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Preparation and Evaluation of Mouth Dissolving Tablets of Sildenafil Citrate

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ABSTRACT

Sidenafil citrate is the first oral therapy for erectile dysfunction and pulmonary arterial hypertension. Sildenafil is a selective inhibitor of cGMP specific phosphodiesterase type (PDE5).It is reported to be effective in men with ED associated with diabetes, prostrate cancer, psychological conditions. Pulmonary hypertension is a progressive disease of diverse origin with devastating consequences in adults as well as in children. The phosphodiesterase 5 inhibitor sildenafil successfully lowers pulmonary vascular resistance. However, it is reported,Sildenafil citrate because of its poor enteral absorption results in ineffective plasma concentrations(41%) in infants and children. The major objective of this study is to prepare rapidly disintegrating, mouth dissolving tablets of Sildenafil citrate to achieve rapid onset of action and to circumvent first pass loss. Various tablet formulations were prepared by direct compression method using well known excipients. The tablets prepared using Pharmaburst® (a co-processed excipient system) in comparison with well known super disintegrants showed better results in terms of tablet hardness, content uniformity, disintegration time and wettebility. Tablets containing sildenafil citrate 10mg,20mg & 40mg were prepared Pharmaburst® and the bioavailability in rabbits was compared with conventional enteral. The C*max* values were found to be 0.72µg for 10mg tablet, 0.92µg for 20mg tablet, 1.38 µg for 40mg tablet, 0.64µg for the 100mg conventional tablets and the corresponding T*max* readings were at 2.5mins, 2.5mins, 5mins and 45mins. The study indicate mouth dissolving tablets of Sildenafil citrate prepared using Pharmaburst® provide rapid onset of action , better bioavailability over entral tablets.

Keywords: Mouth dissolving tablets, Sildenafil citrate, Pharmaburst®, *In-vitro* & *In-vivo* studies

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INTRODUCTION

Erectile dysfunction (ED) is a widespread condition with a markedly negative impact on quality of life[1]. Until recently, no effective oral therapy existed: the only treatment available were highly cumbersome or invasive and many men found them unacceptable as solutions to the problem of achieving or maintaining a satisfactory erection[2]. Sildenafil citrate (Viagra ®, Pfizer), is the first oral agent to be introduced for the treatment of ED[3]. Sildenafil citrate is a phosphodiesterase type 5 inhibitor. In countries worldwide, sildenafil is approved for the treatment of erectile dysfunction as conventional film-coated tablets of 50-mg and 100-mg strengths for oral administration with water. Sildenafil citrate is rapidly absorbed, reaching a mean maximum plasma concentration (C*max*) of 514 ng/mL within 30 to 120 minutes (median, 60 min) after oral administration of the 100-mg dose in the fasted state. Mean terminal half-life (t½) is approximately 4 hours[4]. The absolute average bioavailability after oral administration is about 41%[4, 5]. For doubling the dose, across the range of 25–200 mg, a small and clinically insignificant degree of non-proportionality was observed in predicted increases in C*max* (2.1-fold) and in area under the plasma concentration versus time curve(AUC, 2.2-fold)[4] . Although some patients reported times to erection of less than 30 minutes[6], most studies evaluating the efficacy of sildenafil as therapy for ED directed patients to take sildenafil approximately 1 hour before sexual activity[7] and hence, it is commonly thought that sildenafil takes at least 1 hour before it begins working. The phosphodiesterase 5 (PDE5) inhibitor sildenafil lowers pulmonary vascular resistance in patients with pulmonary hypertension (PH)[8]. Whereas enteral bioavailability in adults is about 40% absorption in neonates and infants is often poor[9, 10], thus limiting sildenafil's effectiveness[11] .In pediatric cases, intravenous administration effectively increases exposure[12] and vasodilator responses[11]. However, intravenous administration is not practicable for long-term maintenance therapies. Nonetheless, oral dosing remains the preferred mode of administration for many types of medication due to its simplicity, versatility, convenience, and patient acceptability[13]. Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients[14] Oral routes of drug administration have world wide acceptance up to 50-60% of total dosage forms[15]. To avert the problems associated with conventional dosage forms, MDTs have been developed, which combine hardness, dosage uniformity, stability and other parameters, with extremely easy administration, since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and travelling patients[16-20].United States Food and Drug Administration(US FDA) defined MDTs as "A solid dosage form containing medicinal substance or active pharmaceutical

ingredients(API) which disintegrates rapidly usually within seconds when placed upon the tongue[20].Mouth Dissolving Drug Delivery System (MDDDS) have started gaining popularity and acceptance as a new drug delivery system. These tablets disintegrate into smaller granules or melts in the mouth from a hard solid to a gel like structure, allowing easy swallowing by patients. The disintegration time for good MDTs varies from several seconds to about a minute[21]. Advantages of this drug delivery system include administration without water, accuracy of dosage, easy portability, alternative to liquid dosage forms, ideal for paediatric and geriatric patients with rapid onset of action. As the oral mucosa is highly vascularized, drugs that are absorbed through the oral mucosa can directly enter into the systemic circulation, bypassing the gastrointestinal tract (GIT) and avoiding first pass metabolism in the liver[22, 23]. The basic approach in development of MDT is the use of superdisintegrants like crospovidone, croscarmellose sodium (Ac-Di-Sol), sodium starch glycolate etc. as synthetic superdisintegrants in the formulation of MDTs, which provide instantaneous disintegration of tablet after keeping on tongue, their by release the drug in saliva[24]. The proper selection of disintegrant or superdisintegrant and its consistency of performance are of critical importance in formulation development of such tablets[25].Various technologies used for manufacturing MDTs include freeze drying, spray drying, tablet molding, sublimation, direct compression, sugar-based excipients, and disintegrant addition[26]. Recent market studies indicate that more than half of the patient population prefer MDTs to other dosage forms such as regular tablets or liquids (>80%)[27].

MATERIALS AND METHOD

Sildenafil citrate was received as gift sample from Cipla Ltd, Mumbai. Lactose monohydrate and magnesium stearate were procured from Merck India, Mumbai. MCC, sodium starch glycollate, avicel, talc were purchased from Yarrow Chem products, Mumbai. Colloidal silicon dioxide, Povidone K 30procured from Himedia Labs Mumbai. Pharmaburst® was received from SPI Pharma, Bangalore, as gift samples. Reagents, chemicals used in the studies were of analytical grade.

Preparationof Mouth Dissolving Tablets of Sildenafil Citrate by Direct Compression Method

Five different mouth dissolving tablet formulations each containing 10mg,20mg & 40mg of sildenafil were prepared by mixing various types of excipients **(**Table I). The mixture of each formulation was compressed into flat tablets using ‘ Rimek Minipress’ a constant rate tablet machine of Kalweka make. All tablet formulations were prepared by adjusting the machine to

punch out tablets of hardness values of 3-4Kg/cm^2. Similarly conventional tablets for *in vivo* study were prepared as per the formula[28] the composition is shown in Table IV

EVALUATION OF MOUTH DISSOLVING TABLETS OF SILDENAFIL CITRATE

Hardness

Hardness of tablets is a measure of resistance to the forces of wear and tear that the tablets may undergo during their handling right from their manufacture till their usage. Hardness of a tablet is defined as the force applied across the diameter of the tablet till the tablet breaks and is expressed in kg/cm^2 .Usually average of 10 readings is accepted for a batch of tablets.

Weight Variation

From a batch of tablets manufactured, twenty tablets are randomly selected and are weighed individually, average weight is deduced and percentage weight deviation for an individual tablet from mean value is noted and compared with the official standards.

Friability

To ensure that the tablets manufactured will withstand the post production mechanical damages due to transportation and handling conditions. Dedusted, weighed tablets are subjected to a closed circuit tumbling process using a friabilator. The friabilator consists of a circular plastic chamber with a radial partition such that the tablets are dropped freely at a distance of six inches with each revolution. The tablets are subjected to 100 revolutions and are taken out , dedusted and reweighed. The loss in weight is expressed as percentage friability ie.

% Friability = (Initial weight of tab - Final weight of tab/ Initial weight of tab) X100

Wetting Time

Wetting time of a dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets. For this purpose, a tablet is placed on piece of tissue paper folded twice kept in a glass petridish of 6.5cm internal dia and filled with 6 ml water. Time for complete wetting of the tablet was noted.

Water Absorption Ratio

A circular piece of tissue paper folded twice was placed in a glass petridish of 6.5cm internal dia, containing 6ml water. A tablet from each formulation was randomly selected, weighed and then placed on the tissue paper. Once the tablet was completely wet, the wet tablet weight was noted. The water absorption ratio in percentage was determined using the following formula.

$$R = 100 X(Wa – Wb / Wa)$$ where ,

Wa= Wt of tablet after water absorption, Wb = Wt of tablet before water absorption

Mouth Feel

It is an in-vivo evaluation carried out on a trained panel of healthy volunteers with their prior consent. The study was designed as follows –

Formulation Code	Volunteer I			Volunteer II			Volunteer III		
	DAY1	DAY2	DAY3	DAY1	DAY2	DAY3	DAY1	DAY2	DAY3
MDT5	+					+		+	
MDT10		+		+					+
MDT15			+		+		+		

+ indicates treatment.

A tablet was placed in the oral cavity of each volunteer, the disintegration time was noted, after which it was held in mouth for 60 seconds more. After 60 seconds , the tablet mass was spitted out and the oral cavity was rinsed thoroughly with mineral water. The observation of mouth feel was rated as:

Good = Smooth & Palatable, Bad = Gritty & Unpalatable feel

***In-Vitro* Disintegration Time[29]**

The *in-vitro* disintegration time was determined using disintegration test apparatus as per Indian Pharmacopeia. The apparatus consists of a circular basket having six cylindrical tubes of SS screen. A tablet was introduced in each tube and a plastic disc of negligent weight was added. As per the standard working procedure the basket moves up and down at a specified rate and while it moves down into glass beaker containing water it breaks the surface of the liquid , this process simulates the movement of tablet in the GIT. The time in seconds taken for complete disintegration of tablet with no visible mass remains on the screen was noted as the disintegration time.

Assay

Twenty tablets from a batch of tablets was weighed and powdered. The drug powder equivalent to average weight of the tablet was taken and dissolved into 50ml of 0.01N hydrochloric acid. From the solution prepared 5ml was pipetted out further diluted to 100ml with distilled water. The UV absorbency at 225nm against 0,01N hydrochloric acid as blank was read using UV Spectrophotometer (UV-1700, Shimadzu, Japan) . The results were noted and the drug content was calculated from the standard graph.

***In-Vitro* Dissolution Test**

The in-vitro dissolution studies were carried out using USPXXIII test apparatus type II (LABINDIA DS 8000) at 50 rpm. The dissolution composition was 0.01N hydrochloric acid (900ml) maintained at 37±0.50 ºC. Aliquots of dissolution media were withdrawn at 5 min interval, diluted suitably and absorbance was measured at 225nm using UV spectrometer (SHIMADZU Japan, UV-1700) The dissolution experiments were conducted in triplicate. *In-vitro*

drug release kinetics: Different models of drug release kinetics like zero order, first order, matrix, Hixon crowell and Korsemeyer Peppas were studied for MDT5, MDT10, MDT15 formulations using the software PCP Disso 2 to determine the best fit model.

***In-Vivo* Drug Kinetics in Rabbits**

Four groups of rabbits, each containing six animals were chosen for in vivo study. Study was designed to understand, the extent and amount of sildenafil absorbed from the mouth dissolving formulations prepared using Pharmaburst ® as the direct compression vehicle. When compared with that of conventional tablet. Formulation MDT5, MDT10, MDT15 were applied over the tongue of each rabbit (after anesthetizing by ether) and the conventional formulation was administered orally using an intragastric tube[28]. The blood samples were collected from the ear vein at 2.5 mins, 5mins, 15mins, 30mins, 60mins and 120 for MDT5, MDT10, MDT15 formulations and for conventional formulations besides above time intervals additional samples were collected at time intervals 45mins, 180mins & 240mins. The blood samples were collected and analyzed using the HPLC method for the determination of Sildenafil concentration. The drug was chromatographed on reverse phase C18 column using mixtures of buffer-acetonitrile. The method was validated for its linearity, accuracy and robustness. The mobile phase being a mixture of 0.02M disodium hydrogen phosphate and acetonitrile (60:40 ^{v}/v) while the pH was adjusted to 4 by adding orthophosphoric acid, 290nm and attenuation of 0.01 absorbance unit per full scale(AUFS) was used[30]. The samples were prepared by mixing 0.1ml of plasma with 0.4ml of methanol and filtered and injected into HPLC.

RESULTS AND DISCUSSION

The mouth dissolving tablets (MDTs) of Sildenafil citrate were prepared by direct compression method using well known excipients including Pharmaburst ® a co-processed excipient system. The objective was to achieve rapid onset of action, bypass drug loss due to first pass metabolism and to provide a dosage form suitable to all age group patients including patients with various dysphagia conditions. The composition of tablets prepared are shown in Table I. All batches of mouth dissolving tablets were formulated under similar conditions to avoid processing variables. The results of post compression study parameters are shown in Table II. The tablets were found to be free from chipping and capping. The hardness of prepared tablets ranged between 3-4kg/cm^2 except for the formulation MDT7 which was above 4kg/cm^2, hardness between 3-4kg/cm^2 is most acceptable for MDTs. For uncoated tablets the friability less than 1% at 100rpm/4 minutes is most acceptable. For all MDT formulations the friability was found to be less than1%. The Indian

Pharmacoepia prescribes weight variation limits as ± 7.5% for uncoated tablets weighing between 8mg-250mg. All MDT formulations prepared were found to be in compliance with the IP standard for weight variation parameter. Similarly the content uniformity for Sildenafil citrate drug in the MDT formulations were found to be in compliance with the IP standard prescribed for the drug. According to Indian Pharmacoepia , a dispersible tablet must disintegrate within 3 minutes. In our study , we found that the formulations MDT5, MDT10 & MDT15 disintegrated in ≈ 10 seconds, whereas formulations MDT2, MDT7 and MDT12 were found to take more than 60 seconds to disintegrate, further, for formulations MDT3, MDT4, MDT6, MDT8, MDT9, MDT11, MDT13 and MDT14 the disintegration time was between 11 seconds to 16 seconds. As the DT for the three formulations MDT5, MDT10 & MDT15, which were prepared using Phramaburst® a co-processed excipient system, was found to be ≈ 10 seconds, it can be said that the Phramaburst® is an excellent excipient in the development of MDTs. Since, the post compressional studies gave a promising picture for the formulations MDT5, MDT10 & MDT15 in terms of hardness ≥3kg/cm^2, friability less than 1%, Pharmacoepial compliance to weight variation and content uniformity and DT ≤ 10 secs, they were selected for further studies. Next, the wetting time, water absorption ratio and mouth feel parameters were studied and results are tabulated in Table III. For the 3 selected formulations, the wetting time was found to range between 10secs-11 secs, the water absorption ratio was found to range between 140%-142%. The mouth feel was found to be good and palatable in all the three formulations. The formulations, MDT5 contains 10mg, MDT10 contains 20mg and MDT15 contains 40mg of drug Sildenafil citrate. These three dose levels were selected to investigate whether or not the drug upon release into the oral cavity is absorbed in required proportions[31]. The 3 formulations along with a conventional formulation prepared as per the formula shown in Table 4, were subjected to *in vitro* drug release studies, the results are shown in figure 1 and figure 1 A. All 3 selected MDT formulations were found to release more than 98% drug within 6-8 minutes, whereas the time for the conventional formulation to release more than 98% drug was found to be around 150minutes. To determine the best fit model the drug release data was analyzed using the software PCP Disso V2, results are shown in Table V. It was found, for all 3 MDT formulations, the drug release data fits the Korsmeyer Peppas model whereas the conventional formulation drug release data fits the Matrix model. The formulations, MDT5, MDT10, MDT15 and the conventional tablets were evaluated for comparative bioavailability in rabbits. The results are shown in Figure 3. The C*max* values were found to be 0.72µg for 10mg tablet, 0.92µg for 20mg tablet, 1.38 µg for 40mg tablet and 0.64µg for the 100mg conventional tablet and the corresponding T*max* values were 2.5mins, 2.5mins, 5mins and 45mins respectively.

The study indicates that MDTs of Sildenafil citrate prepared using Pharmaburst ® namely. MDT5, MDT10, MDT15. rapidly release the drug in the oral cavity and is absorbed immediately. From the in-vitro cumulative drug release v/s time profile, the in-vivo bioavailability profile and the drug release data analyses to best fit Peppas model , it can be said that the drug was found to be absorbed by passive diffusion[32]. The important observation is that the MDT5 containing 10mg of the drug, MDT10 containing 20mg of the drug, found to follow dose proportional kinetics[31] whereas the MDT15 containing 40mg drug, found to show a shift in C*max* and T*max* values, which means the absorption of the drug is restricted by the area available for absorption during the drug's stay in the oral cavity. Loading of higher doses, more than 40mg of Sildenafil citrate into the tablet matrix of Pharmaburst® for a mouth dissolving formulation may not be advantageous. However, for the dose levels studied good results are achieved to get a palatable, pharmaceutically acceptable mouth dissolving tablet formulation that rapidly disintegrates to dissolve out the drug and provide a clinically effective plasma concentration of sildenafil citrate.

Table 1: Composition of Mouth Dissolving Tablet formulations of Sildenafil Citrate

Ingredients (mg) ↓	**Formulation code**														
	MDT1	**MDT2**	**MDT3**	**MDT4**	**MDT5**	**MDT6**	**MDT7**	**MDT8**	**MDT9**	**MDT10**	**MDT11**	**MDT12**	**MDT13**	**MDT14**	**MDT15**
Sidenafil Citrate	10	10	10	10	10	20	20	20	20	20	40	40	40	40	40
Lactose Monohydrate	164	-	82	82	-	154	-	77	77	-	134	-	67	67	-
MCC		164	82	82	-		154	77	77	-	-	134	67	67	-
Pharmaburst 500					172					162					142
Povidone K 50									4					4	
Starch 1500			4	4				4					4		
Cross Carm ellose Sod	4	4				4	4				4	4			
Sod Starch glycollate			4	4				4	4				4	4	
Mango Flavour	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Sucralose	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Aspartame	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Colloidal Silicon Dioxide	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3

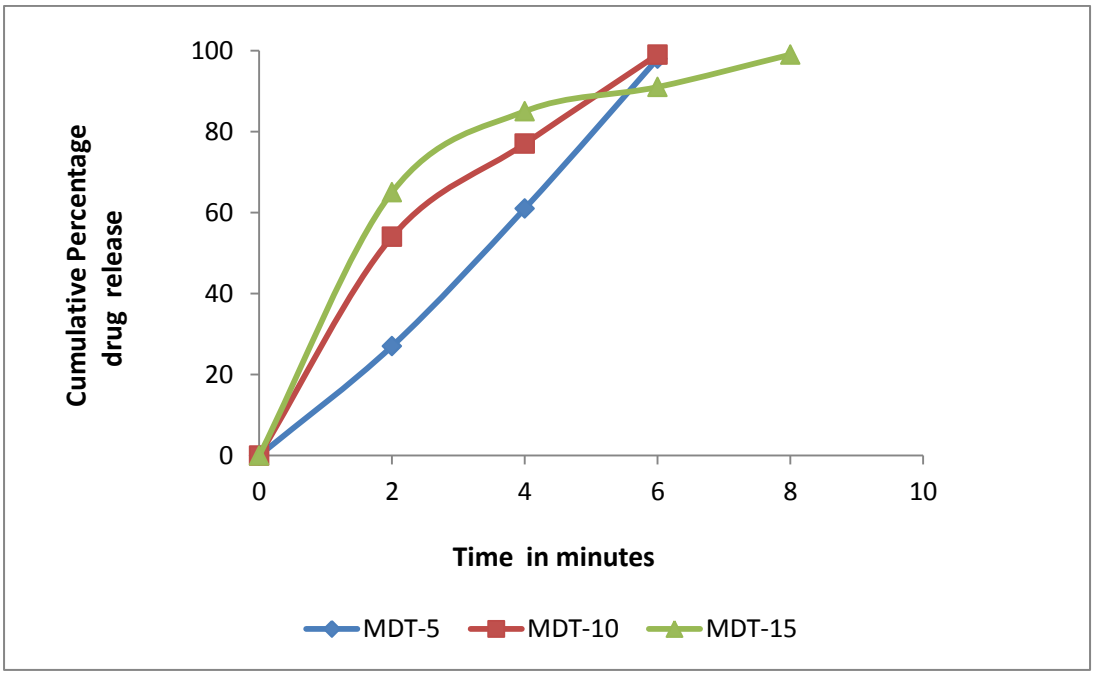

Figure 1: *In-vitro* Dissolution studies of MDT formulations

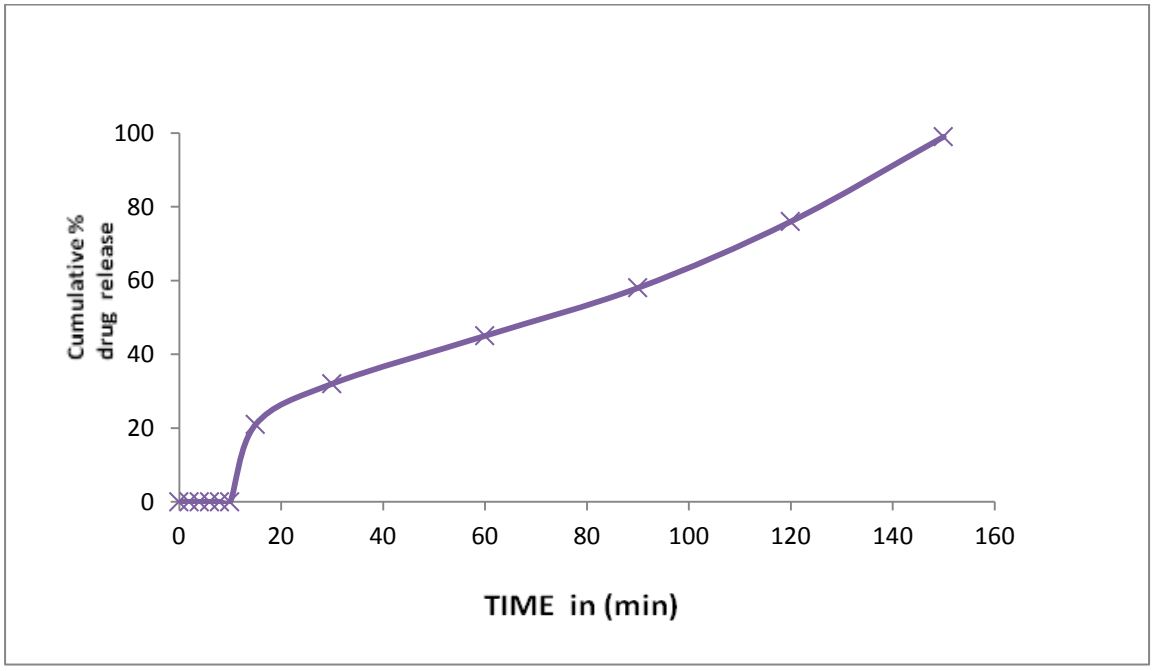

Figure 1A: *In-vitro* Dissolution studies of Conventional formulation

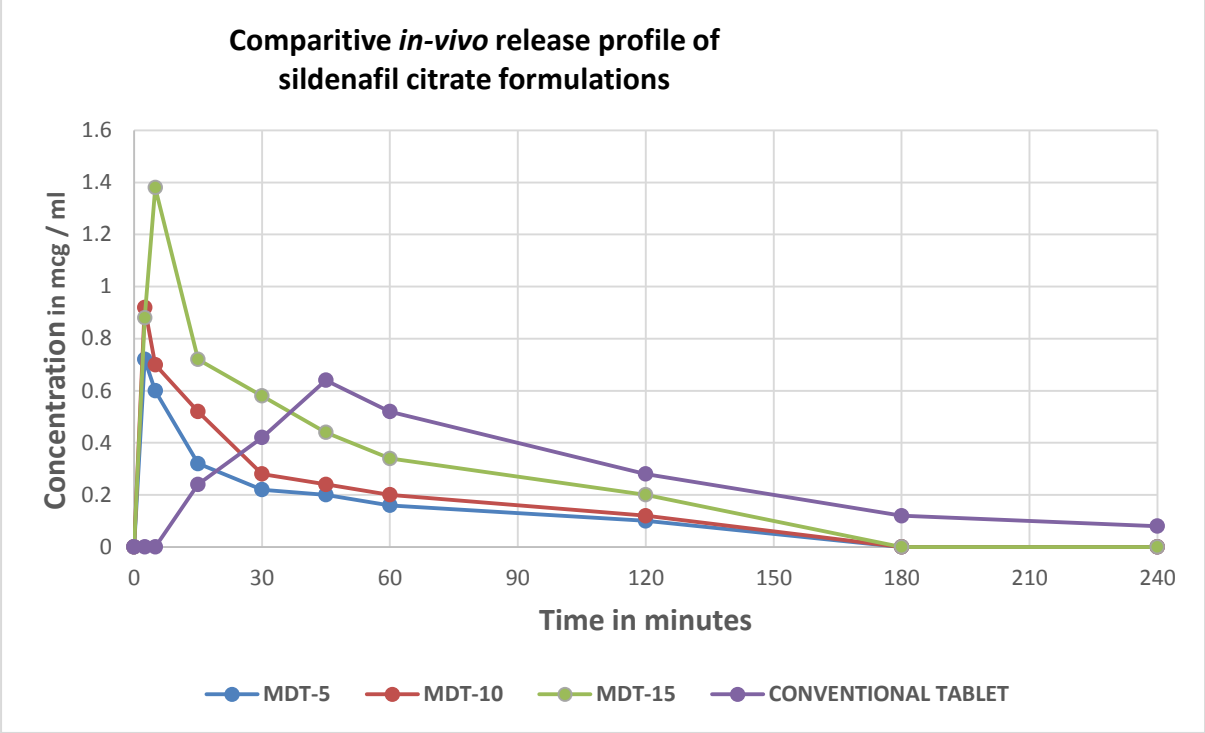

Figure 2: Comparative *in-vivo* Bioavailability studies of Formulations of Sildenafil citrate

Table 2: Post Compression Properties of MDTs with different Superdisintegrants

Formulation Code	Hardness* (KG/CM^2)	Friability* (%)	Weight Variation*(mg)	Drug Content*(%)	Disintegration Time*(sec)
MDT1	3.2±0.24	0.72±0.06	198±.7	99.4±1.2	13±1.32
MDT2	4.0±0.12	0.68±0.02	197±2	96.1±1.2	61±0.95
MDT3	3.4±0.36	0.76±0.04	201± 6	96.8±1.1	14±1.42
MDT4	3.2±0.40	0.72±0.06	199±5	103.2±1.9	11±1.65
MDT5	2.9±0.12	0.92±0.02	199±5	99.6±2.4	09±0.90
MDT6	3.4±0.24	0.78±0.06	198±.3	99.4±1.2	13±1.32
MDT7	4.2±0.12	0.65±0.02	196±2	96.1±1.2	61±0.95
MDT8	3.5±0.36	0.79±0.04	201± 6	96.8±1.1	14±1.42
MDT9	3.2±0.40	0.71±0.06	199±5	103.2±1.9	11±1.65
MDT`0	2.8±0.12	0.91±0.02	200±7	99.8±2.7	09±1.00
MDT11	3.0±0.30	0.89±0.03	200±5	98.3±1.9	11±2.34
MDT12	4.0±0.41	0.68±0.06	198±7	96.2±2.4	86±1.90
MDT13	3.2±0.20	0.69±0.07	195±4	98.2±2.1	16±2.34
MDT14	3.4±0.12	0.63±0.04	203±6	99.2±1.8	11±1.45
MDT15	3.0±0.12	0.91±0.03	200±6	99.8±1.6	10±0.94

Values are represented as mean +/-SD (n=3)

Table 3: Post Compression Studies of selected formulations of MDTs of a co-processed excipient system -Pharmaburst®

Formulation Code	Hardness (KG/CM^2)	Friability (%)	Weight Variation (mg)	Drug Content (%)	Disintegration Time (sec)	Wetting time (in sec) SD+/-	Water absorption ratio (%) SD+/-	Taste/ Mouth feel
MDT5	2.9±0.12	0.92±0.02	199±5	99.6±2.4	09±0.90	10+/-1.26	142+/-2.1	Good
MDT10	3.1±0.04	0.91±0.02	200±7	99.8±2.7	09±1.00	10+/-1.02	140+/-1.8	Good
MDT15	3.1±0.12	0.91±0.03	200±6	99.8±1.6	10±0.94	11+/-1.2	141+/-1.6	Good

Values are represented as mean +/-SD(n=3)

Table 4: Composition of Conventional tablets of Sildenafil citrate

Sildenafil citrate	100mg
Avicel	68mg
Anhydrous lactose	28mg
Talc	04mg

Table 5: Best Fit Model for the selected Formulations

		Formulations			
Parameters		MDT5	MDT10	MDT15	CONVENTIONAL
Zero order	R^2	0.8861	0.852	0.964	0.928
	k	7.608	11.7	10.437	18.431
First order	R^2	0.953	0.96	0.976	0.9302
	k	-0.2710	-0.47	-0.3365	-0.6259
Matrix	R^2	0.931	0.963	0.9895	0.9960
	k	26.697	35.07	30.399	39.786
Hix Crow	R^2	0.988	0.911	0.96	0.9823
	k	-0.050	-0.087	-0.0685	-0.1220
Korsmeyerpeppas equation	R^2	0.9942	1.00	0.992	0.9876
	n	0.329	0.04	0.5608	0.3919
	k	40.103	89.11	27.70	46.687
Best Fit Model	-	Peppas	Peppas	Peppas	Matrix

CONCLUSION

The MDTs of sildenafil citrate can be successfully prepared using Pharmaburst® as direct compression vehicle. From the studies it can be concluded that the co-processed excipient system Pharmaburst®, will comply the requirements of pharmaceutical manufacturer and a clinician. The process of tablet making is simple and cost effective. The formulations can be scaled up for further studies.

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