone (Polyplasdone XL), L-Hydroxy propyl cellulose (LH-11) Sifted the above material through 40# sieve (ASTM)

Preparation of Binder solution:

The binder solution was prepared by mixing the Povidone (PVP K30) with purified water after mixing for 5–10 min, citric acid monohydrate, sucralose and colour sunset yellow supra FCF was added and solution was mixed for 15 min.

Fluid Bed Granulation:

The above sifted dry mix material was placed in the fluid bed and were mixed by using air, conditioned for the specific run at a flow rate at 500 Nm3/h, for 5–6 min. Set the Process parameter (Table No 2) and after achieving Bed temperature 40°C, the binder solution was sprayed on the fluidizing powder bed using a peristaltic pump (adjusting the spray rate, using a micro

motion system). The spraying process was carried out according to the settings of the process variables for the specific run. Spraying was continued until all the binder solution was used and afterwards 0.5 l of water was sprayed in order to rinse the tubes. The wetted granules were dried by fluidizing them with an inlet air temperature of 75°C. The drying cycle was terminated when an outlet air temperature of 35°C was reached, indicating that the granules were dried sufficiently. After this cycle, a approximate 1 g sample was taken from the top, middle and the bottom of the powder bed and loss on drying (LOD) was checked. Dried granules passed through 20 # sieve. Sized dried granules were stored in an airtight plastic bag for the determination of the granule properties. The dried granule was lubricated with 1 % magnesium stearate and tablets was compressed using single rotary compression machine.

Table 1: Process Parameters for fluid bed granulation

Sr.No	*Parameter*	*Set Values*
1.0	Inlet Temperature	$60^0C \pm 5^0C$
2.0	Bed Temperature	40^0C
3.0	Outlet air Temperature	42^0C
4.0	Inlet air Pressure	1 to 2
5.0	Spraying nozzle Diameter	1.2mm
6.0	Liquid Spray nozzle Pressure	1-3 bar
7.0	Filter Air purging Pressure	1-3bar
8.0	Peristaltic Pump RPM	1 to 2

PHYSICAL CHARACTERISTICS OF THE GRANULES

Granule size:

The granule size distribution was measured according to the methods described by Rambali et al [14]. A set of sieves (20, 40, 60, 80,100,150,200 mesh) in combination with the Octagoan Digitals 4417-01 sieve shaker (Lombard RD London England) were used for this analysis. A 100-g granule sample was transferred to the pre-weighed sieves and shaken at amplitude of 1.5 mm for 5 min. The sieves were then re-weighed to determine the weight fraction of granules retained on each sieve. These weights were converted in mass percentage. The geometric mean granule size was calculated from these mass fractions according to Fonner et al [15].

Loss on drying:

A 3 g sample of the granules was dried at 105°C for 3 min in a Mettler HG63 (Mettler- Toledo, Switzerland), immediately after the granulation process. This time setting was sufficient to reach a constant mass. The loss in weight after 3 min gave the loss on drying (LOD in %, w/w).

Hausner index:

The Hausner index is the ratio of the bulk density and the tapped density of the granules. A100-g granule sample was weighed and poured into a graduated 250-ml cylinder. The volume of the granules in the cylinder was read and the bulk density was determined in g per ml. The cylinder was tapped 100 times on a tapping device (Bulk density Apparatus QE 169, Quality Instrument and Equipments Kudal Maharashtra) and the tapped density was determined in g per ml. The tap settings were sufficient to reach a constant volume [21].

Angle of repose:

The angle of repose was determined by an angle of repose tester (Janssen Pharmaceutica, Beerse, Belgium). A 145-ml granule sample was allowed to flow through a 4.6-cm orifice. The granules formed a pile on a 5.0-cm circular platform. The instrument measured the height of this granule

pile. The arctangent of the height and the radius of the platform determined the angle of repose [21].

PHYSICAL CHARACTERISTICS OF TABLETS

Weight uniformity:

Weight uniformity is an important criterion for evaluation of tablets within a batch as it provides an indication of the content uniformity of that batch. Therefore it can be seen as an indication of the efficiency of mixing of an API and the excipients that make up a formulation. If the tablets tested exceed the limits of weight variation as set out by the United States Pharmacopoeia (USP). The individual weights of 10 randomly selected tablets were measured using a Sartorius BSA 224S-Cw top-loading balance (Sartorius AG, Weender Landstrasse 94-108 Gottingen Germany) that had a sensitivity of 0.1mg.

Mechanical strength of tablets:

The mechanical strength of a tablet is an important characteristic that must be measured as it provides a formulation scientist with an indication of the extent to which a tablet can withstand the mechanical shock that it will be exposed to during manufacture, packaging and transportation. The most commonly used methods for testing mechanical strength are attrition-resistance or fracture resistance methods [16].

Attrition-Resistance Tests:

Attrition-resistance test methods, mimic forces to which tablets is subjected during handling through production to administration of a tablet to a patient and are also referred to as friability tests [16]. During friability testing, tablets are subject to repeated abrasion through rotation for a specified number of cycles in a friability tester. The tablets are held in a transparent drum containing a blade that carries tablets to a central height that permits them to fall as the drum rotates [18]. The movement of the drum and tablets results not only in continuously falling from a set, small height but that they also rub against each other. The tablets are dusted and weighed prior to and following testing and the percent lost from the original weight is calculated. A friability of less than 1% is considered acceptable, whereas friability values > 1% are cause for batch rejection.

The friability of the tablets was determined using a Model TA3R friabilator (Automated Tablets Friabilator EF-1W Electro labs; Mumbai, Maharashtra). Twenty tablets were randomly selected, de-dusted and weighed using a Sartorius BSA 224 S-CW top-loading balance (Sartorius AG, Weender Landstrasse 94-108 Gottingen Germany). The tablets were tumbled at a rate of 25 rpm for 4 minutes or 100 drop cycles and then removed from the friabilator, de-dusted and reweighed. The friability of the tablet was calculated using Equation 1.

$$\% \text{ Friability } (F_r) = \frac{W_a - W_b}{W_b} X\ 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ 1$$

Where, W_a = weight prior to testing W_b = weight after testing F_r = friability

Fracture-Resistance Tests:

Analysis of the fracture resistance of tablets involves the application of a load to the tablet and the determination of the force needed to fracture or break the tablet along the diameter of the compact [18]. A schematic representation of the tensile strength test is shown in Figure 1

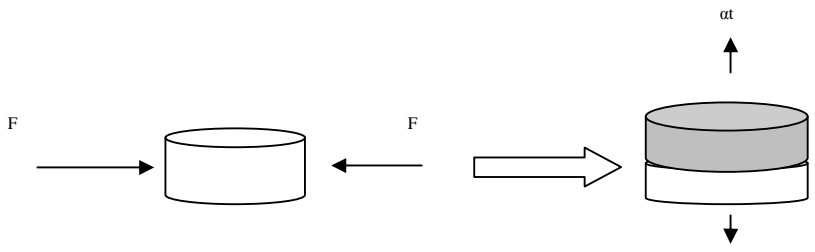

Figure 1 Diagram of the tensile strength of a tablet

The tensile strength of the manufactured tablets was calculated using Equation 2.

$$\alpha o = \frac{2F}{\pi dt} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots 2$$

Where, σo = tensile strength (MPa) F = crushing strength (N) d = tablet diameter (mm) T = tablet thickness (mm)

Crushing strength and diameter:

The crushing strength of the tablet is defined as the force that is applied across the diameter of a tablet in order to break the tablet. The harder the tablet the greater resistance the tablet exhibits to chipping, abrasion or breakage when stored or handled prior to use [17].

The crushing strength and diameter of the tablets were measured using a Model PTB 411 Hardness Tester (PharmaTest AG®, Hainburg, Germany). Each tablet was placed in the tester and a crushing force applied to the tablet and the crushing strength and diameter were measured simultaneously.

Disintegration test:

The disintegration time is a crucial characteristic that must be monitored during the development of a ODT, due to the fact that the formulation needs to disintegrate rapidly to exert a therapeutic effect. The disintegration time of tablets was measured using a Model ED-2L tablet disintegration apparatus (Electro lab Mumbai India). Six tablets were randomly selected from each batch and a single tablet was placed into separate cylinders of the basket-rack and covered with a disc. The basket was set to oscillate vertically at a speed of 30 oscillations per minute in a beaker containing 800ml of distilled water that was maintained at 37 ± 0.2°C. The time for disintegration of each tablet was recorded and noted at the completion of disintegration testing

Water absorption ratio studies:

The water absorption ratio is usually investigated in the development of ODT to provide an understanding of the capacity of the disintegrants included in the formulation to swell and/or wick in the presence of a small amount of water [19].

The most popular method used to determine the water absorption ratio is undertaken by using a piece of tissue paper folded twice and placed on a petri dish containing 6ml buffer solution. The tablet is placed on the tissue paper and allowed to completely wet. The tablet is then removed from the petri dish and weighed. As the tablets disintegrated rapidly after wetting, it was not possible to be move and reweigh the individual units. Therefore a simple approach was to place the tissue paper and petri dish on a tarred scale and then to place the tablet on the petri dish to ascertain the initial weight of the system. Buffer was then added drop wise with a plastic pipette until the tablet was completely wetted. The final weight of the tablet was then established and the water absorption ratio calculated. All studies were performed in triplicate. The water absorption ratio was calculated using Equation 3.

$$\text{Absorption Ratio} = \frac{W_a - W_b}{W_b} X\ 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots 3$$

Where, W_a= weight of the tablet after wetting W_b= weight of the tablet before wetting

Wetting time:

The wetting time of ODT is an important physical characteristic as it provides an indication of the disintegration efficiency of the tablet with faster wetting times implying faster tablet disintegration and more rapid drug release [20]. The wetting time of the tablets (n=3) were determined by folding a piece of tissue paper twice (12cm x 10.75cm) and placing the tissue paper onto a petri dish containing 6ml buffer solution (pH 6.8). The tablet was placed on the tissue paper and the time taken to completely wet the tablet was recorded. All determinations were performed in triplicate.

Table 3: Optimization Formulation Powder Evaluation Parameters

Formulation	Granule size (µm)	% Moisture at 105°C	Bulk density (g/cc)	% CI	Hausner index	Angle of Repose (°)
PF1	354±0.37	2.58	0.52	21.17	1.39	29.48
PF2	344±0.46	3.01	0.50	20.15	1.49	30.15
PF3	379±0.78	3.15	0.48	22.15	1.29	28.98
PF4	472±0.89	1.29	0.66	22.36	1.23	31.25
PF5	479±0.59	1.28	0.67	24.15	1.26	33.26
PF6	489±0.28	1.18	0.62	24.15	1.28	34.15
PF7	253±0.35	1.10	0.57	22.16	1.27	31.05
PF8	245±0.54	1.09	0.54	19.60	1.23	21.56
PF9	259±0.29	0.94	0.51	19.87	1.19	28.28
PF10	399±0.74	2.11	0.78	19.00	1.28	29.65
PF11	381±0.12	2.05	0.74	21.15	1.38	27.19
PF12	402±0.48	1.59	0.71	23.18	1.44	28.64

Table 4: Optimization Formulation Tablets Evaluation Parameters

Formulation	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3	Wetting time (sec) (n=3)	Friability (%) (n=3)	Disintegration time (sec) (n=3)	Tensile strength (MPa) (n=3)	Water Absorption ratio (%) (n=3)
PF1	3.71±0.46	4.2±0.42	54±1.4	0.32±0.47	36±1.2	0.88±0.10	86±1.2
PF2	3.89±0.51	4.2±0.54	41±1.6	0.32±0.51	29±1.5	0.84±0.12	79±1.5
PF3	3.85±0.34	4.5±0.62	35±1.8	0.21±0.24	22±21	0.91±0.21	72±21
PF4	3.75±0.40	4.6±0.34	57±1.9	0.28±0.18	49±2.5	0.95±0.14	89±2.5
PF5	3.78±0.99	4.7±0.49	47±1.4	0.27±0.02	32±2.4	0.97±0.15	82±2.4
PF6	3.79±0.47	3.9±0.77	41±1.7	0.48±0.14	26±3.1	0.80±0.04	76±3.1
PF7	3.80±0.48	4.1±0.50	49±1.8	0.36±0.82	35±1.9	0.84±0.09	85±1.9
PF8	3.91±0.54	4.0±0.96	31±1.9	0.21±0.71	19±2.1	0.79±0.51	95±2.1
PF9	3.74±0.28	3.88±0.76	32±2.1	0.45±0.68	12±1.9	0.80±0.25	92±1.9
PF10	3.90±0.25	3.97±0.47	67±1.8	0.41±0.89	55±3.6	0.79±0.43	85±3.6
PF11	3.92±0.13	4.0±0.58	61±1.8	0.40±0.82	45±2.1	0.79±0.40	85±2.1
PF12	3.90±0.14	3.94±0.66	59±2.1	0.51±0.88	31±1.4	0.78±0.2	91±1.4

RESULTS AND DISCUSSION

Physical properties of the powder blend:

A summary of the properties of the different powder blends that were tested is summarized in Table 3. Batches which made use of microcrystalline cellulose, lactose monohydrate and Dibasic calcium phosphate as the primary diluent exhibited slightly poorer flow properties than other blends, as can be seen from the relatively low angle of repose for Batch PF8 in comparison to the other batches. This is an indicator to potential content uniformity problems. When mannitol was used as the primary diluent, the powder blends exhibited improved flow properties when compared to microcrystalline cellulose, lactose monohydrate and dibasic calcium phosphate.

As can be seen from the data for Batch PF8 the incorporation of a glidant improved the flow properties of the blend further and inclusion of a glidant is most likely necessary to ensure uniformity with regards to the content of API present in the tablets.

The addition of increased or decreased amounts of disintegrant in Batches PF1, 3,4,6,7,9,10 and PF12 did not reduce the flow properties of the blend, suggesting that an increase in the amount of disintegrant to facilitate faster disintegration times should not have a negative impact on the flow very important consideration when formulating dosage forms as large variations in weight may be an indication of poor flow properties of powders and will most likely result in the production of batches of tablets that are not uniform with regards to API content. However since when we formulate low-dose product, weight variation cannot be the only method used to assess content uniformity and other methods such as quantitative determination of the content of API in each tablet must be established using a validated analytical method.

The tablets manufactured with microcrystalline cellulose, lactose monohydrate and Dibasic calcium phosphate showed a large variation in disintegration times and may assay values that exceeded the USP limits of 100±10%. This is likely due to the large particle size of microcrystalline cellulose, lactose monohydrate and dibasic calcium phosphate. Larger particles tend to have better flow properties than smaller particles but when formulated with smaller particle sizes, the different particles may segregate. Segregation of the powder blend may then result in inaccurate filling of dies and lead to the production of tablets that have a large variation in dose within a single batch Mannitol was therefore thought to be a more appropriate diluent as the particle size of mannitol was similar to the other excipients used in the formulation.

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properties of powder blends and should not result in large variations in content uniformity.

Physico-mechanical properties of the tablets:

A summary of the physico-mechanical properties of following testing of all batches manufactured are summarized in Table 4.All tablets that were produced passed the uniformity of weight test as all batches had weight data with relative standard deviations of < 7.5%. Weight variations tests are

All tablet batches conformed to the friability limit of 1% despite exhibiting relatively low hardness, that is a required feature of MDT. These results indicated that the tablets were mechanically strong enough to withstand shock but not excessively hard so as to result in increased disintegration times. The water absorption ratio is an important characteristic that needs to be investigated in the development of an MDT formulation as it provides a relatively good indication of the speed of disintegration. The data produced in these studies suggest that there is an inverse relationship between the water absorption ratio and the disintegration time for these tablets, as an increase in the disintegrant concentration led to an increase in the water absorption ratio. Since the water absorption ratio is indicative of the time for disintegration it can be inferred that an increase in disintegrant concentration will result in an increase in the water absorption ratio and ultimately a decrease in disintegration times. An inverse relationship was noted for wetting and in vitro dispersion times and the concentration of the disintegrant and it was revealed that increased disintegrant concentrations shortened the wetting and dispersion times for these products. The short disintegration time is a necessary and desirable property of orodispersible tablets and therefore an important factor that needs to be monitored in the development of an appropriate formulation

Table 2: Optimization of Platform Formulation

Batch Code → / Ingredients	PF1 (mg/tab)	PF2 (mg/tab)	PF3 (mg/tab)	PF4 (mg/tab)	PF5 (mg/tab)	PF6 (mg/tab)	PF7 (mg/tab)	PF8 (mg/tab)	PF9 (mg/tab)	PF10 (mg/tab)	PF11 (mg/tab)	PF12 (mg/tab)
Microcrystalline Cellulose PH102	158.65	148.30	137.95	--------	--------	--------	--------	--------	--------	--------	--------	--------
Lactose Monohydrate	--------	--------	--------	158.65	148.30	137.95	--------	--------	--------	--------	--------	--------
Mannitol (Perlitol SD 200)	--------	--------	--------	--------	--------	--------	158.65	148.30	137.95			
Dibasic Calcium Phosphate	--------	--------	--------	--------	--------	--------	--------	--------	--------	158.65	148.30	137.95
Crospovidone (Polyplasdone XL)	10.00	15.00	20.00	10.00	15.00	20.00	10.00	15.00	20.00	10.00	15.00	20.00
Low substituted hydroxy propyl cellulose LH 11	2.00	4.00	6.00	2.00	4.00	6.00	2.00	4.00	6.00	2.00	4.00	6.00
Sodium Saccharin	2.00	3.00	4.00	--------	--------	--------	--------	--------	--------	--------	--------	--------
Aspartame	--------	--------	--------	2.00	3.00	4.00	--------	--------	--------	--------	--------	--------
Sucralose	--------	--------	--------	--------	--------	--------	2.00	3.00	4.00	--------	--------	--------
Neotame	--------	--------	--------	--------	--------	--------	--------	--------	--------	2.00	3.00	4.00
Citric Acid Monohydrate	2.00	4.00	6.00	2.00	4.00	6.00	2.00	4.00	6.00	2.00	4.00	6.00
Povidone (PVP K30)	0.25	0.50	0.75	0.25	0.50	0.75	0.25	0.50	0.75	0.25	0.50	0.75
Colour Sunset Yellow Supra FCF	0.10	0.20	0.30	0.10	0.20	0.30	0.10	0.20	0.30	0.10	0.20	0.30
Purified Water	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS

CONCLUSIONS

An orodispersible platform has been successfully developed and manufactured using the direct compression approach. The tablets have acceptable mechanical strength attributes while at the same time disintegrate rapidly which is acceptable for these types of dosage form. The use of intermediate level (15 mg/tablet) of superdisintegrant in the formulation resulted in tablet disintegration occurring in approximately 19 seconds.Direct compression was successfully used to manufacture an MDT formulation. The use of direct compression is a convenient method of manufacture as the approach facilitates shortened manufacturing times whilst making use of commonly available equipment and excipients. Mannitol was selected as appropriate filler as it has a similar particle size to the other excipients that were used to manufacture the MDT. The similar particle size decreases the chance of particle segregation during blending and manufacture as witnessed when microcrystalline cellulose, lactose monohydrate and dibasic calcium

phosphate was used as a diluent. The minimization of segregation resulted in the manufacture of tablets of suitable content uniformity and the batch fell within the specification for the dose limits that had been set for this parameter All tablets that were manufactured met the specification limits for friability and mechanical strength and would be able to withstand transport and handling and yet exhibited desirable and fast disintegration times.

Research efforts have now turned to producing orodispersible tablets to offer pharmacists a safe and effective alternative to using extemporaneous preparations. Extensive research is however required with regard to developing and manufacturing these formulations as they are not without their own challenges in considering excipient selection and stability attributes.

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