IJPSR (2014), Vol. 5, Issue 3 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 20 October, 2013; received in revised form, 01 January, 2014; accepted, 16 February, 2014; published 01 March, 2014

APPLICATION OF SURFACE RESPONSE METHODOLOGY FOR SPRAY DRIED- FLUID BED PROCESSED TECHNOLOGY OF MOUTH DISSOLVING PLATFORM FOR SILDENAFIL CITRATE IN PULMONARY HYPERTENSION

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Keywords:

Pulmonary Hypertension, Mouth Dissolving Tablets, Platform Technology, Response Surface Methodology

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ABSTRACT: Now day's formulation research is breaking barriers of conventional methods. Today, active ingredients can be delivered with a level of convenience, performance and bioavailability never seen in the market place. Fast disintegrating or Mouth dissolving tablet (MDTs) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self-administration without water or chewing. The objective of this research was to develop the mouth dissolving tablets platform for sildenafil citrate for pediatric patient in pulmonary hypertension**.** Mouth dissolving tablets platform was developed using mannitol, crosspovidone, low substituted hydroxypropyl cellulose and povidone. Sucralose and orange flavor are used as sweetener and taste masking agent respectively. Spray dried fluid bed processed technology was utilized to prepare granules. Direct compression technology was used to prepare tablets. Response Surface Methodology was utilized to establish relationships between identified independent variables and selected responses. The quality of mouth dissolving tablets was evaluated by evaluation of the in vitro release profiles, as well as friability, crushing and tensile strength, disintegration time, wetting time, *in vitro* dispersion time and the water absorption ratio of the tablets. All parameter was found satisfactory and tablets can deliver the required amount at onset time.

INTRODUCTION: From the last decade Mouth dissolving tablets are gaining more prominence as a novel drug delivery system & emerges as one of the popular & widely accepted dosage forms [1], especially for pediatric patients because of incomplete development of muscular & nervous system & in case of geriatric patients suffering from Parkinson's disorder or hand tremors, from both pharmaceutical industries as well as patients because they are convenient to be manufactured & administered, free of side effects [2, 3], offering immediate release & enhance bioavailability , so as to achieve better patient compliance [4, 5].

MDT is a good choice of drug delivery for paediatric & geriatric patients because it troubleshoots the problem of dysphagia i.e. difficulty in swallowing which is seen in many elderly patients.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(3).928-41

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(3).928-41

Mouth dissolving tablets offers rapid disintegration so as it dissolves very fast in saliva & then easily swallowed without the need of water which is a major benefit over conventional dosage form [6]. The popularity and usefulness of the formulation resulted in development of several mouth dissolving tablet technologies for preparation [7, 8].

Unless a disease affects the pediatric population to a large extent, most medicines are not tested or labelled for use in infants and children. The main reason for the lack of appropriate dosage forms for pediatric patients is the fact that pediatrics are seen as being a relatively small population group and therefore provide a limited return on the substantial investment pharmaceutical companies make in drug product development studies [9].

The lack of pediatric formulations is a worldwide challenge, with approximately 70% of drugs approved for adult use in the United States of America not labelled for use in infants and children.[10] In Europe a similar situation is observed, where only 33% of all medicines licensed by the European Agency for Evaluation of Medicinal Products (EMEA) in the period from October 1995 to September 2005 were labelled for paediatric use, 23% for use in infants and 9% in newborn babies.[11] The lack of availability of suitable dosage forms for use in this population group often results in the use of extemporaneously manufactured medicines.

Consequently it is common practice to crush Sildenafil Citrate (SC) tablets, dissolve the residue in water and to administer this mixture to the patient via a naso-gastric tube. Alternatively SC suspensions are manufactured using methylcellulose or a combination of Ora-Sweet and Ora-plus as the suspending agent [12]. These suspensions have been shown to be stable over a period of 91 days with no change in pH, odor or physical appearance noted [12]. Stability issues however are not the only concern with regard to extemporaneous preparations.

Pulmonary Hypertension in pediatrics was characterized by high pulmonary vascular resistance and low pulmonary blood flow. There is no cure for pulmonary hypertension (PH) and treatment is therefore aimed at relieving the symptoms of the disease [13].

In the past, the treatment for PH included inhalation of nitrous oxide, the use of calcium channel blockers, and extracorporeal membrane oxygenation (ECMO) [13, 14]. The disadvantage of this treatment is that it is expensive and, in the case of ECMO, is not readily available, particularly in developing countries [14]. The advantage of treating PH with SC relates to the availability of the compound and the lower cost compared to other modes of PH treatment. An additional benefit of SC is that its use in paediatric patients is safe, with only a few side effects having been reported [15].

Extemporaneous preparations are not ideal dosage forms for use in paediatric patients as there are many issues in respect of the stability, safety and dosing of these preparations. For example, potent drugs such as morphine are too concentrated for accurate measurement of the small doses required to treat pediatrics [9].

This clearly highlights the need for more research on the use of SC in paediatric patients. Available research is however promising and results so far suggest that SC is an acceptable alternative to ECMO for the treatment of PH in paediatric patients.

Spray drying methods are widely used in pharmaceutical and biochemical processes. Spray drying provides a fast and economical way producing highly porous, fine powders. Allen and Wang produced a particulate support matrix for use in making MDTs by a spray-drying technique [16].

The objectives of this study were to develop mouth dissolving tablets platform and optimize a suitable method of manufacture. Response Surface Methodology (RSM) was used to establish relationships between identified independent variables and selected responses. The quality of the SC MDT was evaluated for the in vitro release profiles, as well as friability, crushing and tensile strength, disintegration time, wetting time, in vitro dispersion time and the water absorption ratio of the tablets.

MATERIALS AND METHOD:

Materials: Sildenafil citrate was procured form Symed laboratories, Mumbai, Mannitol was procured from Roquette, Signet Chemical Corporation Mumbai India, Crospovidone was

procured from ISP sales Calvert City UK, Low substituted hydroxypropyl cellulose was procured from ShinEstu, Joetsu- shi , Japan, Citric acid Monohydrate was procured from Amijal Chemicals, Ankleshwar India. Sucralose was procured from M.B. Sugars India, Povidone 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 of manufacture: Tablets were manufactured using a direct compression method to produce dosage forms that each contained 2 mg SC. The dose of SC was based on the data following a literature review and evaluation of the typical doses used to treat pediatrics patients [14, 18, 19, 20, 21].

Mannitol was used as the primary diluents in combination with crospovidone (CRP) were included in the formulation as disintegrants. Low substituted hydroxypropyl cellulose was included as wetting agent. Magnesium stearate and Colloidal silicon dioxide (CSD) were included as anti-frictional agents. Sucralose used as sweetener while orange flavour included as flavouring agent. The formulation details was mention in table 1

TABLE 1: FORMULATION DETAILS OF 3^2 FACTORIAL DESIGNS

S. NO.	Ingredients	SC1 (mg)	SC2 (mg)	SC3 (mg)	SC4 (mg)	SC5 (mg)	SC6 (mg)	SC7 (mg)	SC8 (mg)	SC9 (mg)
1.0	Mannitol	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100	Qs to 100
2.0	Low Substituted Hydroxypropyl cellulose	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
3.0	Crospovidone	3.50	7.50	15.00	3.50	7.50	15.00	3.50	7.50	15.00
4.0	Sucralose	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
5.0	Povidone (PVP K-30)	0.25	0.25	0.25	0.50	0.50	0.50	0.750	0.750	0.750
6.0	Citric Acid Monohydrate	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
7.0	Color Sunset Yellow FCF	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
8.0	Purified Water	QS	QS	QS	QS	QS	QS	QS	QS	QS
9.0	Sildenafil Citrate	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
10.0	Orange Flavor	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50
11.0	Colloidal silicon Dioxide	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
12.0	Magnesium Stearate	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00

METHOD:

Excipient Compatibility Study: For compatibility testing binary mixtures of drug and selected excipients (Mannitol, low substituted hydroxypropyl cellulose, Crosspovidone, povidone, citric acid monohydrate, sucralose, orange flavor and magnesium stearate) in 1:1 ratios were stored at 40°C/75% RH during a period of one month. The tests were conducted in the following manner: 100 mg of each mixture were placed in 50 ml volumetric flask, the flask was sealed with perforated foil and stored in stability chamber at 40°C/75% RH for one month. Approximately 2 mg mixture, were analysed using DSC. DSC thermograms were generated at temperatures between 50 and 250ºC using a Model DS-60(Shimadzu®, Tokyo, Japan) with equipment and PC control unit TAC 60 (Shimadzu®, Tokyo, Japan) at a heating rate of 20ºC/min and a nitrogen flow rate of 20ml/min. Data analysis was undertaken using Pyris™ Manager Software

Preparation of Dry Mix*:* The granules were produced in the (UFBM-1/05Umang fluid bed Multiple 1 Umang Pharamtech, Germany).

The compositions were: Mannitol (MNT), CRP, low substituted hydroxypropyl cellulose (LHPC). Sifted the above material through 40# sieve.

Preparation of Binder solution: The binder solution was prepared by mixing the Povidone (PVP) with purified water after mixing for 5–10 min, citric acid monohydrate (CAM), 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 Nm^3/h, for 5–6 min. Set the Process parameter (**Table 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. The wetted granules were dried by fluidizing them with an inlet air temperature of 65°C.

The drying cycle was terminated when an outlet air temperature of 42°C was reached, indicating that the granules were dried sufficiently. After this cycle, 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.

TABLE 2: PROCESS PARAMETERS FOR FLUID BED GRANULATION

Sr. No.	Parameter	Set Values
1.0	Inlet Temperature	$65^0C \pm 5^0C$
2.0	Bed Temperature	42^0C
3.0	Outlet air Temperature	42^0C
4.0	Inlet air Pressure	1 to 2
5.0	Spraying nozzle Diameter	1.2 mm
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

Blending and lubrication: SC, CSD and orange flavour were screened through mesh 20 # and were placed into the octagonal blender and mixed for 30 minutes. Magnesium stearate (MS) was screened through mesh 60#. The powders were blended for a further three minutes on addition of the magnesium stearate.

The blend was compressed to form 7 mm diameter flat-faced tablets using a single punch press.

Factorial Design*:* Sildenafil citrate mouth dissolving tablets were prepared based on the 3^2 factorial design. Quantity of disintegrant (CRP) (X_1) and concentration of polymer (low substituted hydroxypropyl cellulose) (X_2) were selected as two independent variables. Three levels determined from preliminary studies of each variable were selected and nine possible batches were prepared using different levels of variables. (Table 3, 4) A polynomial equation (Eq. (1)) was used to study the effect of variables on different evaluation responses (Y), where the coefficients in the equation (β_0, β_1, β_2, β_{12}) were related to the effects and interactions of the factors.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_{21} + \beta_{22} X_{22} + \beta_{12} X_1 X_2 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where, β_0 is the arithmetic mean response of nine batches, β_1 and β_2 coefficients of factor X_1 and X_2 and β_{12} the coefficient of interaction of X_1 and X_2. The interaction (X_1X_2) shows how the dependent variable changes when two or more factors are simultaneously changed.

TABLE 3: DIFFERENT BATCHES WITH THEIR RESPECTIVE COMPOSITION (CODED LEVELS OF FACTORS)

Independent variable	Levels Used , Actual (Coded)		
	Low (-1)	Medium (0)	High (+1)
X_1 Qty of disintegrant (Crosspovidone)	3.50	7.50	15.00
X_2 Qty of Polymer (Low substituted hydroxypropyl cellulose)	0.25	0.50	0.75

TABLE 4: DIFFERENT BATCHES WITH THEIR RESPECTIVE COMPOSITION (CODED LEVELS OF FACTORS)

Dependent Variable	Constrains
Y_1 Disintegrations time	Minimal
Y_2 Dissolution	NLT 90 %

Statistical analysis of data: The significance of the model(s) that were elucidated in these studies was analysed using Analysis of Variance (ANOVA) type three (partial sum of squares) studies at a 5% level of significance. Statistical design computer software was used to analyse the data that was generated.

Physical characteristics of the Granules:

1. **Granule size:** The granule size distribution was measured according to the methods described as 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* [22].

2. **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) (%, w/w).

3. **Hausner's index:** The Hausner's 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 [23].

4. **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.

Scanning Electron microscopy (SEM)

Particle morphology of materials was investigated using a Vega LMU© Scanning Electron Microscope (Tescan, Czechoslovakia Republic). A small amount of SC, spray dried granules and crushed tablets were dusted onto separate graphite plates and coated, under vacuum, with gold for 20 minutes. The samples were then viewed using SEM at an accelerated voltage of 20kV.

Physical characteristics of Tablets:

1. **Uniformity of Weigh:** Uniformity weight 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 [23]. 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.

2. **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 [24].

3. **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. During friability testing, tablets are subject to repeated abrasion through rotation for a specified number of cycles in a friability tester [24]. 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 2.

$$\% \text{ Friability (Fr)} = \frac{Wa - Wb}{Wb} X\ 100 \quad \ldots(2)$$

Where, Wa = weight prior to testing; Wb = weight after testing; Fr = friability

4. **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.

   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 [26].

5. **Disintegration Test:** The disintegration time is a crucial characteristic that must be monitored during the development of a MDT, 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.

6. **Water absorption ratio studies:** The water absorption ratio is usually investigated in the development of MDT 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 [27]. 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 petridish containing 6 ml buffer solution. The tablet is placed on the tissue paper and allowed to completely wet. The tablet is then removed from the petridish 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 petridish on a tarred scale and then to place the tablet on the petridish 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.

$$\text{Absorption Ratio} = \frac{Wa - Wb}{Wb} \times 100 \quad \ldots\ldots (3)$$

Where, Wa= weight of the tablet after wetting; Wb= weight of the tablet before wetting

7. **Wetting time:** The wetting time of MDT 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. 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 [28].

8. **UV Spectroscopy (Determination of λ_{max}):** Accurately weighed 10 mg quantity of sildenafil citrate was dissolved in 10 ml of 6.8 pH phosphate buffer and further volume was adjusted to 100 ml by same to make stock solution (100µg/ml). UV spectrum was recorded in the wavelength range 200- 400 nm and λ_{max} of drug was determined.

9. **Tablet assay:** Twenty tablets were randomly selected and ground into a fine powder using a mortar and pestle. An aliquot equivalent to the weight of one tablet (200mg) was weighed using a Sartorius BSA 224S-Cw top-loading balance Sartorius BSA 224 S-CW top-loading balance (Sartorius AG, Weender Landstrasse 94-108 Gottingen Germany).The powder blend was transferred into a 10 ml A-grade volumetric flask and dissolved in pH 6.8 phosphate buffer and sonicated for 5 minutes using a Equitron Ultrasonic bath (The science House, Chennai, India). The solution was then made up to volume with pH 6.8 phosphate buffer.

10. ***In vitro* dispersion test:** The use of in vitro dispersion tests as additional indicator of the disintegration time of the tablets is common and the dispersion test defines the time taken for tablets to undergo uniform dispersion. The in vitro dispersion time of tablets (n=3) from each batch that was manufactured was determined by placing the tablet in a beaker containing 10ml buffer solution (pH 6.8).

    No degree of agitation was used to enhance dispersion and the end point of the test was set at the time taken for the tablet to lose its original shape. Upon visual inspection the separation of the tablet into clearly defined particles was considered the end-point and this time was noted as the *in vitro* dispersion time.

RESULTS AND DISCUSSION:

Excipient compatibility study: Thermal analysis is a popular analytical technique that provides crucial information with respect to the existence of polymorphic forms of an API as well as the compatibility of an API with excipients.

However, as far higher temperatures than those to which a product would usually be exposed are used, preformulation studies should also include IR absorption spectroscopy to confirm or negate the results generated using DSC [29].

DSC analysis (**Figure 1**) highlighted the fact that there are no interactions between excipient and active pharmaceutical ingredients albeit at high temperatures

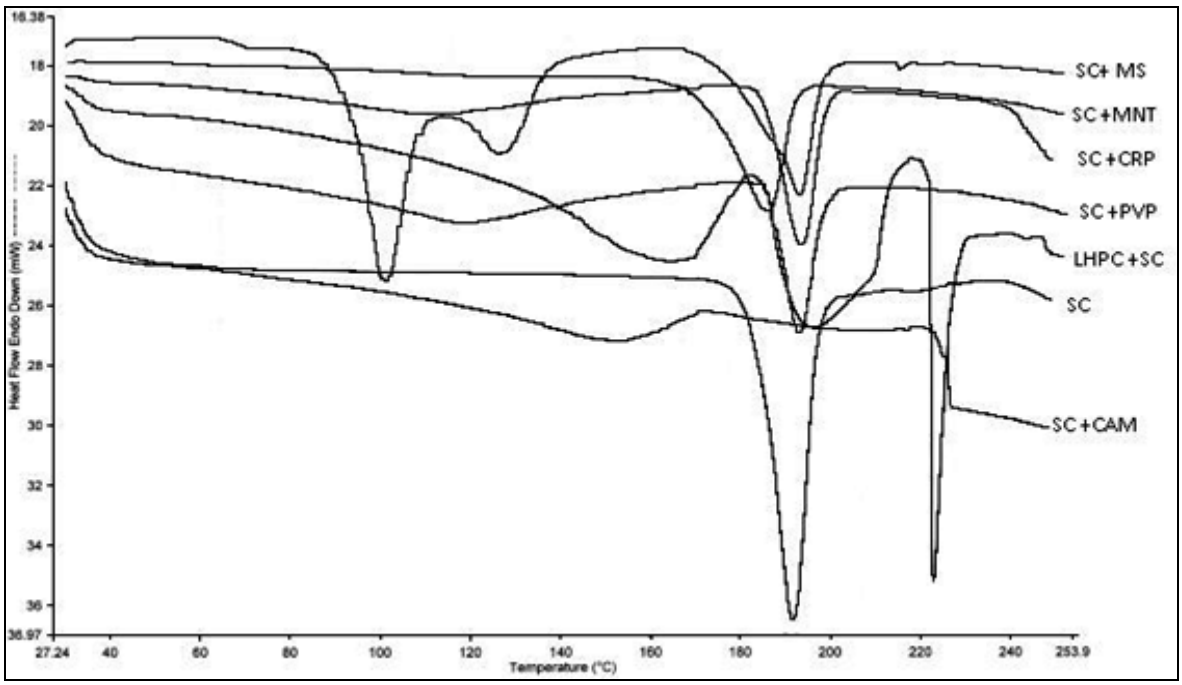

FIGURE 1 EXCIPENT COMPATIBILITY STUDY WITH DSC

Physical properties of the powder blend: A summary of the properties of the different powder blends that were tested is summarized in **Table 5**. All the Batches show the significant and satisfactory powder flow properties such as bulk density, tapped density, angle of repose, compressibility index and Hausner's ration. There was no significant change in powder properties upon the increase and decrease in quantity of polymer and disintegrants.

TABLE 5: SUMMARY OF THE PROPERTIES OF THE DIFFERENT POWDER BLENDS THAT WERE TESTED

Batch Code	Granule size (µm) (n=3)	% w/w Moisture at 105°C	Bulk density (g/cc) (n=3)	Tapped density (g/cc) (n=3)	% CI (n=3)	Hausner's index (n=3)	Angle of Repose (°) (n=3)
SC1	325±0.31	1.48	0.39±0.45	0.51±0.45	23.52±0.48	1.30±0.01	26.56±0.28
SC2	345±0.47	1.49	0.41±0.64	0.48±0.78	14.58±0.67	1.17±0.05	27.15±0.25
SC3	347±0.71	1.40	0.42±0.15	0.48±0.97	12.50±0.56	1.14±0.25	28.56±0.32
SC4	362±0.64	1.41	0.35±0.25	0.48±0.56	27.08±0.79	1.37±0.69	24.89±0.36
SC5	329±0.15	1.46	0.38±0.61	0.51±0.23	25.49±0.89	1.34±0.95	26.17±0.14
SC6	349±0.47	1.39	0.38±0.85	0.57±0.15	33.33±0.84	1.50±0.64	32.15±0.45
SC7	353±0.31	1.47	0.39±0.26	0.50±0.23	22.00±0.78	1.28±0.28	30.10±0.62
SC8	347±0.48	1.61	0.39±0.27	0.51±0.56	23.52±0.97	1.30±0.34	26.15±.0.48
SC9	359±0.21	1.10	0.37±0.94	0.49±0.47	24.48±0.99	1.32±0.25	24.29±0.57

Scanning Electron microscopy (SEM): SEM imaging is used to obtain information relating to the size and shape of materials and in this case the API and excipients. This provides additional information about the potential flow properties and compressibility of raw materials and the powder blend. SEM was chosen as a suitable method because of the high resolution of the images obtained and its rapidity and ease of operation, which enables the generation of suitable images within a short period of time. Furthermore, SEM has a high depth of field which allows for analysis of the surface texture of particles, resulting in excellent characterization of particle morphology. An understanding of the texture of particle surfaces is important, as this property may influence the surface area, settling velocity and adherence of a powder or raw material to the particle [30].

SEM images of SC and raw materials that were considered as components of a tablet formulation are depicted in Figure SEM imaging of SC (**Figure 2**) reveals the presence of many well-defined rod-shaped crystals. These crystals may at times be brought together forming irregular flat aggregates and therefore suggests that SC may exhibit poor bulk flow properties.

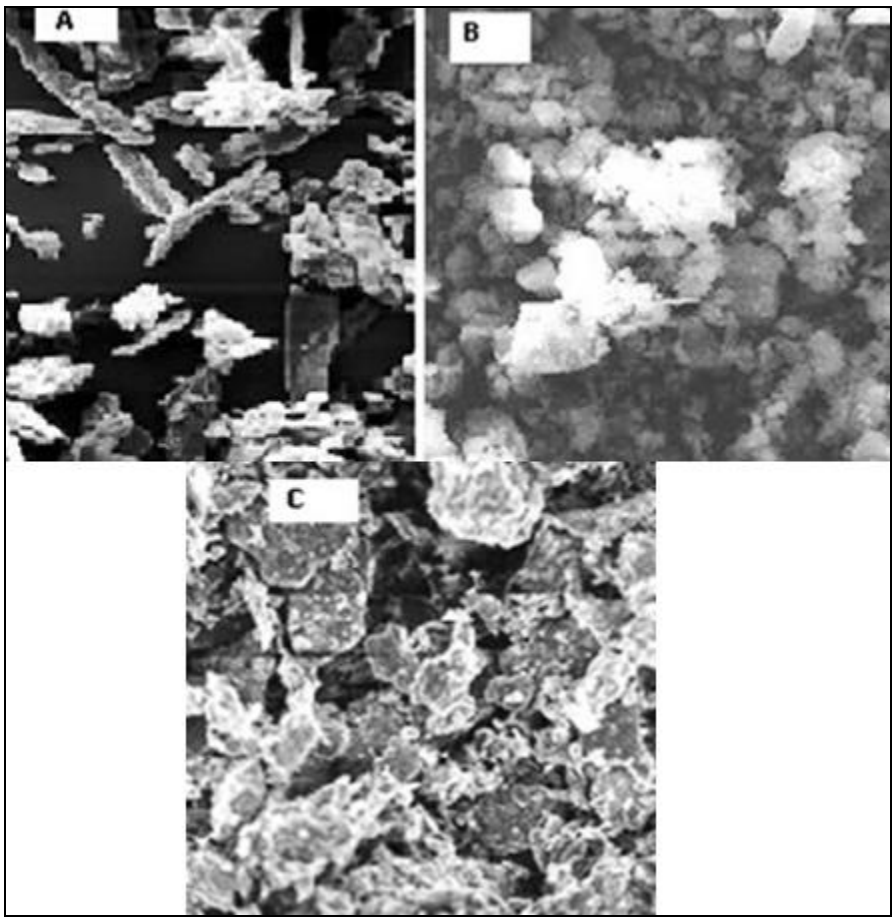

FIGURE 2A): SEM PHOTOGRAPH OF SILDENAFIL CITRATE B): SEM PHOTOGRAPH OF SPRAY-DRIED BLEND C) SEM PHOTOGRAPH OF COMPRESSED TABLETS

Physico-mechanical properties of the tablets: A summary of the physico-mechanical properties of following testing of all batches manufactured are summarized in **Table 6.**

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 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 developed platform with Mannitol [31; 32] as diluents were more appropriate as its particle size was similar with other excipients. 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. This study we have done during the development of platform [33].

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.

TABLE 6: TABLETS EVALUATION PARAMETERS

Formulation	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability (%) (n=3)	Disintegration time (sec) (n=3)	Wetting time (sec) (n=3)	Water Absorption ratio (%) (n=3)	Assay (%)	Dissolution (%)	Content of uniformity (%) n =6
SC1	3.78 ±0.01	4.9 ±0.24	0.58 ±0.01	69 ±0.25	79 ±1.52	95 ±0.87	99.82	100.02	98 ±0.82
SC2	3.84 ±0.02	4.8 ±0.34	0.49 ±0.35	62 ±0.47	61 ±1.25	94 ±0.79	98.11	101.11	97 ±0.19
SC3	3.85 ±0.06	4.9 ±0.56	0.49 ±0.24	42 ±0.94	58 ±2.10	96 ±.69	91.42	97.15	92 ±.59
SC4	3.81 ±0.07	5.1 ±0.64	0.21 ±0.56	31 ±0.58	41 ±1.55	98 ±.0.84	92.63	96.37	93 ±.0.14
SC5	3.82 ±0.01	5.2 ±0.48	0.20 ±0.76	19 ±0.59	34 ±1.54	95 ±0.98	99.99	93.97	97 ±0.10
SC6	3.85 ±0.01	5.3 ±0.57	0.19 ±0.81	21 ±0.48	51 ±1.69	99 ±0.99	99.21	99.39	100 ±0.12
SC7	3.86 ±0.02	5.1 ±0.74	0.12 ±0.61	61 ±0.61	44 ±1.54	98 ±0.87	93.61	97.55	95 ±0.37
SC8	3.84 ±0.02	5.4 ±0.91	0.20 ±0.25	58 ±0.73	57 ±1.66	97 ±0.82	95.28	96.99	96 ±0.12
SC9	3.86 ±0.08	5.1 ±0.18	0.21 ±0.64	42 ±0.11	65 ±1.5	94 ±0.47	96.39	98.08	94 ±0.67

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. Figure 3 shows the water absorption of batch SC5.

FIGURE 3: WATER ABSORPTION RATION OF SC5

UV Spectroscopy: (Determination of λ_{max}): The λ max of drug in 6.8 pH phosphate buffer was found to be 294 nm (**Figure 4**) which is in compliance with reported value. Calibration curve of drug was prepared at λ max of drug which was 274 nm. It obeys Beer Lambert's law over concentration range of 05 -60 µg/ml. It showed r^2 value of 0.9998.

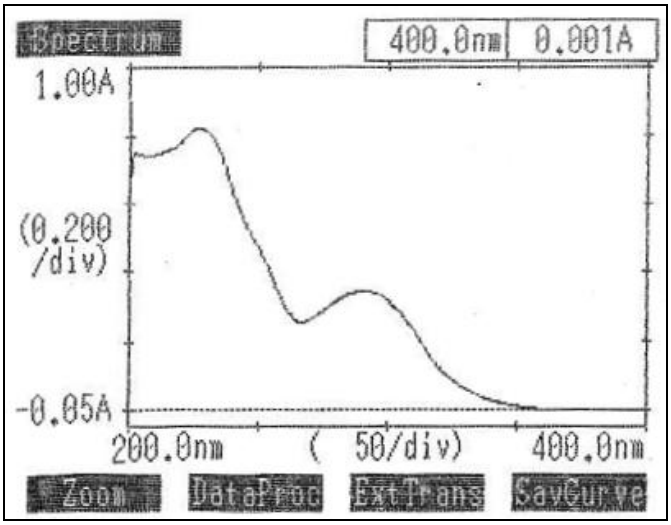

FIGURE 4: UV SPECTRUM OF SILDENAFIL CITRATE IN 6.8 pH PHOSPHATE BUFFER

Content Uniformity: The use of weight as an indicator of the uniformity of dose is not appropriate for tablets, unless the expected dose to be delivered is high and the API forms a large proportion of the tablets. For tablets in which low doses of drug are included, low variations in weight do not guarantee uniformity of content, whereas large weight variations are likely to preclude content uniformity being achieved [27].

It is therefore necessary to assay a small number of dose units from each batch to ensure that the correct dose is present in each of those units.

The content uniformity limit set [23] by the USP is of 85-115% and the results of content uniformity testing are summarized in Table 6

The data reveal that despite changes in the amount of and disintegrants used in the formulation a blend time of 10 minutes was sufficient to produce tablets that were uniform in content and that falls within the USP limits set for that parameter. It can therefore be concluded that the method of manufacture is suitable to produce SC tablets formulated and manufactured using the proposed method.

Response Surface Modeling:

Wetting Time: The wetting time for SC MDT tablets was best described by the use of a quadratic model. The polynomial model used to investigate the relationship between the input factors and the wetting time is summarized as $Y = 35.85\text{-}7.11X_1 + 10.67X_1X_1 + 16.88X_1X_2 + 9.22X_2X_2$

CRP cause tablets to disintegrate by process of wicking as liquid as drawn through pathway in the core resulting in disruption of inter particulate bonds and tablets break up. It rapidly exhibit high capillary activity and pronouns hydration capacity with little tendency to form gel.

CRP does affect the wetting times of the tablets and as the amt of CRP in the formulation increase there is decrease in the wetting time of the tablets. This can be clearly observed in 3D plot (A) where there is steep decline in the surface plot as the amount of CRP increase in the formulation. In contrast to the plot remain straight when there increase amount of Povidone in the formulations. The surface response graph is shown in the **figure 5**.

Disintegration time (Dt): As the purpose of these studies was to develop an mouth dissolving tablets, the impact of the Dt of the tablets was investigated using RSM to establish which of the input variables may have had a significant impact on the performance of the dosage forms. The critical concentration of disintegrants plays an important role in the disintegration time of an MDT and use of amounts of material below this concentration usually results in disintegration times that are inversely proportional to the disintegrant concentration, whereas higher concentrations result in approximately constant or increased disintegration times. The polynomial model used to investigate the relationship between the input factors and the disintegration time is summarized as $Y = 23.66\text{-}9.33X_2 + 32.00X_1X_1$ the surface response graph shown in the **figure 6.**

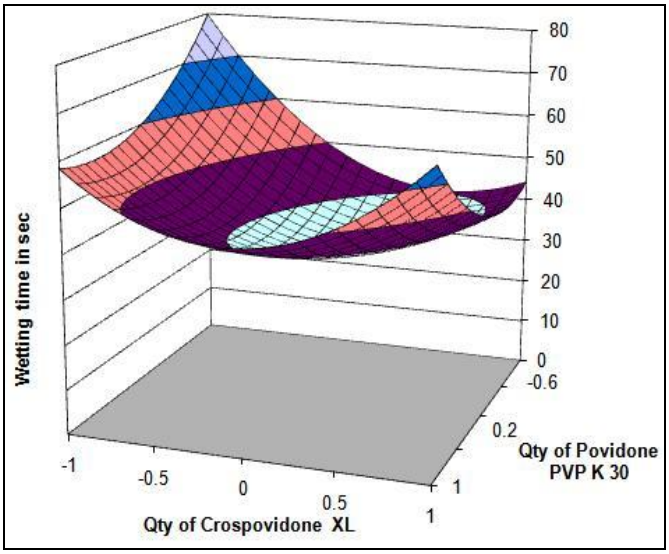

FIGURE 5: WETTING TIME SURFACE RESPONSE PLOT OF SILDENAFIL CITRATE

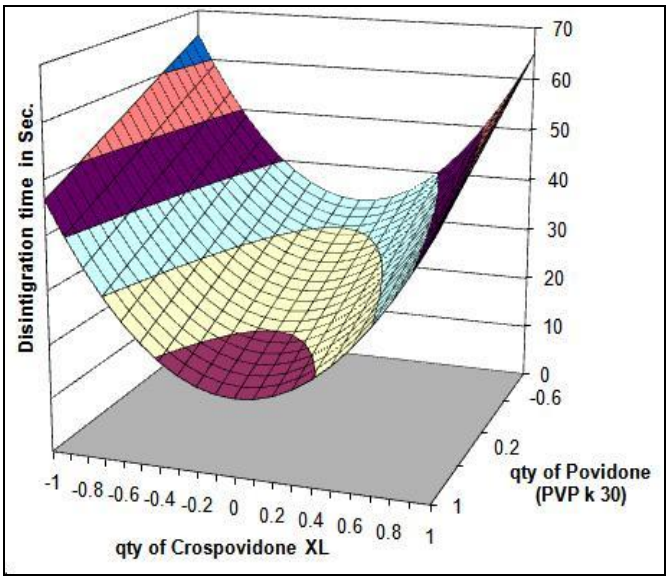

FIGURE 6: DISINTEGRATION TIME SURFACE RESPONSE PLOT OF SILDENAFIL CITRATE

Dissolution: Unless an API falls into the Biopharmaceutics Classification System (BCS) Class I quadrant which is indicative that 80% of the API dissolves in 15 minutes across the pH range or using one of three preferred media *viz.*, 0.1M HCl, an acetate buffer of pH 4.5, or a phosphate buffer of 6.8, it is necessary to develop a dissolution method that is able to generate a dissolution curve with a discernible profile shape [35].

Essentially the dissolution of an API should be - gradual so that the results generated from dissolution testing can be compared at several time points. SC is a BCS Class I compound and dissolution testing was performed using a phosphate buffer of pH 6.8 to mimic the pH of the oral cavity.

Furthermore since the tablets disintegrate rapidly, plotting dissolution profiles for comparison is difficult as the individual profiles tend to be superimposable. Consequently the % drug released at 5 minutes (Q_5), 10 minutes (Q_{10}) and 15 minutes (Q_{15}) was monitored from each batch of tablets manufactured and these data are summarized in **Table 7**.

TABLE 7: DISSOLUTION OF 3^2 FACTORIAL BATCHES

Batch Code	$Q_{5\%}$	$Q_{10\%}$	$Q_{15\%}$
SC1	78±0.58	88±0.69	95±0.54
SC2	79±1.2	87±0.88	96±0.79
SC3	81±0.98	86±0.97	94±0.64
SC4	78±0.97	89±0.99	91±0.58
SC5	86±0.85	88±0.91	90±0.78
SC6	79±0.58	87±0.86	97±0.99
SC7	81±0.95	89±0.79	94±0.87
SC8	80±0.97	90±0.88	95±0.49
SC9	78±0.88	86±0.89	96±0.58

A suitable drug release for tablets that disintegrate rapidly is a quantum of 85% API released in 15 minutes. It can be concluded therefore that all matches meet the specification (U.S. Food and drug administration, Guidance for industry, 2000). Since the disintegration time of the tablets is short, model drug release from the respective tablets relates exclusively to dissolution rate of the API and not the disintegration of the tablet [36].

The incorporation of magnesium stearate into a formulation may impart some useful properties for MDTs including a resultant decrease in disintegration times [37] or crushing strength. A decrease in crushing strength can be attributed to the reduction in interparticulate bonding caused by the formation of the lubricant film around the particles of a formulation [38, 39]. The lubricant may however have a negative impact on drug dissolution and retard the rate at which the drug dissolves.

Lubricants are in general, hydrophobic in nature and magnesium stearate which is an extremely fine material can coat other particles that are present in a powder blend. This renders the particle surface hydrophobic and may result in an increased disintegration time with a resultant decrease in the dissolution rate. In the context of these studies and evaluation of *in vitro* release data it can be concluded that the lubricant, does not delay the dissolution of SC from these MDT.

All manufactured MDT meet the specification for rapidly disintegrating tablets and at least 85% of the SC is released in 15 minutes (Q_{15}) and changes in the amount of disintegrant did not appear to affect the rate of drug release, to any great extent. **Figure 7** shows the release profile of batch SC6

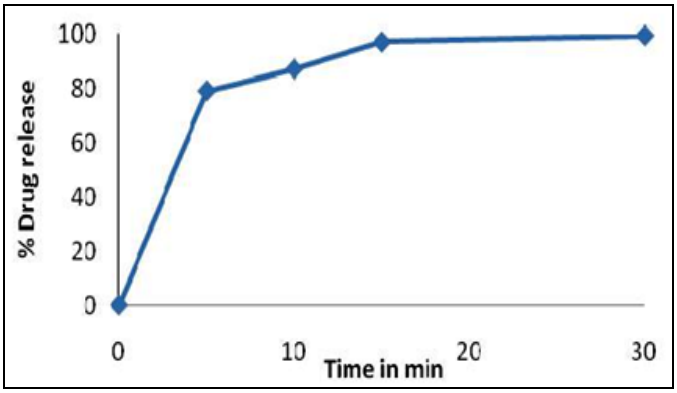

FIGURE 7: DISSOLUTION GRAPH OF OPTIMIZED SC6 BATCH

CONCLUSIONS: Many of the available treatments for PH are not suitable for use in children and despite the fact that SC is well tolerated and has reasonable efficacy in this patient group, a major problem is the fact that SC is only available in tablet form, for adult use. These dosage forms are not suitable for use in paediatric patients who are not able to swallow large dosage units.

Therefore, the pharmacist is left with no other option other than to formulate an extemporaneous product that contains SC derived from a raw material source or commercially available dosage forms. These extemporaneous suspensions can at times, be harmful as the stability of the formulation in the vehicle that is use is often unknown and there is also always the chance of human error in respect of calculating the amount of API required for the manufacture of such products.

Therefore, the formulation and manufacture of an MDT may be a viable alternative to the use of extemporaneous preparations SC administration. Since these tablets offer an advantage in terms of oral delivery due to rapid disintegration they can be administered to paediatric patients with minimal risk of choking.

The use of Response Surface Methodology can play an important role in the pharmaceutical industry for the purposes of formulation, manufacturing process and analytical method optimization. In order to generate accurate data using a RSM approach it is important that the experimental procedures are performed in a manner such that reproducible and precise results can be generated for each individual experimental run.

All tablets that were produced were assessed in terms of their friability, weight, tensile and crushing strength, DT, wetting time, *in vitro* dispersion time and water absorption ratio. All tablets that were manufactured had no cracks and exhibited satisfactory friability and crushing strength results.

The mouth dissolving tablets platform has been successfully developed and manufactured using the fluid bed granulation approach with top spray granulation technology. 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 (7.5 mg/tablet) of superdisintegrants 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.

ACKNOWLEDGMENT: Author was very much thankful to Mr. Mukesh Shinde for his help during research work.

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How to cite this article:
Gharge V, Sharma P, Gonjari I and Bhandari A: Application of surface response methodology for Spray dried- Fluid bed processed technology of mouth dissolving platform for Sildenafil citrate in Pulmonary Hypertension. *Int J Pharm Sci Res* 2014; 5(3): 928-41.doi: 10.13040/IJPSR.0975-8232.5(3).928-41

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