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FORMULATION AND EVALUATION OF SILDENAFIL CITRATE MOUTH DISSOLVING TABLET

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ABSTRACT

Mouth dissolving tablets are best suited and have gained popularity in recent years in oral drug therapy. These tablets disintegrate instantaneously when put on tongue, releasing the drug that dissolve or disperses in saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases; bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. The major criteria for the mouth dissolving tablet is to disintegrate or dissolve rapidly in oral cavity with saliva in 15 seconds to 60 seconds, without need of water and should have pleasant mouth feel. It has been reported that sildenafil citrate possess bitter taste hence primary objective is to mask the bitter taste and further developing the drug into mouth dissolving tablets. Bitter taste of sildenafil citrate is masked with addition of sodium bicarbonate which decrease the solubility of sildenafil citrate in mouth, further mild effervescent reaction between dry acid (Citric acid) and dry base (sodium bicarbonate) favour both faster disintegration and pleasant mouth feel. Direct compression was used as it required conventional tablets machinery and thus is an economical process. The tablets produced were evaluated for thickness, hardness, friability, weight variation, disintegration test, wetting time. The dissolution data were treated to check dissolution efficiency and dissolution rate. Based on the result it was concluded that formulation with 8% disintegrating agent (4% in mannitol granules and 4% in agglomerated disintegrate granules) show better disintegration and dissolution profile.

KEY WORDS: Sildenafil, Mouth dissolving tablets, Disintegrating agents.

INTRODUCTION

Tablets and capsules are the most preferable, convenient and extensively used dosage forms as it offers versatile advantages when compared to other dosage forms. On the other hand they face one important drawback for some patients, which is the difficulty to swallow and access to water for easy swallowing of the dosage form. Tablets that rapidly dissolve in the mouth have become popular in the recent times and emerged as a drug delivery system with good patient compliance (Kumar *et al.* 2016). Fast dissolving tablets could be a preferred choice to deliver drugs to the oral cavity, for local action or in some cases, absorption across the oral mucosa, thereby avoiding first-pass hepatic metabolism and potentially increasing the rate and extent of uptake and reducing undesirable metabolites.

Fast dissolving tablets combines the benefit of both liquid dosage and conventional tablet formulations. They offer the advantage of significantly more accurate dosing than the primary alternative i.e. oral liquids. They disintegrate and/or dissolve rapidly in saliva, therefore, water is not required during administration. These formulations are particularly intended for pediatric, geriatric, bed-ridden, dysphasic and psychotic patients who are having difficulty in swallowing .[3]

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conventional oral formulations (Fu *et al*. 2004). They are considered to be the most convenient dosage forms as these tablets disintegrate/dissolve very fast when placed in the mouth. These tablets are a good alternative for travelers and for bedridden patients as they do not require water for administration. They cannot be hidden in mouth by psychotic patients as they just vanish when placed in the mouth [1].

Several technologies have been introduced for the formulation of fast dissolving tablets (FDTs) with exceptionally remarkable features [2]. FDTs are known by different names such as mouth dissolving, fast melting, oral disintegrating or orodisperse tablets.

Apart from erectile dysfunction FDTs are also valuable as cardiovascular agents, analgesics, antiallergics, and neuroleptics. The ideal properties of FDTs include high drug load capacity, compatibility with the taste masking and other excipients, pleasant mouthfeel, minimal or no residue in the mouth after oral administration, adequate vigor to withstand the firmness during the manufacturing and handling, and low sensitivity to environmental conditions such as humidity and temperature [3].

MATERIALS AND METHODS

Selection of Excipients

Active drug blended with individual excipients taken in 1:1 ratio. It was filled in closed vials and placed in stability chambers at 35˚ ± 2˚C / 65±5% RH and 40˚±/2˚C/75± 5% RH. The compatibility studies were done. Samples were observed for any physical changes at the end of 1st, 2nd, 4th and 6th weeks.

Formulation of sildenafil citrate mouth dissolving tablets

Manufacturing Procedure

a. **Sieving**

First active ingredient (Sildenafil Citrate) was passed through the sieve no.40. Then other ingredients (Detailed in trials) were passed through the desired sieve number.

b. **Dry mixing**: The ingredients (Detailed in trials) to be mixed in taken poly bag and mixed for 5 minutes to ensure uniform distribution of drug.

c. **Granulation**

Wet Granulation: The dye solution was added slowly to the dry mixed ingredients with constant mixing till to get solid mass to form uniform and optimum granules. The way of determine the optimum granules is to press a portion of the mass in the palm of the hand, if the ball crumbles under the moderate pressure, the mixture is ready for the next stage in processing.

d. **Drying:** Granules are dried at **50**˚C, while drying at different time intervals, samples were removed randomly from the total bulk of the granules.

e. **Mixing of Part A, Part B and Part C:** The proper proportion of dried granules of Part A, Part B and Part C are thoroughly mixed.

f. **Sieving:** The dried granules were passed through the sieve no.24.

g. **Lubrication:** The lubricant (Magnesium stearate) are passed through the sieve no.40 and mixed together with dried granules in a poly bag for 5 minutes to get a uniform blend. Then the granules were compressed into tablet using punches 21 station punching machine.

Precompression Parameter

Percentage moisture content: The prepared granules (5gm) were taken and the moisture content is determined at 60 ^{0}C. using IR moisture balance.

Measurement of the moisture in a wet solid is the calculated on a dry-weight basis.

$$\% \text{ Moisture Content} = \frac{\text{Wt. of the water in Sample}}{\text{Wt. of the dry sample}} \times 100$$

Bulk density: Apparent bulk density was determined by pouring blend into a graduated cylinder. The bulk volume (v_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula.

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}}$$

$$\rho_b = \frac{m}{V_b}$$

True Density: True density is the ratio of the mass of powder to the true volume (excludes void volume).

True volume = Bulk volume – void volume

$$\text{True Density} = \frac{\text{Mass of the powder}}{\text{True volume of the powder}}$$

Tapped density: Tapped density of the powder depended primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Volume after tapping}}$$

Porosity: The Fraction of powder which consists of free air a space in between the neighbouring particles is known as Porosity.

Ratio of total volume of void spaces to the bulk volume of material is often selected to monitor the progress of compression. This ratio is referred to as porosity. It was calculated by using the formula

$$\text{Porosity} = \left(1 - \frac{\text{Bulk density}}{\text{True density}} \times 100\right)$$

$$\text{Porosity E} = V_v / V_b = V_b - V_t / V_b = 1 - V_t / V_b$$

Where,

t = true volume of tablets.

Post-compression Parameter

Weight variation: It is desirable that every individual tablet in a batch is uniform in weight and weight variation it any is within permissible limits. Non uniformity in weights may lead to variation in dosing. All finished batches of tablets should be sampled and tested for weight uniformity.20 tablets were weighed collectively and individually and from the collective weight, average weight was calculated. Each tablet weight was compared with average weight to ascertain whether it is within permissible limits or not. The tablets meet the B.P test if not more than 2 tablets are outside the percentage limit and if no tablets differ by more than 2 times the percentage limit.

Weight variation tolerances for uncoated tablets:

Weight Variation Specifications

Average Weight of Tablet (mg)	Maximum Percentage Difference Allowed
<80	10
80-250	7.5
>250	5

Thickness, length and width: Thickness depends mainly upon die filling, physical properties of materials to be compressed and compression force. The thickness and diameter were measured by using vernier caliper.

Hardness: It is defined as a force required breaking a tablet in a diametric compression test. To perform this test Monsanto test is used. It consists of a barrel containing a compressible spring held between two plungers. The tablet is placed in contact with the lower plunger and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded blot until the tablet fractures. As the spring is compressed a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded. This parameter is important to know that the tablet has sufficient strength to withstand mechanical shocks of handling in manufacturing, packaging and shipping.

Friability: It is intended to determine the loss of mass under defined conditions. The friability of uncoated tablets is determined by using Roche friabilator in the laboratory. In a wider sense chipping and fragmentation can also be included in friability. It reflects cohesion of tablet ingredients [4].

The Roche friability test apparatus consists of acicular plastic chamber, divided into two compartments. The chamber was rotated at a speed of 25 rpm and the tablets were dropped to a 15 cm distance. Reweighed tablets were placed in the apparatus which was given 100 revolutions after which tablets were weighed once again. The difference between the two weights represents friability. The weight loss should not be more than 1%. Then the tablets are dusted and reweighed and the friability percentage is calculated using the formula

$$F = \left(\frac{W_0 - W}{W}\right) \times 100$$

Where,

F= Friability

w_0 - Weight of the 20 tablets before friability

w - Weight of the 20 tablets after friability

Conventional compressed tablets that lose less than 0.5 to1.0 % of their weight are generally considered acceptable. When capping is observed on friability testing, the tablet should not be considered for commercial use, regardless of the percentage of loss seen.

Disintegration: The USP device to test disintegration uses to glass tubes that are 3 inches long, open at the top, and held against a co-mesh screen at the bottom end of the basket rack assembly to text for disintegration time, one tablet is placed in each tube, and the basket rack is positioned in a one liter beaker of H_2O, stimulated gastric fluid, or stimulated intestinal fluid, at 37° ± 2°C such that the tablets remain 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker. A standard motor – driver device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minutes. Perforated plastic disc may also be used in the test. These are placed on top of the tablets and impart an abrasive action to the tablets. To be in compliance with the USP standards the tablets must disintegrate, and all particles must pass through the 10-mesh screen in the time specified.

Wetting time

Filter paper was kept in petridish (Diameter 9.5 cm) containing 6 ml purified water. A small amount of amaranth powder was placed on it. Time required to develop red color on the upper surface of tablet was recorded as wetting time.

***In-vivo* dispersion time and mouth feel**

In-vivo dispersion time of a tablet was checked in healthy human volunteers by putting a tablet on tongue instructed to roll tablet in the mouth without biting and time required for

complete dispersion and bitterness of tablet was checked.

***In-vitro* dissolution test**

Dissolution conditions for Sildenafil Citrate (UV)

Medium	:	0.1N HCl
Volume	:	900 ml
Apparatus	:	USP type II (Paddle)
Sampling time	:	2,4,6,8,10,12,14 and 16 minutes
Temperature	:	37 ± 2^0 C

Estimation of Sildenafil Citrate

a. Standard preparation

50 mg of sildenafil citrate Rs was weighed into 100 ml volumetric flask. Dissolve and dilute to volume 0.1 N HCl. Transfer 2 ml of this solution into a 50 ml volumetric flask and dilute to volume with 0.1N HCl.

b. Sample preparation:

Put 6 tablets individually in six dissolution flask containing 100 ml 0.1N HCl that has been equilibrated to 37± 0.5°C. Take care to exclude air bubbles from the surface of the tablets start the apparatus immediately. Collect the sample at 2,4,6,8.10,12,14,16 minutes zone midway between the surfaces of medium and top of the rotating blade and not less than 1 cm from the vessel wall and filter through Whatman No.1 filter paper by discarding first 5 ml. Pipette out 5 ml of filtrate into a 25 ml volumetric and make up to volume with 0.1N HCl.

Measure the absorbance of standard and sample preparation at 290 nm using 0.1 N HCL as blank

c. Calculation:

Content of Sildenafil Citrate:

$$\frac{\text{Test absorbance}}{\text{Standard absorbance}} \times \frac{SW}{100} \times \frac{2}{50} \times \frac{1000}{100} \times \frac{25}{5} \times P$$

Where,

SW = Standard weight taken in mg

P = Percentage purity of Sildenafil Citrate

Content of Sildenafil Citrate

$$\frac{\text{Test area}}{\text{Standard area}} \times \frac{SW}{TW} \times \frac{P}{100} \times \text{Av.wt}$$

Where,

SW = Standard weight taken in mg

TW = Test weight taken in mg

Av.wt = Average weight in mg

P = Purity of Sildenafil Citrate

Stability study of the tablets

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of new drug substances and product" (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and United States of America. ICH specifies the length of study and storage conditions.

- Long –term testing: $25^0 \pm 2^0$C/60 $\pm$ 5%RH for 12 months
- Accelerated testing: 40^0 C $\pm$ 2^0C75 $\pm$ 5%RH for 6 months

Stability studies for the present work carried out at 25^0 C/ 60% RH and 40^0 C/75% RH for selected formulation for 12 weeks.

FORMULATION OF SILDENAFIL CITRATE MOUTH DISSOLVING TABLETS

Trial 1 (Batch Size: 150 Tablets)

In this trial batch 15% of sodium bicarbonate is added in core granules to mask the bitterness of sildenafil citrate 1% and 1.5% of crospovidone is added as disintegrating agent in mannitol granules and Agglomerated disintegrate granules respectively, passed through sieve no 18 before compression.

Trial 2 (Batch Size: 150 Tablets)

In this trial batch Sodium bicarbonate is increased to 27% and aspartame concentration is reduced to 9%. Crospovidone amount is increased to 2.5% in mannitol granules, passed through sieve no 18 before compression.

Trial 3

In this trial crospovidone concentration is increased to about 4% in mannitol granules and 3% in agglomerated disintegrant granules passed through the sieve no.18 before compression.

Trial 4

In this trial the concentration of crospovidone is increased to 4% in agglomerated granules are Passed through the sieve no 18 before compression.

Trial 5

No change is made in the granules made but granules are passed through the sieve no. 24 before compression.

Trial 6&7

From the results the trial no - 5 passes the USP acceptance criteria so this trial-5 is considered to the final formula. To get the reproducibility of results obtained the trial -5 has been taken two more time by keeping the composition & processing method unaltered, dissolution test was performed for this trial, this trial was passed the USP acceptance criteria. So, this feasible to do large scale manufacturing.

RESULTS

Table 1. Precompression Parameters

Parameters	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
Moisture content(%)	1.2	1.1	1.3	1.1	1.0	1.2	1.1
Bulk density(gm/ml)	0.5076	0.5050	0.4854	0.4830	0.4629	0.4255	0.4424
Tapped density(gm/ml)	0.5551	0.5464	0.5464	0.5347	0.5208	0.4926	0.5102
Compressibility index (%)	8.62	8.57	11.16	9.66	11.31	13.31	13.27
Porosity	9.61	12.24	12.06	13.19	15.13	15.02	14.75

Table 2. Precompression Parameters

Parameters	Trial-1	Trial-2	Trial-3	Trial-4	Trial-5	Trial-6	Trial-7
Weight of 20 tablets (mg)	5.624	5.635	5.625	5.612	5.642	5.631	5.62
Hardness (kg/cm3)	9.3	9		8.5	9	8.7	8.8
Thickness (mm)	5.3	5.2	5.4	5.3	5.3	5.3	5.3
Width	8.3	8.25	8.3	8.25	8.3	8.3	8.3
Length	11.3	11.3	11.2	11.4	11.3	11.4	11.3
Friability (%)	0.01	0.2	0.02	0.2	0.21	0.223	0.205
Disintegration	120 sec	90 sec	60 sec	50 sec	35 sec	30 sec	30 sec
In vivo disintegration test	135 sec	106 sec	84 sec	62 sec	48 sec	50 sec	45 sec
Mouth feel	Bitter	Grittiness	Grittiness	Grittiness	No grittiness felt	No grittiness felt	NO grittiness felt
Wetting time	128 sec	95 sec	66 sec	54 sec	41sec	35 sec	36 sec
Assay (%)	99.78	99.55	98.68	98.95	99.52	101.5	100.37

Table 3. *In vitro* Release of Sildenafil Citrate Mouth Dissolving tablets 0.1N HCl

Trials	% Drug Release							
	2Mts	4Mts	6Mts	8Mts	10Mts	12Mts	14Mts	16Mts
1	53.1	54.3	60.9	69.4	78.8	84.5	90	93.5
2	54.4	64.3	69	77.4	86.5	96.5	-	-
3	64.8	72.6	83.9	90	94.6	-	-	-
4	61.2	69.4	80.1	85.6	97.5	-	-	-
5	77.1	95	98.1	-	-	-	-	-
6	80.1	90	98.6	-	-	-	-	-
7	77.4	87.7	97.3	-	-	-	-	-

Table 4. Stability Data of Sildenafil Citrate Mouth Dissolving Tablets

S. No	Tests	0 Days	30 Days	60 Days	90 Days
1.	Description	Complies	Complies	Complies	Complies
2.	Average weight	5.6200	5.629	5.632	5.635
3.	Average thickness	5.2	5.2	5.2	5.2
4.	Average width	8.3	8.3	8.3	8.3
5	Average length	11.4	11.4	11.4	11.4
6.	Average hardness	8.8	8.82	8.85	8.89
7.	Friability NMT 1.0 %	0.205%	0.1842%	0.1720%	0.1540%
8.	Disintegration time	30 sec	42 sec	65 seconds	105 seconds
9.	Assay of Sildenafil Citrate	100.34%	99.98%	99.72%	99.04%

Storage conditions: 24^0C ±2 at 60% ±5%RH

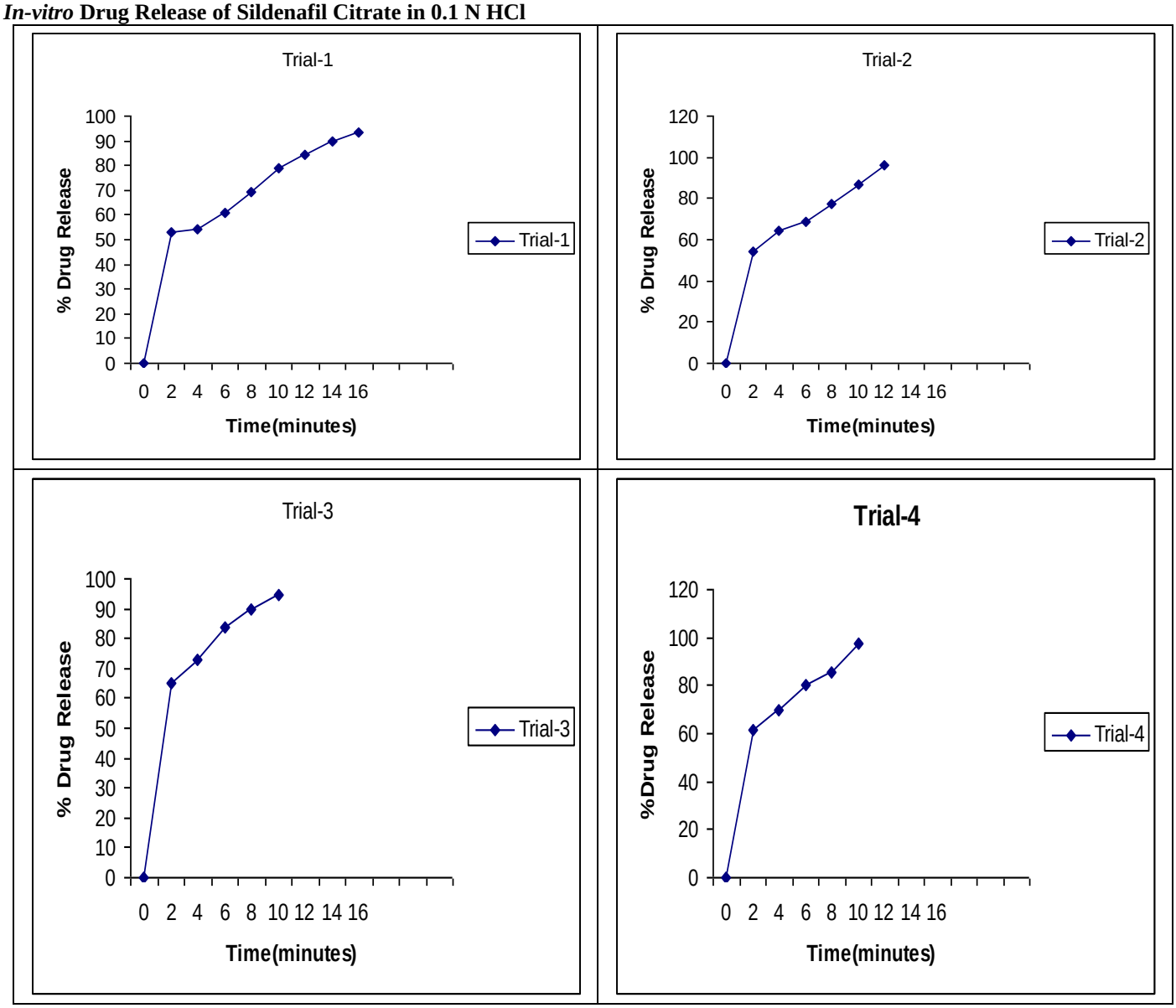
Table 4. Stability Data of Sildenafil Citrate Mouth Dissolving Tablets

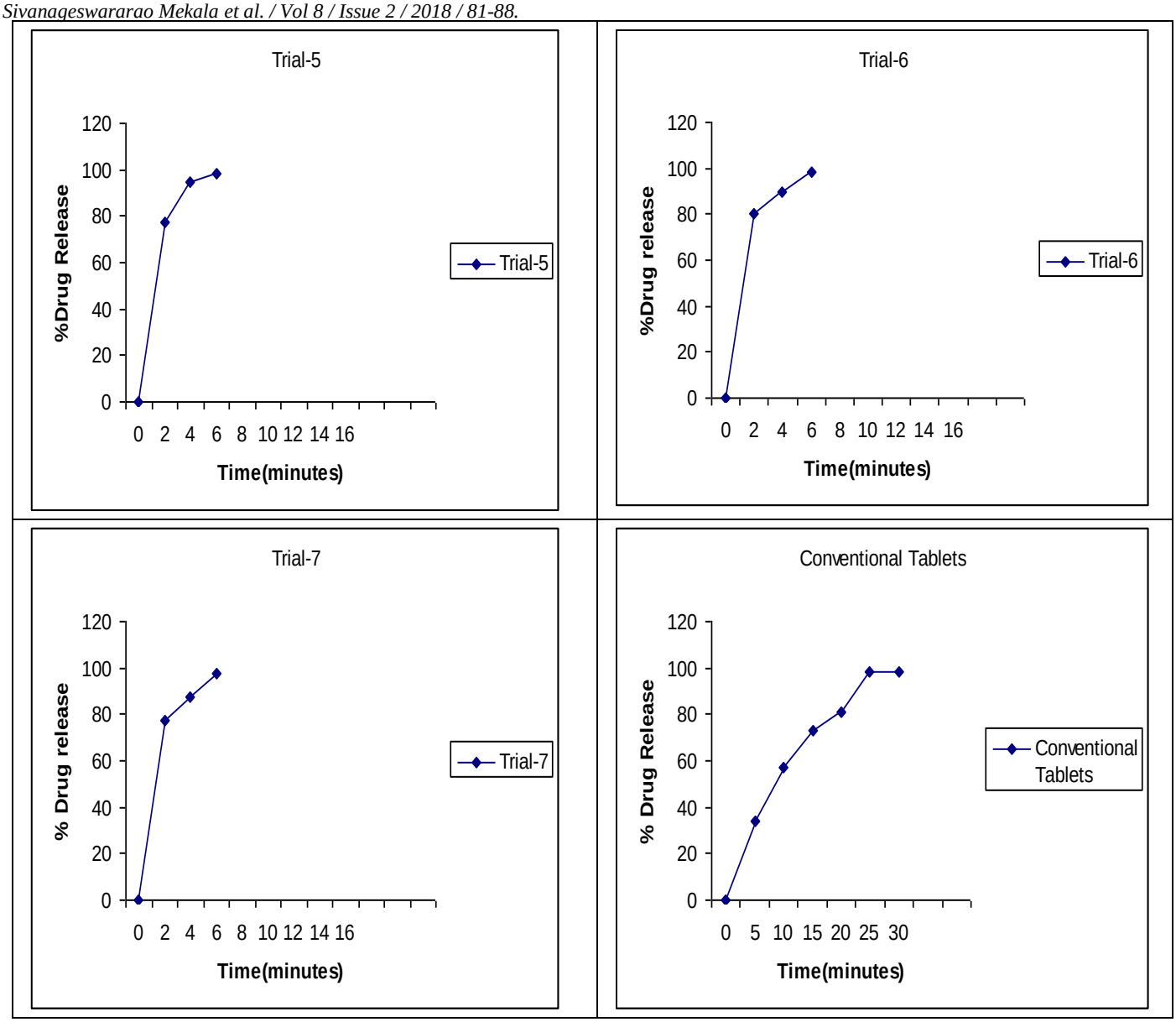
S.No	Tests	0 Days	30 Days	60 Days	90 Days
1.	Description	complies	complies	complies	Complies
2.	Average weight	5.6200	5.6148	5.6152	5.6156
3.	Average Thickness	5.2	5.2	5.2	5.2
4	Average Width	8.3	8.3	8.3	8.3
5	Average Lengh	11.4	11.4	11.4	11.4
6.	Average Hardness	8.80	8.84	8.84	8.86
7.	Friability NMT 1.0 %	0.205%	0.228	0.232	0.253
8.	Disintegration Time	30 sec	38 Sec	1 mint 45 sec	2 mint 15 sec
9.	Assay of Sildenafil citrate	100.34%	100.14%	100.02%	99.88%

Storage conditions: 40^0 ±2˚ C at 75 ±5%RH

Description : Blue coloured, uncoated and diamond shaped tablets

***In-vitro* Drug Release of Sildenafil Citrate in 0.1 N HCl**





DISCUSSION

The main objective of present study to investigate the possibility of developing mouth dissolving sildenafil citrate tablets. The tablets were made using common excipients such as Aspartame, mannitol, citric acid and sodium bicarbonate is used to mask the taste. The formulated granules were found to have almost uniform aerated bulk density and tapped density, while the compressibility index for all formulations was found to be below 16%. All the formulated tablets were found to contain Sildenafil Citrate within 100±5% of labeled claim. Hardness of the tablets was found to be satisfactory. Friability of all the tablets was less than 1%. All the formulation disintegrate rapidly within 120 seconds and *in-vivo* within 135 seconds but rapid disintegration and dispersion was observed from the trials 5, 6 and 7.The rest of the formulation took more time but still were below120 seconds. Thus the rapid disintegration of tablets in the oral cavity may be contributed to the use of super disintergrants and formation of pores due to the liberation of carbon-dioxide. The porosity leads the saliva to penetrate into the tablets which further swelling of disintegrant with enough hydrodynamic pressure to induce complete disintegration with secondary burst effect by capillary action.

The dissolution profile indicated that all the formulation released almost 100 % drugs at the end of 16 minutes. The rapid drug dissolution was observed from trial 5, 6 and 7 which release 98.1%, 98.6% and 97.3% respectively just end of 6 minutes than remaining formulation and conventional formulation (VEETAB) which need 30 minutes to release 100% of drug. Thus rapid drug dissolution of formulated tablets may be due to easy

breakdown of particles and dissolution of the drug into the medium. Feel of gridiness in mouth is not felt when the granules are passed through the sieve no 24 before compression.

The result of the influence of disintegrates concentration on dispersion time showed that an increase in the concentration of crospovidone from 4-8 % causes increase in the dispersion. Thus tablets containing 8 % of crospovidone could be considered as an optimum concentration which demonstrated excellent *in-vitro* and *in-vivo* disintegration power and faster dissolution profile than other formulation. Hence at this concentration there may be more amount of water uptake and consequent strong swelling of the superdisintegrant causing sufficient hydrodynamic pressure to induce complete disintegrates. Thus, mouth dissolving tablets, apart from full filling all official and other specifications, exhibit faster release rate of Sildenafil Citrate.

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