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Evaluation and Characterization of Sildenafil 50 mg Orodispersible Tablets Using Sublimation Technique

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ABSTRACT

Objective: The aim of this work focused on formulation and evaluation of sildenafil 50 mg orodispersible tablets by sublimation technique. **Methods:** Active ingredient and excipients mixtures were evaluated for physicochemical changes of the drug utilizing FTIR spectroscopy and DSC thermal analysis. Nineteen proposed formulae N1-N19 were prepared by sublimation technique using menthol as a sublimating agent. Three different types of superdisintegrants (sodium starch glycolate, croscarmellose sodium and plasidone XL) were used in three different ratios (3, 6 and 9 % w/w), percentage of inter-granular and intragranular disintegrant. Hydrophilic filler such as mannitol and hydrophobic filler such as microcrystalline cellulose were used in the ratio (1:1, 2:1 and 4:1 w/w).Elimination of bitterness using sucralose as a potent sweetener. Granulation was achieved by alcoholic solution of PVP K25 as binder at Diosna® high shear mixer. Lubricant (hydrophobic magnesium stearate and hydrophilic sodium stearyl fumarate). Un-lubricated granules were characterized for bulk density, tapped density, true density, particle size distribution, Carr'sindex, Hausner ratio, flow rate and angle of repose. Tablets were firstly compressed on rotary machine then subjected to vacuum oven at 60°C for 6 hours. Post compression characterization for tablets after sublimation including content uniformity, average weight, hardness, thickness, In-vitro disintegration, friability, wetting time, assay and dissolution profile of the proposed formulae against the immediate release marketed tablet Viagra ® 50 mg tablet. **Results:** The formula (N 16) which granulated using 1% PVP k25 with 9% plasidone XL (60% of it is inter-granular while 30% intra-granular), menthol 1%, Microcrystalline cellulose: Mannitol 1:1 and magnesium stearate was the most effective formulation as it showed wetting time of 30.7 seconds, disintegration time of 25 seconds and cumulative % drug release of 92.8 and 95.8 % after 1 and 3 minute respectively. **Conclusion:** Sildenafil 50 mg ODT successfully was prepared by sublimation technique with better wetting time, disintegration time, assay dissolution profile, hardness and friability.

***Keywords**: Orodispersible tablets; Sildenafil; Superdisintegrant; Sublimation technique; Tablet porosity*

INTRODUCTION

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance[1].US FDA defined fast dissolving or disintegrating tablets (FDT) as "A solid dosage form containing medicinal substances which disintegrates rapidly within a matter of seconds, when placed upon the tongue". Fast disintegrating tablets are also known as fast dissolving, mouth dissolving, rapid dissolving, quick dissolving, orally disintegrating, rapid melt, orodispersible, porous tablets[2]. The most evident drawback of the commonly used oral dosage

forms like tablets and capsules is difficulty in swallowing, leading to patient's incompliance particularly in case of geriatric patients. Dysphagia is commonly found among all age groups. Due to this problem, approximately 50% of population suffers. The difficulty in swallowing may be due to the taste, size and surface of dosage form. During journey, sometimes water is not easily accessible so a patient feels difficulty in swallowing solid dosage form[3].

The presence of a highly porous surface in the tablet matrix is the key factor for rapid disintegration ofODT[4].Improving the porosity, volatile substances such as sublimating agents can be used in tableting process for improving porosity[5,6].

The basic approach used in development of FDTs is the use of superdisintegrants and the elimination of bitterness. These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets. Superdisintegrants can help to facilitate drug dissolution and subsequently improve bioavailability. In sublimation method, the rapid disintegration of the tablets is achieved by creation of pores in the tablets up on sublimation of volatile components added in the tablets[7]. The saliva will enter these pores and cause the rapid disintegration of the tablets in the oral cavity. The porous structure is responsible for the faster water uptake; hence it facilitates wicking action in bringing about fasterdisintegration[8].

Orally disintegrating tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, efficacy and increased bioavailability compared with conventional oral dosage forms[9].

Because of low porosity, compressed tablets containing highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in water. Some inert volatile substances like urea, urethane, ammonium carbonate, naphthalene and camphor are added to other tablet excipients and the blend is compressed into tablet. Removal of volatile substances by sublimation generates a porous structure. Additionally, several solvents like cyclohexane and benzene can be used as pore forming agents[10]**.** Some researchers mentioned that the prepared tablets were subjected to vacuum at 80 ºC for 30 minutes to eliminate camphor and thus create pores in the tablet. Porous tablet exhibits good mechanical strength and dissolve quickly[10, 11]. The low porosity of compressed tablets may reduce water penetration into the tablet matrix resulting in slow disintegration or dissolution because these processes only occur at the surface. However, when volatile solids are compressed into tablets using a conventional method, they can be removed by sublimation to produce highly porous structures[12].

Various scientific techniques including freeze drying, molding, spray drying, sublimation, direct compression, cotton candy process, mass extrusion, melt granulation can be used in ODTs manufacture[13].

MATERIALS AND METHODS

Materials

Sildenafil citrate , Rakshit Drugs Private Limited, India; Menthol powder ,Bhagat Aromatics Ltd, India; Spray dried mannitol (Mannogem EZ®) , SPIpharma, USA.; Sodium starch glycolate (Explotab®) Roquette,France; Croscarmelosesodium (Ac-Di-Sol®), FMC biopolymer,Ireland.;Crospovidone (Plaisdone XL®), ISP, Switzerland; Pineapple powder flavour, Givudan, France; Sucralose , Food chem, China; Collidal silicon dioxide (Aerosil 200®) , Wacker Chemie, Germany.; Magnesium stearate , Peter Greven, Malysia. Sodium stearyl fumarate (PRUV®), JRS, Germany; Polyvinyl pyrrolidone K25, BASF, Germany; Potassium bromide, Merck, Darmstadt, Germany. Ethanol absolute, Fischer, Germany. Carmosin red, Sensient, USA.

Methods

Pre-formulation study by estimation of possible interaction between sildenafil citrate and some proposed excipients using spectroscopy DSC and by IR

Differential Scanning Calorimetry (DSC)

DSC is the measurement of the energy change that occurs as a sample is heated at a constant rate[14-15]. The principal process involves the heating of two ovens to the same temperature at the same rate. One heater contains the sample in a sealed pan and the other containing an empty pan serving as the reference[14,16]. Approximately (3-7 mg) samples of pure drug sildenafil citrate and binary mixtures of sildenafil citrate and the proposed excipients such as (Mannitol, microcrystalline cellulose, PVP k25, Croscarmelose sodium, sodium starchglycolate, crospovidone, sucralose, pineapple powder, Aerosil 200,menthol,magnesium stearate and sodium stearyl fumarate). DSC thermograms of sildenafil citrate and each of the excipients were compared with their corresponding physical mixtures. The blending ratio was determined based on the common drug excipient ratio of (1:1 in case of filler, binder and subliming agent, 1:0.5 ratio in case of disintegrant and 4:1 ratio is used for drug /lubricant and glidant. The 1:1 w/w ratio was chosen because it maximizes the observation of any reaction. DSC thermograms were generated at temperatures between 30 and 400ºC using a Model (DSC 4000, PerkinElmer, Waltham, MA, USA) with equipment and

Table 1. Composition of Sildenafil citrate ODTs prepared by sublimation technique

Ingredients	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12	N13	N14	N15	N16	N17	N18	N19
Sildenafil citrate	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70	70
Mannitol	161.6	142.4	142.4	89	101	95	142.4	156.8	89	98	137.6	161.6	152	89	95	92	114.65	114.66	114.66
MCC	40.4	35.6	35.6	89	101	95	35.6	39.2	89	98	34.4	40.4	38	89	95	92	57.35	57.34	57.34
PVPk25	3	9	3	9	3	9	3	9	9	3	9	3	9	3	9	3	9	9	9
CCS (Inter)	2.7	16.2	8.1	8.1	5.4	5.4													
CCS (Intra)	6.3	10.8	18.9	18.9	3.6	3.6													
SSG (Inter)							16.2	5.4	8.1	2.7									
SSG (Intra)							10.8	3.6	18.9	6.3									
Plasidone XL(Inter)											8.1	2.7	5.4	16.2	2.7	16.2	12.15	12.15	12.15
Plasidone XL(Intra)											18.9	6.3	3.6	10.8	6.3	10.8	14.85	14.85	14.85
Menthol	3	3	9	3	3	9	9	3	3	9	9	3	9	9	9	3	9	9	9
Pineapple flavour	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Sucralose	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil 200	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mag.stearate	6	6		6			6			6			6		6	6			
PRUV			6		6	6		6	6		6	6		6			6	6	6
Total weight	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

N: code for each formula

PC control unit at a heating rate of 10ºC/min and a nitrogen atmosphere. Data analysis was undertaken using Pyris™ Manager Software[14].

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra were captured for binary blends in closed vials which kept under stress conditions (14 days at 50º C) and mixed with Potassium bromide. Data were used to confirm the results of DSC. The FTIR spectra were obtained on FTIR spectrometer (Nicolet iS10, Thermo Scientific, USA) over the range 400 – 4000 cm-1[14].

Preparation of ODT by sublimation Method

Tablets were prepared according to **Table 1** by wet granulation technique using (PVP k25/Ethanol absolute). Dry blend sildenafil citrate, Avicel 101 (MCC), mannitol and specific ratio of inter granular disintegrant. Granulation process was preceded using high shear mixer (DIOSNA, Germany). The granulation process was standardized on basis of preliminary trials occurs on three steps:(a) Pre-blind (b) Binder addition (c) wet massing[9,17].Granules were dried on tray oven with controllable temperature (Heraeus, Germany) at 60º C. Finally were sieved through 500 mm mesh. Addition of Sublimating agent (Menthol dissolved in acetone as solvent). Allow the granules to dry at room temperature to evaporate acetone only while maintain menthol inside the granules[18].

Granules characterization (Pre-compression Evaluation)

Densities

Bulk Density (Db) or Envelope Density (gm/ml): It is the ratio of total mass of powder (M) to the bulk volume (Vb). Apparent bulk density was determined by pouring pre-sieved drug excipient blend into a graduated cylinder and measuring the volume and weight it. Bulk density (expressed in gm/ml) was calculated according to formula:

$$Db = M / Vb$$

Where, M = Mass of the Powder Vb= Bulk volume of the powder[19,20]

Tapped Density (Dt) (gm/ml): It is the ratio of total mass of powder to the tapped volume of powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend, on mechanical tapping apparatus. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 seconds interval. The tapping was continued until no further change in volume was noted. Tapped density (expressed in gm/ml) was calculated according to formula: Dt= M/Vt Where, M = Mass of the Powder Vt= Tapped volume of the powder[19,21].

Table 2. Compactability and flowability of granules

Formula No.	Bulk density (g/ml) ± SD	Tapped density (g/ml) ± SD	True density (g/cc) ± SD	Carr's index (%) ± SD	Huasner ratio ± SD	Angle of repose (°) ± SD	Flow rate (g/sec)	Flow
N1	0.396 ± 0.015	0.606 ± 0.016	1.598 ± 0.0028	34.62 ± 0.53	1.53 ± 0.07	37.2 ± 0.7	4	Fair
N2	0.449 ± 0.088	0.588 ± 0.009	1.651 ± 0.0048	23.47 ± 0.39	1.31 ± 0.25	33.6 ± 0.2	5.714	Good
N3	0.420 ± 0.077	0.606 ± 0.077	1.580 ± 0.0059	30.56 ± 0.24	1.44 ± 0.05	36.6 ± 0.8	4	Fair
N4	0.350 ± 0.005	0.500 ± 0.088	1.633 ± 0.0038	29.9 ± 0.11	1.42 ± 0.01	34.4 ± 0.32	4.878	Good
N5	0.350 ± 0.039	0.534 ± 0.072	1.624 ± 0.0017	34.38 ± 0.17	1.52 ± 0.08	38.1 ± 0.85	3.389	Fair
N6	0.384 ± 0.004	0.526 ± 0.065	1.584 ± 0.0005	26.99 ± 0.32	1.36 ± 0.08	34.8 ± 0.64	3.846	Good
N7	0.408 ± 0.007	0.563 ± 0.022	1.584 ± 0.0029	27.49 ± 0.4	1.37 ± 0.03	36 ± 0.35	3.278	Good
N8	0.434 ± 0.09	0.590 ± 0.099	1.757 ± 0.022	26.43 ± 0.8	1.36 ± 0.09	36.7 ± 0.2	4.44	Fair
N9	0.376 ± 0.025	0.470 ± 0.055	1.667 ± 0.0044	19.99 ± 0.11	1.24 ± 0.08	35 ± 0.96	4	Good
N10	0.378 ± 0.046	0.519 ± 0.011	1.679 ± 0.0021	27.11 ± 0.2	1.37 ± 0.02	37 ± 0.1	2.98	Fair
N11	0.373 ± 0.81	0.476 ± 0.044	1.680 ± 0.0044	21.53 ± 0.36	1.27 ± 0.01	34.7 ± 8.1	4.34	Good
N12	0.400 ± 0.006	0.541 ± 0.001	1.690 ± 0.0423	25.99 ± 0.98	1.35 ± 0.09	38.2 ± 1.12	3.03	Fair
N13	0.418 ± 0.008	0.647 ± 0.009	1.695 ± 0.0015	35.44 ± 0.66	1.54 ± 0.01	35.2 ± 0.36	4.081	Good
N14	0.351 ± 0.071	0.510 ± 0.014	1.668 ± 0.0017	31.07 ± 0.99	1.45 ± 0.2	40.1 ±0.084	2.66	Fair
N15	0.360 ± 0.033	0.472 ± 0.013	1.687 ± 0.0029	23.64 ± 0.74	1.31 ± 0.15	34.3 ± 0.4	4	Good
N16	0.344 ± 0.055	0.519 ± 0.025	1.757 ± 0.0415	33.62 ± 1.01	1.50 ± 0.01	38.5 ± 1.39	3.174	Fair
N17	0.348 ± 0.009	0.458 ± 1.04	1.698 ± 0.0092	23.83 ± 0.78	1.31 ± 0.08	33.6 ± 0.75	5.263	Good
N18	0.364 ± 0.005	0.478 ± 0.073	1.584 ± 0.0024	23.70 ± 0.55	1.31 ± 0.05	33.2 ± 0.67	5.128	Good
N19	0.363 ± 0.008	0.513 ± 0.044	1.563 ± 0.0054	29.07 ± 0.35	1.41 ± 0.22	34 ± 0.45	5	Good

True density (Absolute density) (g/cc): The true or absolute densities of finely divided solids are most often measured by pycnometry. Such measurements work by using a displacement fluid such as helium, air, mercury, or oil to penetrate the voids between neighboring particles, thereby providing an estimate of the volume of the solid part of a sample. Powder samples (1 g) were determined using a helium pycnometer (Ultra pycnometer 1000, Quanta chrome Instrument, USA). The helium pycnometer measures the true volume and density of solid powders. Density calculated was the mean of three measurements of each sample[22].

Granules size and shape

Volume surface mean diameter *"D (4, 3)"*

Granule size distribution was determined by laser diffraction method. A Malvern Mastersizer (Malvern 2000Worcestershire, UK) was used to measure granule size distribution. The diffractometer is equipped with a He–Ne laser with 18mm beam diameter collimated and spatially filtered to a single transverse mode. The active beam length was 10 mm, and a 1000mm lens was used for the measurements with a range of 4–500 _m. The samples were introduced using a dry powder feeder (Malvern Instruments, UK) at a feed rate of 3.0gm and a jet pressure of 2.4 Bar. All measurements were made in triplets to assure the reproducibility of the method. The mass or the volume moment mean diameter (or the Brouckere mean, D [4,3]) and the 10, 50 (median).and 90% fractiles were also determined using the Mastersizer software version 2.18 (Malvern Instruments, UK). Particle diameter distribution was evaluated for D [4,3] and the 10, 50 (median).and 90% fractiles for each sample[23].

Flowability parameters

Carr's Index (Consolidation Index or Compressibility index)

It is directly related to flow rate, cohesiveness and particle size. It indicates the powder flow properties.

Table 3. Particle size distribution by diffractometer

Formula	D(0.1) (µm)	D(0.5) (µm)	D((0.9) (µm)	D[4.3] Mean	Span
N1	4.645	34.778	123.998	51.383	3.432
N2	11.746	144.127	397.232	177.577	2.675
N3	8.584	141.579	418.154	181.443	2.893
N4	10.508	95.709	287.131	125.615	2.89
N5	6.422	55.739	152.632	67.916	2.623
N6	9.3	78.677	168.12	83.638	2.019
N7	5.917	43.446	133.03	57.614	2.926
N8	12.923	213.71	432.178	211.897	1.962
N9	9.661	79.425	162.476	82.292	1.924
N10	13.244	237.833	443.062	224.973	1.807
N11	272.451	365.648	471.753	370.343	0.545
N12	3.441	16.833	38.669	19.095	2.093
N13	193.635	331.193	443.834	318.704	0.755
N14	38.516	323.99	440.24	298.161	0.755
N15	34.688	237.764	441.447	235.981	1.711
N16	10.189	86.486	390.666	154.151	4.399
N17	21.083	185.71	427.382	203.045	2.188
N18	25.233	264.217	455.261	247.484	1.628
N19	23.608	255.631	451.193	240.919	1.673

Table 4. Evaluation of different sildenafil citrate oral disintegrating tablet

Formula	Mean weight (mg) ± SD	Mean diameter (mm) ± SD	Mean thickness (mm) ± SD	Drug content (mg) ± SD	% Friability	Hardness (N) ± SD	In-vitro disintegration (Sec) ± SD	Wetting time (Sec) ± SD
N1	303 ± 0.98	3.83 ± 0.14	8.99 ± 0.28	99.6 ± 0.45	1.05 ± 0.22	39 ± 2.93	75 ±0.68	41.3 ± 0.27
N2	304 ± 0.96	3.81 ± 0.03	9.04 ± 0.17	100.3 ± 0.59	1.1 ± 0.0.23	33 ± 2.05	110 ±0.89	75.67 ± 0.64
N3	304 ± 0.54	3.73 ± 0.05	9.14 ± 0.19	98.5 ± 1.36	0.9 ± 0.02	30 ± 2.73	51 ± 1.7	23.83 ± 0.44
N4	301 ± 0.44	3.71 ± 0.06	9.16 ± 0.20	99.6 ± 1.46	0.4 ± 0.05	36 ± 1.73	78 ± 0.9	75.7 ± 0.63
N5	305 ± 0.31	3.84 ± 0.16	8.89 ± 0.3	102.4 ±1.74	0.8 ±0.03	43 ± 3.74	36 ± 0.66	58.3 ± 0.81
N6	308 ± 0.62	3.94 ± 0.09	8.94 ± 0.23	100.3 ± 0.58	0.46 ± 0.05	44 ± 2.56	54 ± 0.55	74 ± 0.57
N7	301 ± 0.55	3.71 ± 0.18	8.99 ± 0.31	97.6 ± 0.69	0.7 ± 0.1	29 ± 2.61	59 ± 0.11	39.5 ± 0.73
N8	304 ± 0.92	3.76 ± 0.13	8.96 ± 0.21	99 ± 1.69	0.4 ±0.23	49 ± 2.54	87 ± 1.01	34.2 ± 0.43
N9	304 ± 0.55	3.81 ± 0.07	8.96 ± 0.26	100.2 ± 0.7	0.6 ±0.09	54 ± 2.80	71 ± 0.51	44.1 ± 0.22
N10	300 ± 0.47	3.78 ± 0.22	9.02 ± 0.33	101.6 ± 1.18	0.63 ± 0.15	42 ± 1.84	53 ± 0.23	59.1 ± 0.37
N11	305 ± 0.62	4.49 ± 0.44	8.91 ± 0.015	98 ± 0.66	0.5 ±0.11	45 ± 2.97	46 ± 0.85	54 ± 0.35
N12	304 ± 0.58	3.71 ± 0.82	8.94 ± 0.44	98.7 ± 0.79	1 ± 0.3	54 ± 6.96	72 ± 0.62	43.3 ± 0.87
N13	303 ± 0.9	3.76 ± 0.95	8.96 ± 0.11	97 ± 0.55	0.36 ± 0.05	52 ± 4	74 ± 0.49	90.83 ± 0.95
N14	305 ± 1.01	3.94 ± 0.25	8.91 ± 0.66	97.5 ± 1.01	0.36 ±0.1	57 ± 4.1	28 ± 0.33	40.33 ± 0.69
N15	302 ± 0.88	3.78 ± 0.05	8.91 ± 0.17	99.8 ± 1.33	0.26 ±0.02	50 ± 2.7	89 ± 0.50	77.83 ± 0.28
N16	305 ± 1.05	4.01 ± 0.03	8.91 ± 0.25	97.4 ± 0.9	0.293 ±0.017	42 ± 1.89	25 ± 0.71	30 ± 0.75
N17	306 ± 0.85	4.27 ± 0.88	8.94 ± 0.45	103 ± 0.75	0.42 ±0.1	48 ± 2.83	29 ± 0.63	70.33 ± 0.56
N18	304 ± 0.77	4.22 ± 0.35	8.99 ± 0.07	98.3 ± 0.2	0.45 ± 0.35	45 ± 2.3	30 ± 0.55	76.83 ± 0.64
N19	307 ± 1.22	4.19 ± 0.14	8.96 ± 0.18	101.1 ± 1.45	0.36 ±0.27	43 ± 4.6	31 ± 0.83	79.67 ± 0.91

It is expressed in percentage and is given by formula: % compressibility (I) = [Tapped density – Bulk density/ Tapped density] x 100[24-25].

Hausner Ratio

It is an indirect index of ease of powder flow. It is calculated by the following formula:

Hausner ratio = Tapped density/ Bulk density

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25)[25-26].

Carr's index and Hausner's ratio measure the propensity of powder to be compressed and the flowability of powder[25,26].

Flow rate gm/sec

Granules flow rate was assessed using flowmeter (Automated powder flow analyzer, model PTG-S4, Pharma Test, Hainburg, Germany). A sample of 50 gm of the granules was poured into the funnel of the flowmeter which has the following dimension; 12 cm the diameter at the top and 0.9 cm the diameter of the efflux orifice. The results were obtained as an average of three measurements for each granulates[27].

Angle of Repose (θ)

Granules flow rate was determined by indirect method using angle of repose. Powders with angles greater than 50º have unsatisfactory flow properties, whereas minimum angles close to 25º correspond to very good flow properties[27].The frictional forces in case of loose powder are measured by the angle of repose. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is determined by funnel method. Angle of Repose was calculated using the formula: Tan θ = 2h/d Tan θ = h/r θ = Tan-1(h/r) Where, θ = Angle of repose H = height of the pile (cm) r = radius of heap (plane surface occupied by the powder) [24, 28].

The Angle of repose and flow rate of granules was evaluated using the automatic powder flow tester (model PTG-S4, Pharma Test, Hainburg, Germany); the results were obtained as an average of three measurements for each granulates.

Compression of sildenafil Oral disintrgrating tablets

Add extra granular disintegrant, sucralose (sweetener),pineapple powder flavor while sieving and Aerosil 200 (glidant).add lubricant magnesium stearate or sodium stearyl fumarate after sieving through 355 micron followed by compression of the blend on a 10 station rotary compression machine (Korsch, Germany) using 9 mm round flat scored punches on 6.5 KN. The tablets were collected and vacuum dried at 60°C until a constant weight was obtained to ensure the complete removal of sublimating components to make the tablet porous[18].

In this approach sublimation occur from the compressed tablet not from the granules. The tablet weight was adjusted to 300 mg ± 7.5%. The tablet press was run at low speed 20 rpm to guarantee accurate filling of the die.

Post-compression evaluation of FDTs (Evaluation of Tablets)

Tablets from all the formulation were subjected to following quality control test.

Visual inspection

Upper and lower punches were inspected by naked eye for presence of sticking or picking. The general appearance of a tablet, its visual identity and overall elegance is essential for consumer acceptance. It indicates tablet size, shape, color, presence or absence of an odour, surface texture, consistency and legibility of any identification markings[29].

Drug Content Uniformity

Drug content for each formula was determined by dissolving 10 tablets from each formula. Accurately weighed portion of the ground tablets equivalent to about 50 mg sildenafil citrate was dispersed in 25 ml of methanol. The flasks were placed in a sonicator till complete dissolution; 1 ml of the solution was filtered through a Millipore filter of 0.45 µm pore size after those samples were filtered using syringe filter, assayed using HPLC [26].

Tablet thickness

The thickness of the tablets was determined using a dial thickness gauge. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm. Thickness measurement were performed directly after compression process.

Uniformity of weight or Weight variation

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity[26, 30, 31].

Hardness (Tablet tensile strength or crushing test)

The average breaking strength of tablets was determined by tablet hardness tester (DR.SCHLEUNIGER Pharmatron, USA). From each formula, 10 tablets were tested for their hardness; the mean hardness (±SD) in Newton (N) of each formula was determined.[27] The tablet was held along its oblong axis

Table 5. In vitro release during different time intervals 1, 3,5,10 and 15 minutes

Formula	1 min	3 min	5 min	10 min	15 min	Similarity factor (f2)
N1	51.4 ± 2.87	99.5 ± 2.06	99.9 ± 1.48	100.7 ± 0.65	101.3 ± 0.72	52.84 %
N2	43.1 ± 3.82	89.8 ±7.66	102.2 ± 1.33	104.1 ±1.04	104.5 ± 1.1	61.05 %
N3	61.7 ± 2.36	93.2 ± 1.99	95.9 ± 2.15	96 ± 1.83	96.8 ± 1.75	43.59 %
N4	43.2 ±3.26	93.6 ± 1.12	98.7 ± 0.66	100.5 ± 0.88	101.2 ± 0.56	65.41 %
N5	62.3 ± 4.4	97.2 ± 0.3	100 ± 0.84	101.4 ± 1.04	103.3 ± 0.82	43.53 %
N6	37.3 ±2.79	84.3 ±2.29	100 ± 0.97	101.6 ± 1.25	102 ± 1.47	63.58 %
N7	65.5 ±0.32	95.8 ± 1.29	100.5 ± 0.25	100.3 ± 0.6	101.1 ± 0.25	41.49 %
N8	33.8 ± 2.09	78 ± 0.9	100.1 ± 0.26	102.4 ± 0.47	103.2 ± 0.29	55.49 %
N9	35.1 ± 1.78	73.7 ± 3.38	96.2 ± 0.41	99.2 ± 2.34	102 ± 1.17	50.71 %
N10	60.7 ± 5.36	96.7 ± 0.87	98.9 ± 0.52	99.8 ± 0.58	100.2 ± 0.89	44.86 %
N11	90.3 ± 5.16	96.2 ± 0.92	96.1 ± 0.79	96.4 ± 0.79	96.5 ± 1	29.24 %
N12	47.1 ± 3.23	93.8 ± 3.05	96.2 ± 0.56	96.9 ± 0.97	96.9 ± 1.1	57.38 %
N13	41.1 ± 8.38	85.6 ± 3.05	90.1 ± 0.8	91.8 ± 2.13	91.1 ± 0.55	52.27 %
N14	79.8 ± 7.16	94.6 ± 2.07	96 ± 1.39	96.7 ± 1.18	97.1 ± 1.14	33.56 %
N15	30.4 ± 3.9	67.8 ± 6.09	95 ± 1.5	98 ± 1.15	99.2 ± 0.46	45.42 %
N16	92.8 ± 2.04	95.8 ± 0.54	95.9 ± 0.35	96.1 ± 0.4	96.1 ± 0.56	28.31 %
N17	81.8 ± 8.19	95.8 ± 2.27	97.7 ± 2.18	100.5 ± 2.68	101.6 ± 0.75	32.82 %
N18	94.3 ± 0.49	100.7 ± 0.49	101.4 ± 0.34	102.3 ± 0.48	101.9 ± 0.26	27.8 %
N19	100 ± 1.08	102.5 ± 1.01	103.5 ± 1.91	103.2 ± 1.59	103 ± 1.79	25.78 %
Viagra®	32.5 ± 2.61	94.8 ± 1.3	99.1 ± 1.97	100.2 ± 2.16	100.8 ± 2.45	

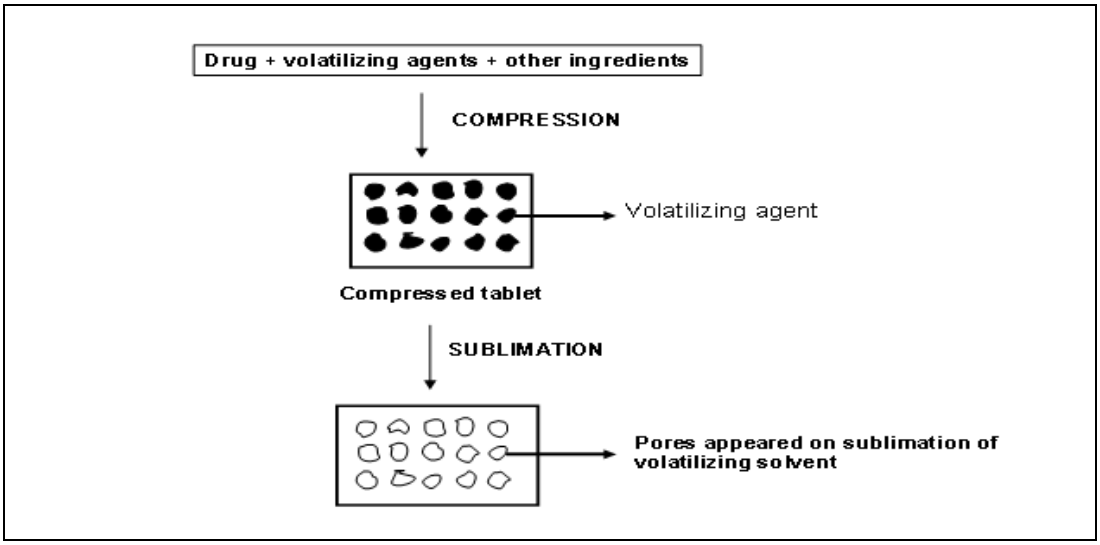

Figure 1. Steps involved in sublimation process.

in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured[24, 25, 26, 32].

Friability test

Ten pre-weighed tablets from each formula were tested, accurately placed in the drum of the friabilator (PharmaTest, Germany) and rotated at 25 rpm for a period of 4 min, then reweighed. The percentage loss in weights was calculated and taken as a measure of friability[26, 33, 34].

% Friability = [(W1-W2)100]/W1
W1= Weight of tablet before test (Initial Weight)
W2 = Weight of tablet after test (Final Weight).

Thus, it is necessary that this parameter should be evaluated and the results are within bound limits not more than 1 % [34, 35].

***In-vitro* wetting time**

Ten milliliters of water soluble dye Carmosine solution 0.1 % is added to petri dish containing five circular filter papers of 10 cm diameter. Tablets were carefully placed on the surface of the filter paper and the time required for water to reach upper surface of the tablet was noted as the wetting time. The test results were presented as mean value of six determinations (± SD) [9,36,37,38].

***In- vitro* disintegration time**

Disintegration times of ODTs were determined using six tablets in distilled water kept at 37 ± 0.5°C using a disintegration tester (ERWEKA,USA).The time when there were no particles of tablets or only a trace amount of soft residue remains on the screen was selected as the disintegration time. The test results presented are the average of three determinations (n=3)[2, 14].

***In- vitro* dissolution time**

The test was performed using a dissolution tester (model VK7010, Varian Inc., USA) equipped with an auto-sampler (model VK8000).The dissolution profile ODTS compared with the immediate release plain drug and market product (Viagra®) were determined using the USP dissolution tester I (Varian dissolution tester, Germany).Dissolution media were 900 ml of the most suitable media0.01 N HCl (PH=1.2) maintained at of 37 ± 0.5°C with a basket rotation speed at 100 r.p.m. The amount of drug used was 70 mg sildenafil citrate equivalent to 50 mg sildenafil base. At specified time intervals (1, 3, 5, 10 and 15 min.), 3 ml of dissolution media were withdrawn, and replaced with an equal volume of the fresh medium to maintain a constant total volume. Samples were filtered through 0.45um Millipore filter and assayed for drug content using HPLC[2,14, 39].

The dissolution profiles of all the ODT formulations for sildenafil citrate were compared with the marketed immediate release formulation by using a model independent approach of similarity factor, f2 is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves of marketed and test formulations[40]. The equation for calculating similarity factor is:

$$f_2 = 50 \times \log \left\{ \left[1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where 'n' is the number of dissolution time intervals and R_t and T_t are the reference (theoretical) and test dissolution values at time 't'. Dissolution profile was considered satisfactory if f2 value is more than 50. Two dissolution profiles are considered similar when the f2 value is 50 to 100[18].

RESULTS AND DISCUSSION

Pre-formulation study by estimation of possible interaction between sildenafil citrate and some proposed excipients using spectroscopy DSC and by IR

Differential Scanning Calorimetry (DSC)

The DSC thermogram of pure sildenafil citrate shows one main characteristic sharp melting endothermic peak at 200°C. The DSC thermograms of physical mixtures of drug and different excipients illustrated in **Figure 2** reveal no significant change in the melting point of sildenafil citrate in the presence of excipients, indicating no interaction between the drug and excipient[14, 41]. The 1:1 w/w ratio was chosen because it maximizes the observation of any reaction. The incompatibilities were detected by appearance, shift or disappearance of the corresponding peaks of each substance. It is clear from **Figure 2** that SC has a main sharp characteristic endothermic melting peak at 200 °C. The sharp endothermic peak signifies that SC was in a pure crystalline state. It notice that there was no shift in SC peak upon mixing with plasidone XL reveal endothermic melting peak at 203°C , Sodium starch glycolate at 202.48 °C , croscarmellose sodium at 202.76 °C, Sucralose at broad endothermic peak at 216 °C , pineapple at 204 °C, PVP K25 have two endothermic peak at 200 °C and other peak 193.84 specific for PVP k25, menthol at 193.84 and other specific peak for menthol 48.76 °C and , microcrystalline cellulose at 199 °C, sodium stearyl fumarate have two peak 197 °C for SC and 125 for sodium stearyl fumarate, magnesium stearate at 202 °C, Aerosil 200 at 203 °C, as shown in

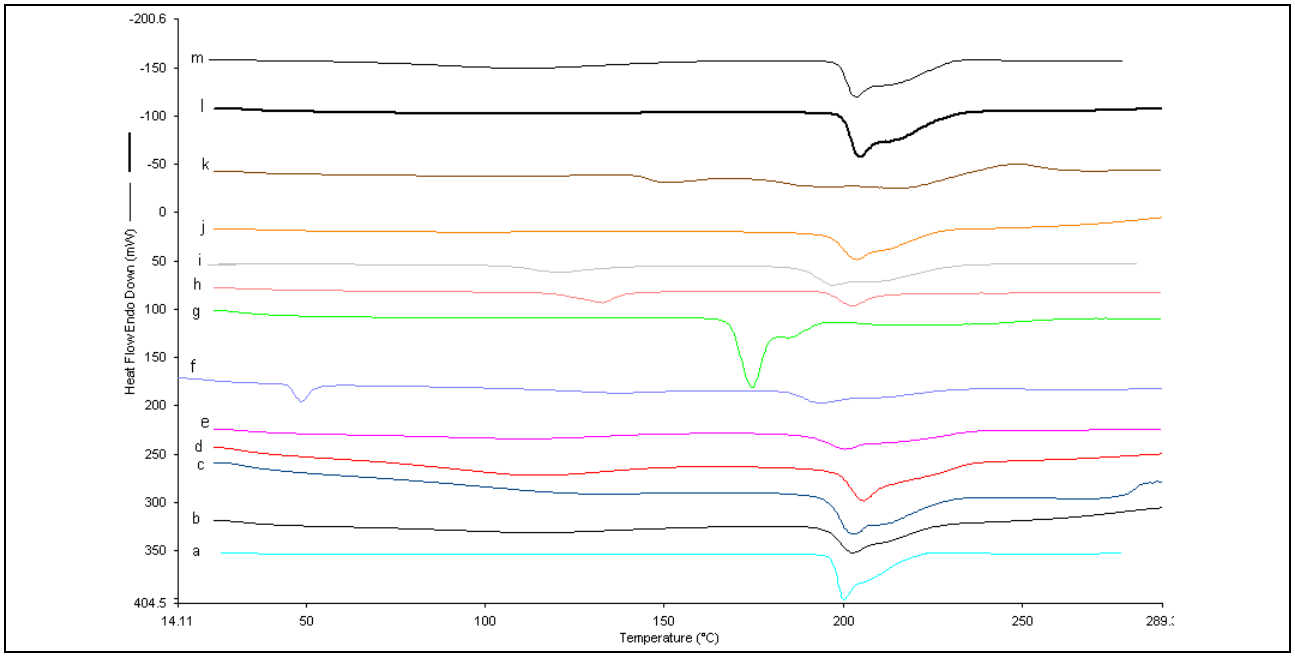

Figure 2. DSC thermograms of sildenafil citrate and its binary mixture. Where (a) Sildenafil citrate pure drug, (b) S+ Croscarmellose sodium 1:1, (c) S + Sodium starch glycolate 1:1, (d) S+ Crospovidone 1:1, (e) S + PVPk 25, (f) S+ Menthol 1:4, (g) S+ Mannitol 1:1,(h) S+ Magnesium stearate 1:4, (i) S+ Sodium stearyl fumarate 1:1, (j)S+ Colloidal silicone dioxide 1:4, (k) S+ Sucralose 1:4, (l)S+ Pine apple 1:4, (m) S+ Microcrystalline cellulose 1:1.

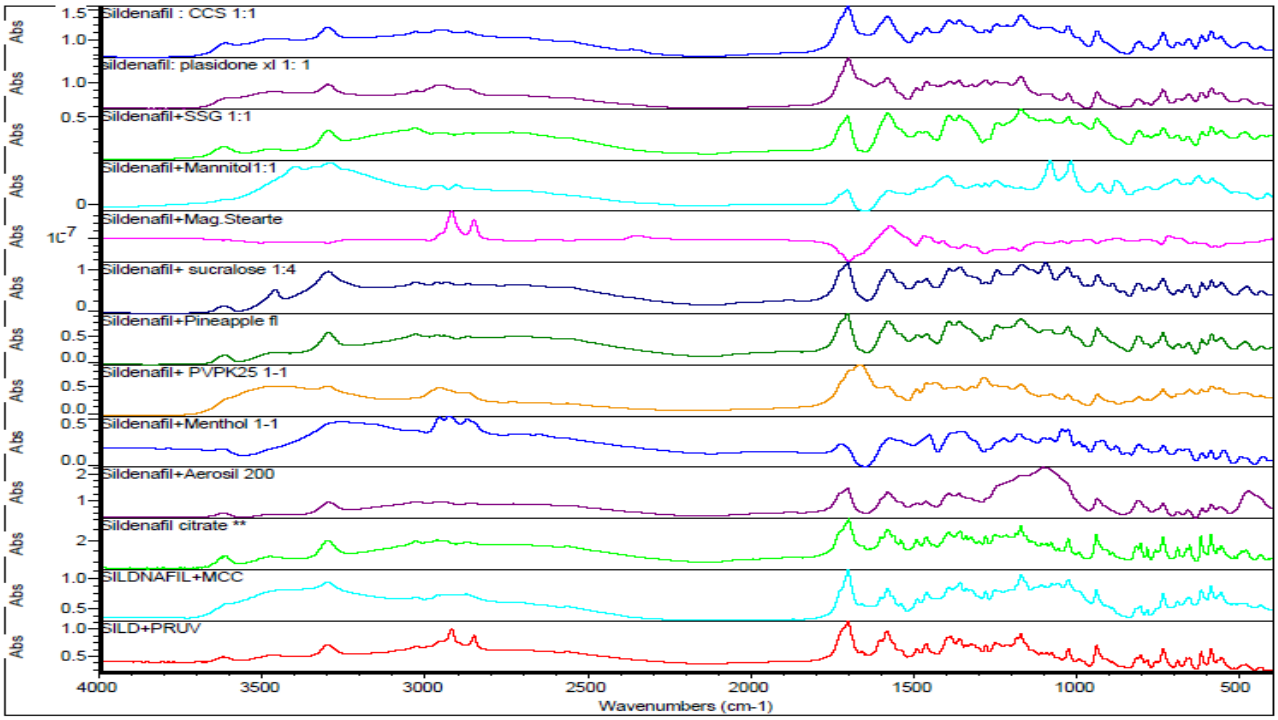

Figure 3. FTIR spectra of sildenafil citrate and binary mixture with the used excipients mimic its concentration in formula.

Figure 2. While the thermogram for mannitol reveals one endothermic peak at 171.51°C and the thermogram of the mixture of sildenafil citrate and mannitol displays a sharp peak at 168 °C, indicating the presence of mannitol. The peak for SC is not present or shifted from its position indicating that at high temperatures an interaction between SC and mannitol occurs. This interaction is more than likely due to a small amount of reducing sugar that may be present in mannitol, thereby precipitating a Maillard reaction[41]. DSC results showed that may there is an incompatibility between mannitol and SC.

Fourier transform infrared (FTIR) spectroscopy

Figure 3 illustrate spectra of sildenafil citrate and binary mixtures with the used excipients mimic its concentration in formula.

Figure 4 shows possible main absorption peaks for **sildenafil citrate** and its near infrared spectrum including peaks at 1172.5 and 1357.84 cm^{-1} for symmetric and asymmetric SO_2, respectively, at 1581.4 and 1700.79 cm^{-1} for symmetric and asymmetric COOH respectively, hydroxyl (OH) at 3616 cm^{-1}, NH symmetric and asymmetric stretching at 3298.4 cm^{-1}(major peak), CH bond aromatic on benzene (=CH) at 3027.85 cm^{-1} and aliphatic methyl and methylene (CH) at 2904.6–2949 cm^{-1}.

Figure 5 shows main absorption peaks for **mannitol** includes a number of characteristic peaks. The very broad peak at 3400.06 cm^{-1} represents OH band stretching. The three peaks at 2984.8 cm^{-1}, 2948.21cm^{-1} and 2910.88 cm^{-1} may be attributed to CH stretching while the peaks at 1281.97 cm^{-1} and 1260.27 cm^{-1} corresponding to primary and secondary alcohol OH plane deformation. The peaks at 1080.49 cm^{-1} and 1045cm^{-1} represent primary and secondary alcohol C=O stretching, respectively.

To ensure that no interaction between SC and mannitol occurred as show in an IR spectra of a 1:1 binary mixture of SC and mannitol was generated as shown in **Figures 5, 6(a), 6(b)** and revealed the presence of all characteristic peaks for SC and mannitol. It was thought that the Maillard reaction had occurred with reducing sugars found in mannitol, reacting with the secondary amine to form an imine. The spectrum highlights that no imine product was formed as a characteristic peak for imine would appear at a wave number of 1630cm^{-1}. The absence of this peak confirms the fact that at room temperatures a Maillard reaction is not likely to have taken place [41]. This result is in accordance to work done Abdel Halim, S. A., 2013.

Granules characterization (Pre-compression Evaluation)

Evaluation for bulk density, tapped density, Carr's index, Hausnerratio, angle of reposes and flow rate

The powder mixtures of all batches (N1-N19) are evaluated for bulk density, tapped density, Carr's index, Hausner ratio and angle of repose and are shown in **Table 4**. **Bulk density** range from 0.344 to 0.449 g/ml, **Tapped density** range from 0.458 to 0.647 g/ml, **True density** range from 1.563 to 1.689 g/cc , **Angle of repose** range from 33.2 ° to 40.1 ° ,Hausner ratio from 1.27 to 1.54 and **Carr's index ranged** from 19.99 to 35.44 %. All these results indicating that the powder mixture have a good flow property and compressibility index.

Granules size and shape

Volume surface mean diameter *"D (4, 3)"*

Formulae N11, N13, N14showed the highest volume surface diameter (370.34, 318.7, 298.16 µm respectively). These formulae have a common variable Plasidone XL (9, 3, 9% respectively) and higher level of PVP k25 (3%) which enhance granule growth.

Formulae N12, N7, N1 showed the lowest volume surface mean diameter (19.09, 51.38, 57.61 µm respectively). **N12, N1** have low percentage of disintegrant (plasidone XL 3% and 3% croscarmellose sodium) while N7 contain 9% sodium starch glycolate. These formulae contain the lowest level of binder 1% PVP k 25. This due the particle size of plasidone XL (58 µm) compared with particle size of croscarmellose sodium (51µm) and sodium starch glycolate (29 µm).

These results were being in accordance with work done by Realpe A. et al who mentioned the initial particle size distribution has a strong effect upon granule growth rate and the mechanism by which wet granulation occur[42].

Post-compression evaluation of ODTs (Evaluation of Tablets)

Uniformity of SC content

Results revealed uniform sildenafil citrate content in ODTs from formulae N1:N19 ranged from (97 ± 0.55to 103±0.21). Results are presented in **Table 4.**

Uniformity of weight

Results are presented in **Table 4** reveals the average weight for ODTs formulae N1:N19 ranged from (300±0.47 mg to 307 ±1.22 mg), therefore all the tablets fall within the acceptable weight variation range; according to the European pharmacopoeia (2017), not more than two tablets deviated from the average weight by more than 7.5% and not deviated by more than twice this percentage.

Friability test

Table 4 reveals the friability results for the prepared ODTs. According to compendial standards (European pharmacopeia 2017), the tablets comply with the friability test if the weight loss during the test was less than 1%, in addition, the tablets should not break or

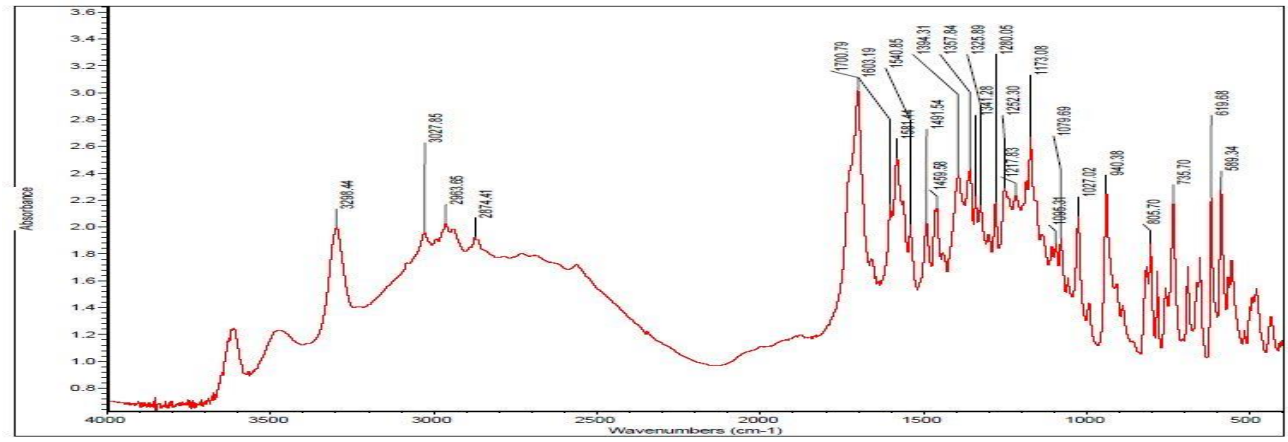

Figure 4. FTIR spectrum of sildenafil citrate pure drug.

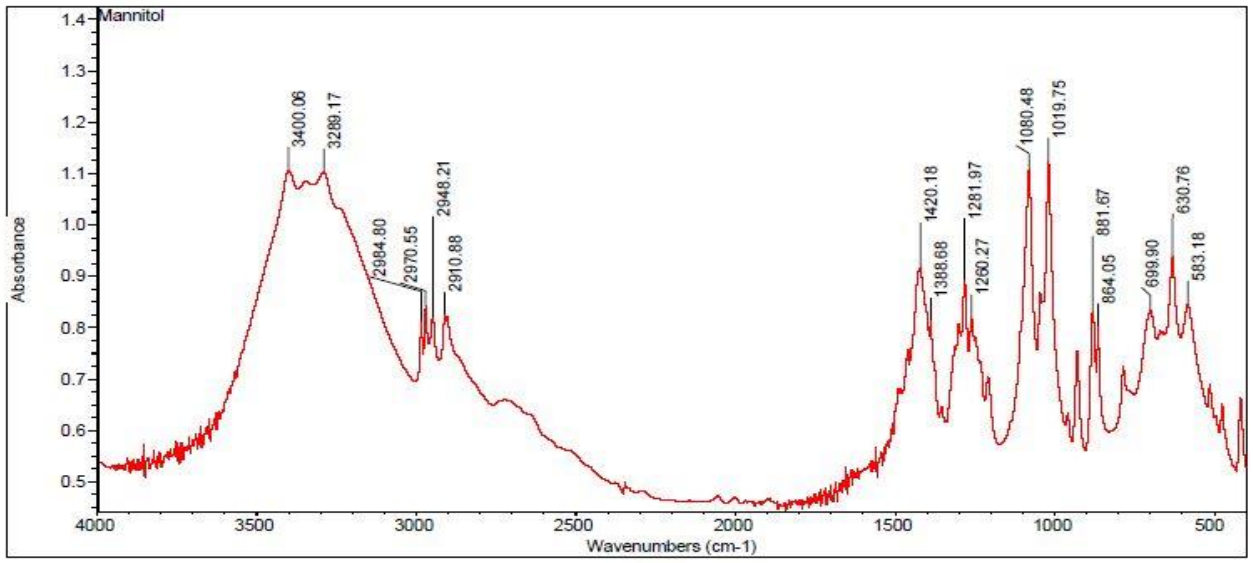

Figure 5. FTIR spectrum of mannitol.

show any capping or cracking during the test. Results showed that ODTs formulated with PVPK25 as a binder former showed percentage fines within the acceptable range for tablets (less than 1%). Some ODTs were more friable than the others, as they showed higher percentage of weight loss. N1,N2 and N12 showed higher percentage weight loss (1.05,1.1,1% respectively) while ODT formulae N9,N7,N5 and N3 showed percentage weight loss of (0.6 , 0.7, 0.8 and 0.9%) respectively while N15,N16,N14 and N13 formulae showed lower amount of friability (0.29,0.26,0.36 and 0.36%) respectively.

In-vitro disintegration time

Results are presented in **Table 4** reveals the average disintegration time for ODTs formulae N1:N19 ranged from (25 ± 0.71 mg to 110 ± 0.89 mg)**.**

ODT formulae **(N16, N17, N14, N18 and N19)** which containing Plasidone XL. It show short disintegration time (25, 29, 28, 30 and 31 seconds) respectively; this may be due to the presence of high percent of super disintegrant 9% in the tablets which rapidly uptake water and swell and exert sufficient pressure inside tablet to break apart into small segments[14,43]. Menthol which added as sublimating agent 3% makes the tablet have a porous structure[44]. Increasing the ratio of microcrystalline cellulose : mannitol (1:1 and 1:2) may have an disintegrant action[45]. This May be due to presence of equal amount of disintegrant intergranular and extragranular (60:40 % and 55:45%).

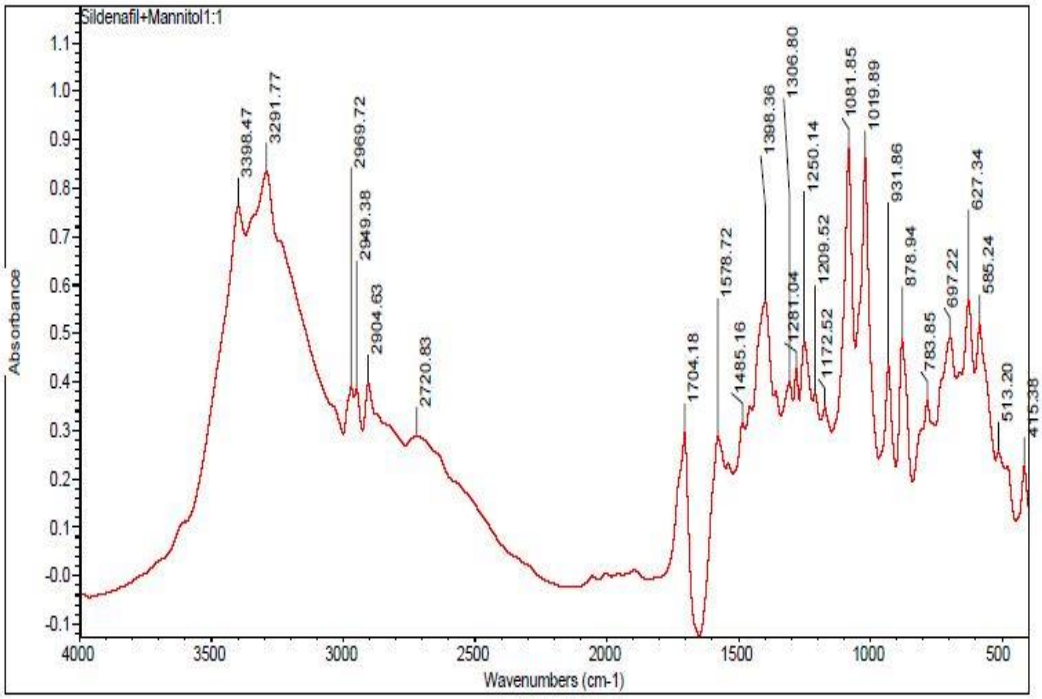

Figure 6 (a). FTIR spectrum of 1:1 binary mixture of sildenafil citrate and mannitol.

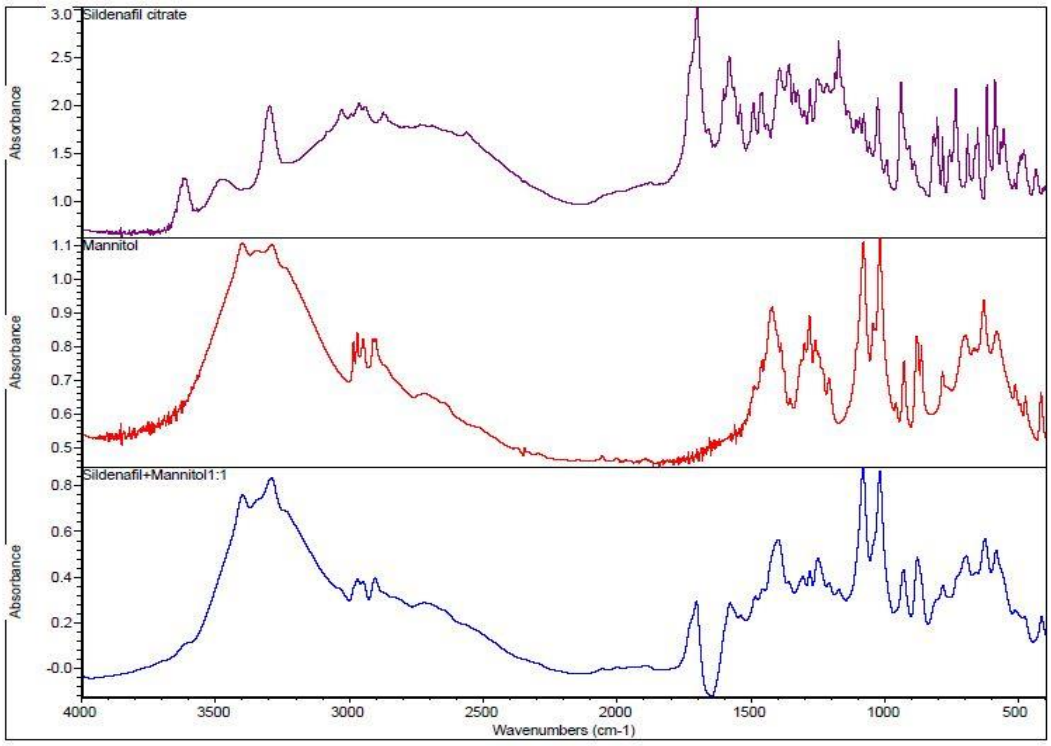

Figure 6 (b). FTIR spectrum of sildenafil citrate, mannitol & their binary mixture 1:1.

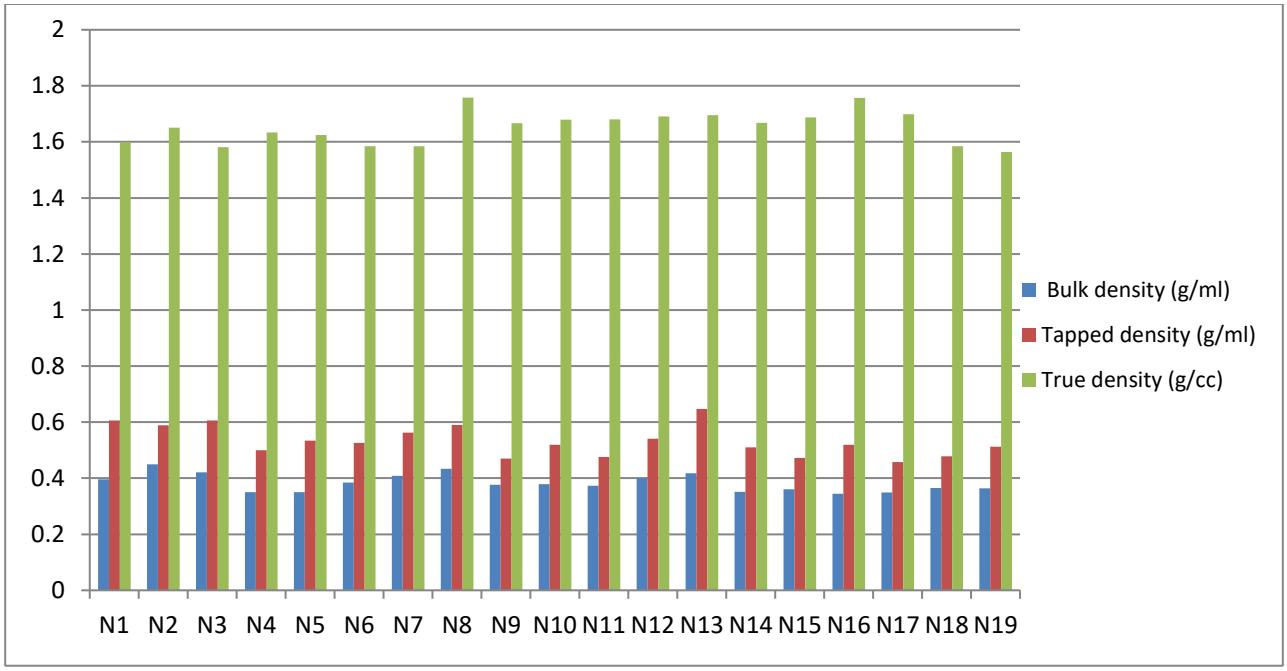

Figure 7. Different types of densities (bulk, tapped and true density).

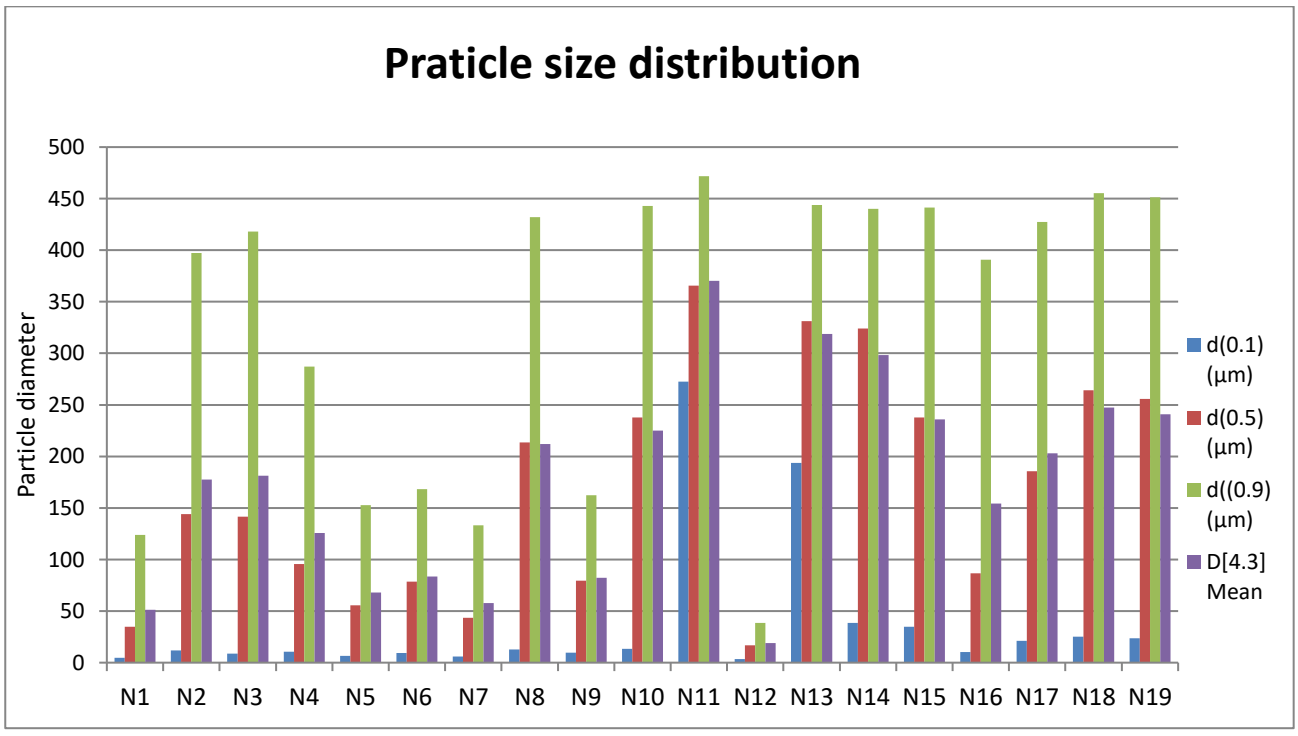

Figure 8. Granule size fractiles prepared by sublimation technique.

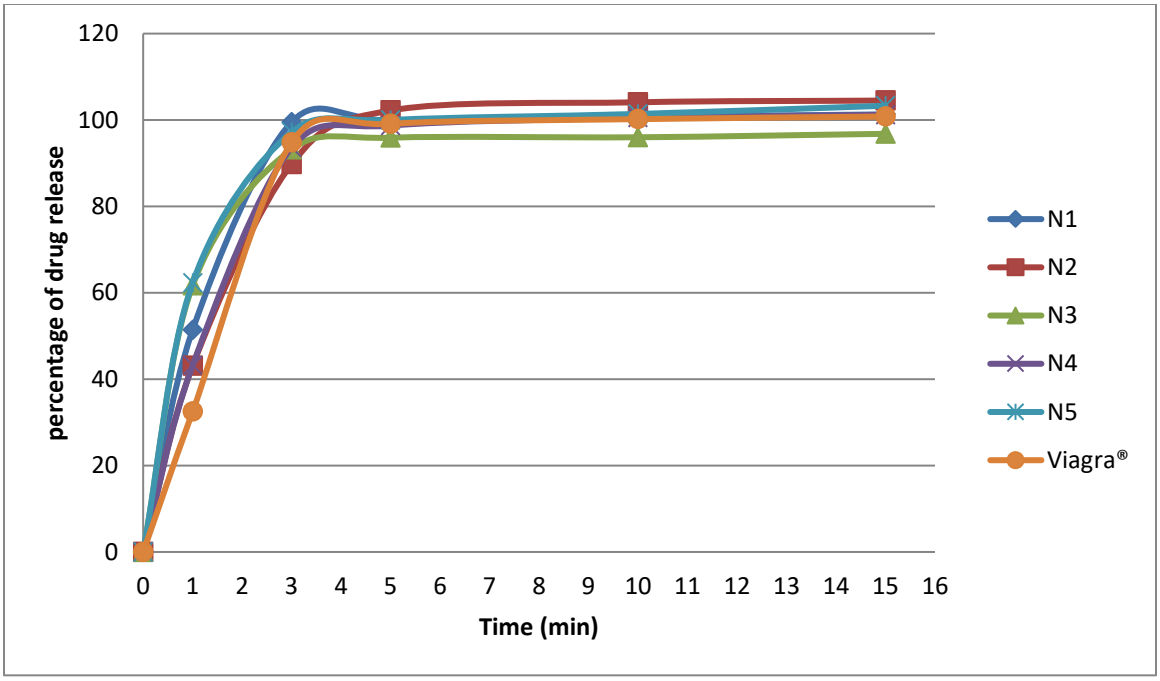

Figure 9. In vitro drug release profile of various sildenafil ODT formulae (N1-N5) against immediate release marketed drug Viagra 50 mg tablet ®

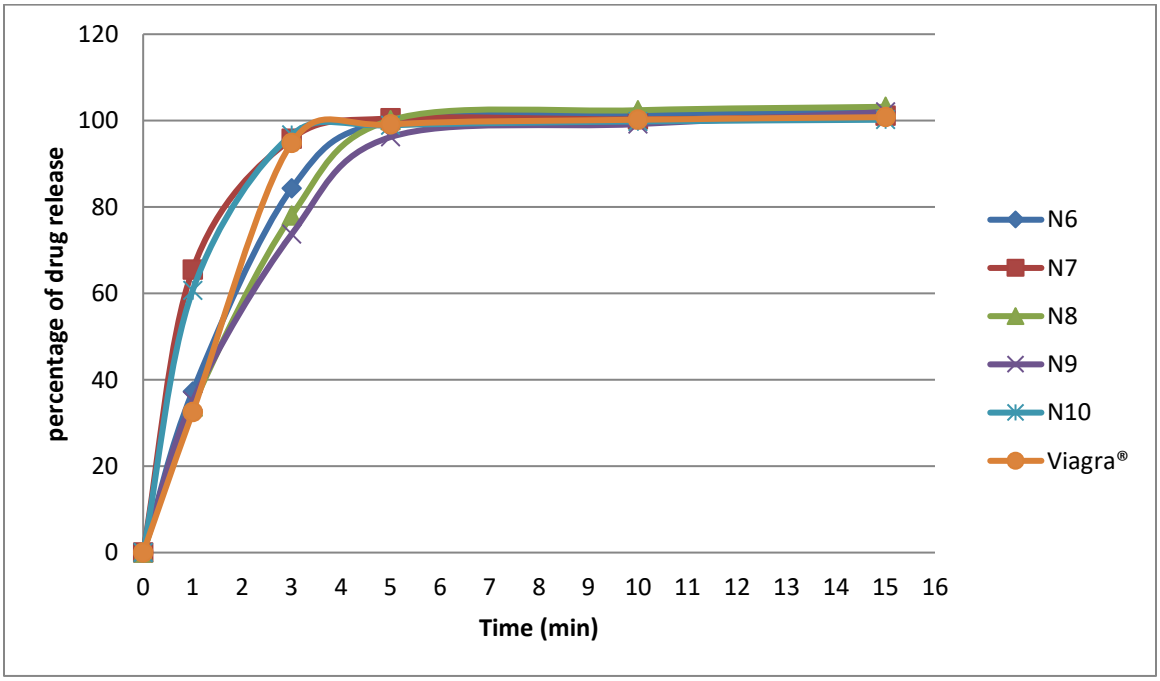

Figure 10. In vitro drug release profile of various sildenafil ODT formulae (N6-N10) against immediate release marketed drug Viagra 50 mg tablet ®

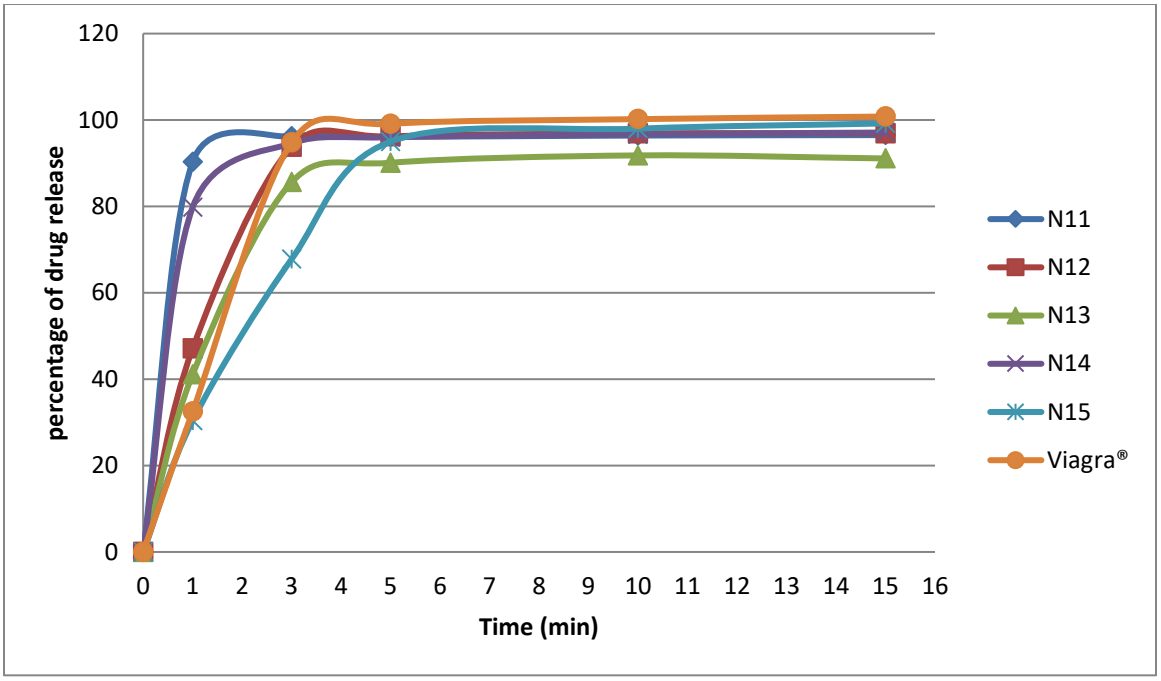

Figure 11. In vitro drug release profile of various sildenafil ODT formulae (N11-N15) against immediate release marketed drug Viagra 50 mg tablet ®

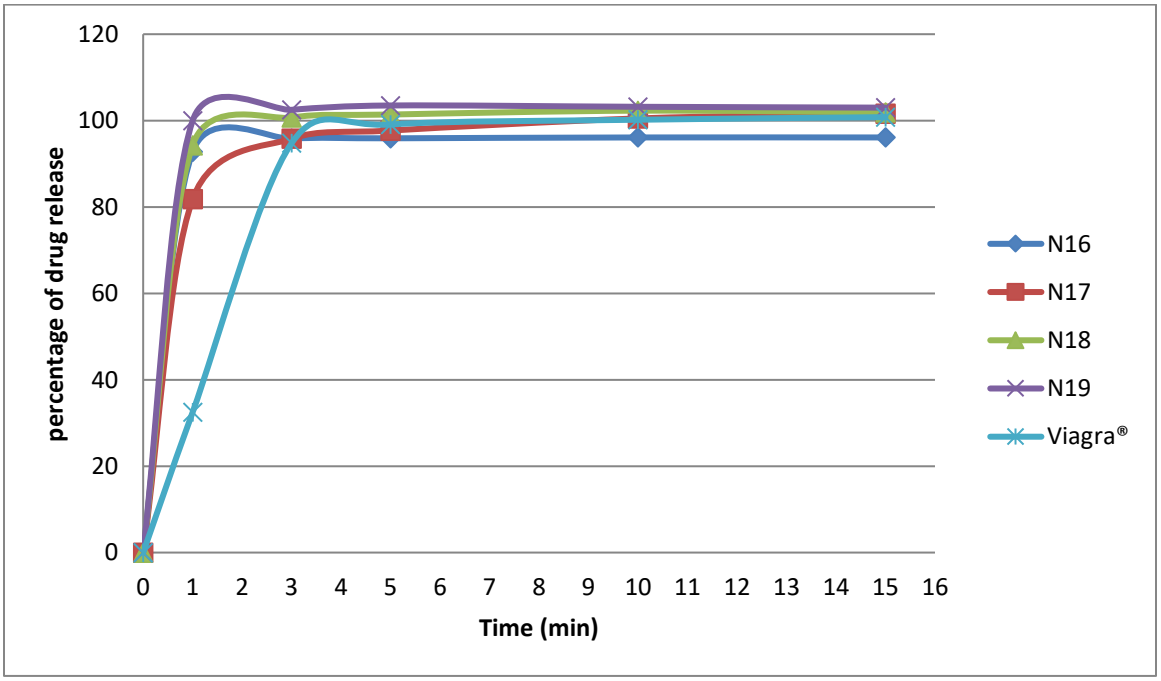

Figure 12. In vitro drug release profile of various sildenafil ODT formulae (N16-N19) against immediate release marketed drug Viagra 50 mg tablet ®

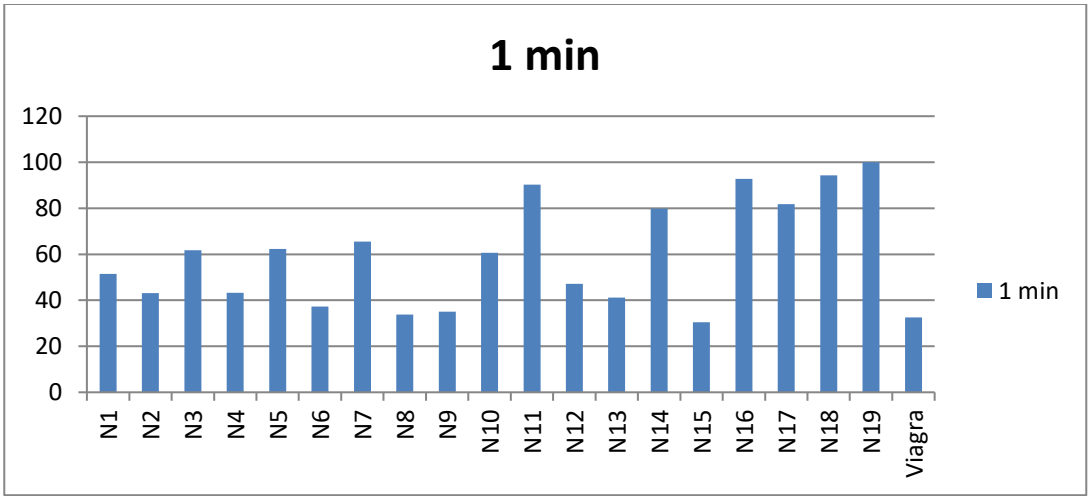

Figure 13. In vitro drug release profile of various sildenafil ODT formulae (N1-N19) against immediate release marketed drug Viagra 50 mg tablet ® after 1 min.

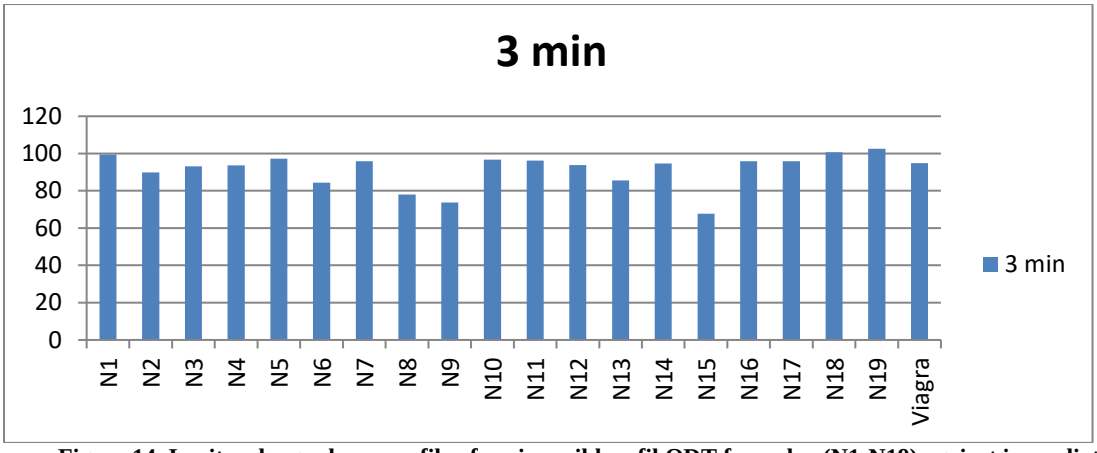

Figure 14. In vitro drug release profile of various sildenafil ODT formulae (N1-N19) against immediate release marketed drug Viagra 50 mg tablet ® after 3 min.

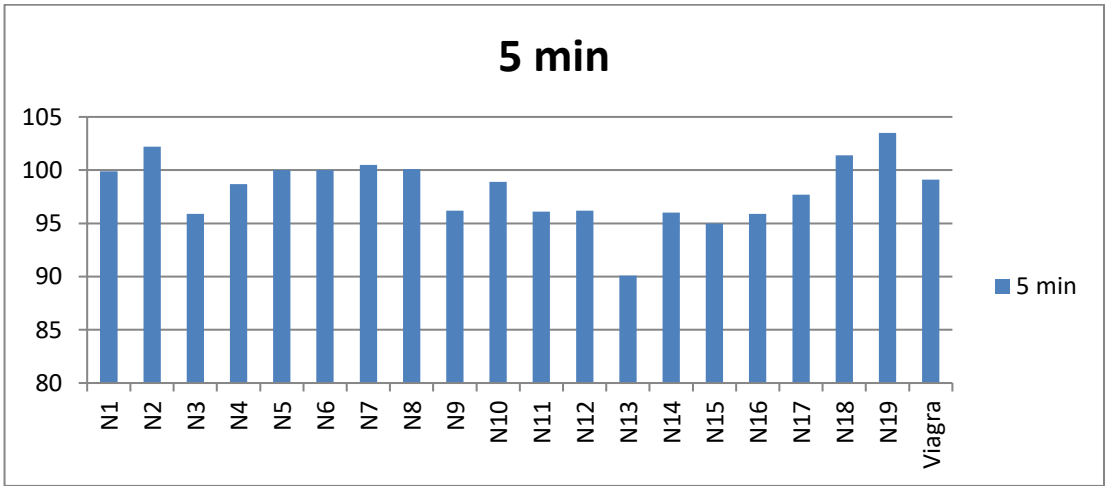

Figure 15. In vitro drug release profile of various sildenafil ODT formulae (N1-N19) against immediate release marketed drug Viagra 50 mg tablet ® after 5 min.

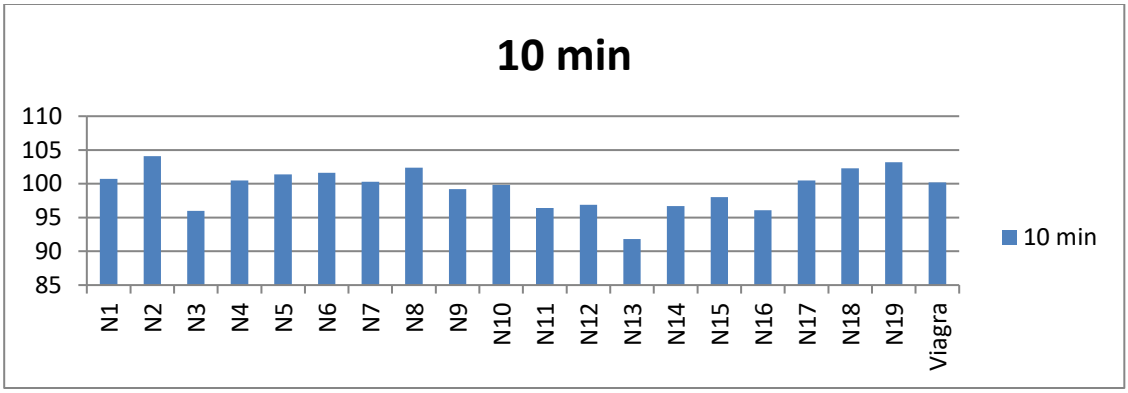

Figure 16. In vitro drug release profile of various sildenafil ODT formulae (N1-N19) against immediate release marketed drug Viagra 50 mg tablet ® after 10 min.

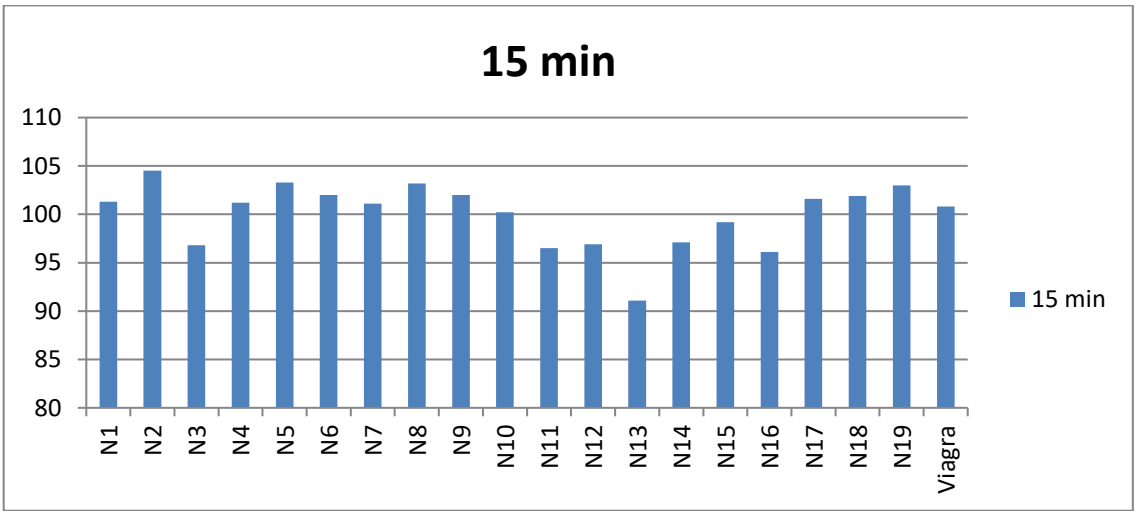

Figure 17. In vitro drug release profile of various sildenafil ODT formulae (N1-N19) against immediate release marketed drug Viagra 50 mg tablet ® after 15 min

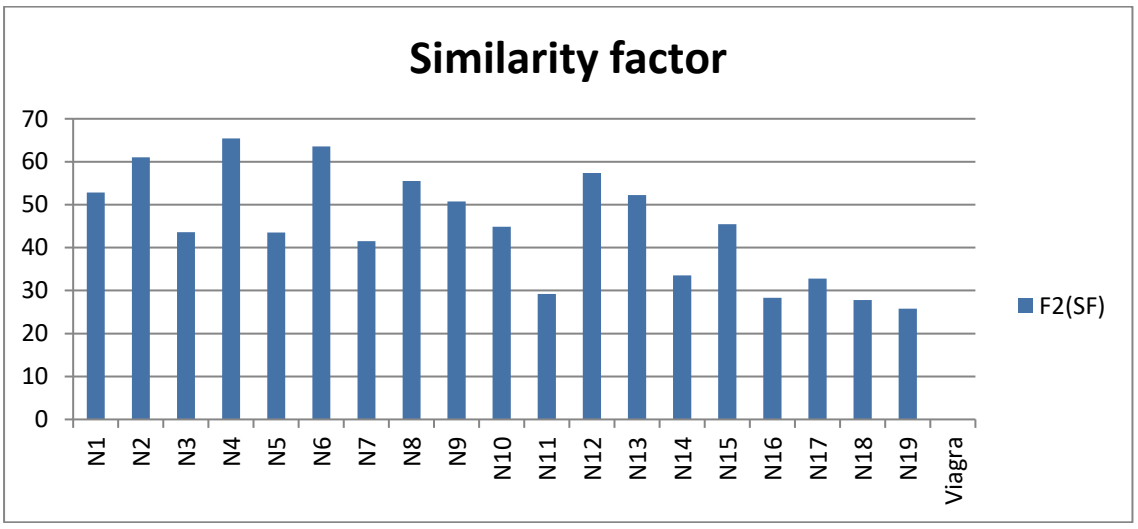

Figure 18. Similarity of various sildenafil 50 mg ODT formulae (N1-N19) against immediate release marketed drug Viagra® 50 mg tablet ®

ODT formulae **(N1, N4, N8, N15 and N 2)** show the highest disintegration time (75, 78, 87, 89, and 110 seconds) respectively. **Formulae (N1, N14, N15 and N2)** contain magnesium stearate hydrophobic lubricant which may hinder disintegration of tablet and dissolution retardant[45].

Wetting time

Table 4 shows the average wetting times of the different formulae. These results correlate with result obtained from disintegration time testing. Wetting time was significant affected by disintegrant type and lubricant. The wetting time range from (23.83 - 90.83 seconds).

The presence of water insoluble disintegrant plasidone XL (3 and 9 %), high level menthol 3% and higher binder concentration. **Formulae (N13, N19, N15 and N18)** show the highest wetting time (90.83, 79.67, 77.83 and 76.83 seconds respectively).

N3 shows the shortest wetting time it contain 9 % CCS, higher % of mannitol and hydrophilic lubricant (sodium stearyl fumarate).The fact of croscarmellose sodium show shortest wetting time followed by sodium starch glycolate then plasidone XL ,the filament structure of croscarmellose sod aid in rapid uptake of water by tablet. Plasidone XL is insoluble disintegrant[46].

In vitro release studies carried out for sildenafil formulae and compared with the marketed immediate release Viagra® 50 mg tablet shown in **Figures 9-17**. All formulae show acceptable dissolution rate were more than 90% in 5 minute. The result indicate that sublimation technique used to prepare the ODTs enhance the extent and the rate of dissolution.

N16, N17, N18 and N19 show fast release after 1 min (92.8, 81.8, 94.3 and 100 %) respectively, wetting time was (30, 70.3, 76.8, 79.67) respectively and disintegration time was (25, 29, 30 and 31 seconds).

Formulae (N4, N6, N2, N12, N8, N1, N13, and N9) show f2 value is between 50 and 100 (65.41, 63.58, 61.05, 57.38, 55.49, 52.48, 52.27 and 50.71% respectively) were shown in **figure 18**.These results indicate the sameness or equivalence of the two curves, and thus the performance of the product[47].

CONCLUSION

Orally disintegrating tablets (ODT) of sildenafil citrate is successfully prepared by using sublimation method. From the study, it can be concluded that sublimation method showed better disintegration and drug release. The prepared tablets disintegrate within few seconds without need of water; thereby enhance the absorption leading to its increased bioavailability. This technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulation of mouth dissolving tablets. Formula N16 is considered to be a future promising formula for sildenafil citrate due to the presence of high percent of plasidone XL 9% as superdisintegrant while 60 % of this ratio was intergranular, 1% menthol was sufficient to produce porous structure, Mannitol /MCC ratio at 1:1, magnesium stearate as lubricant. This formula show better wetting time, disintegration time and in vitro drug release.

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Conflict of interest

The authors declare that they don't have any conflict of interest.

REFERENCES

1. Gandhi, A. Mouth dissolving tablets: A new venture in modern formulation technology. *Pharma Innovation* **2012**, *1* (8), 14-31.
2. Reddy, M. S., Kore, N., Haq, S. M. F. U. Formulation and evaluation of diltiazemHCl fast dissolving tablets using different co-processed excipients by direct compression method. *Int. J. Pharma. Sci. Res.* **2017**, *8* (7), 2853-2861.
3. Sastry, S. V., Nyshadham, J. R., Fix, J. A. Recent technological advances in oral drug delivery–a review. *Pharm. Sci. Tech. Today* **2000**, *3* (4), 138-145.
4. Akhter, S., Hasan, S., Hasan, M. M., Hassan, M. R. Comparative study on formulation and evaluation of fast dissolving Glibenclamide tablets: Opportunity in drug delivery system. *Pharma Innovation* **2018,** *7* (5, Part E), 333
5. Kumar, R., Patil, S., Patil, M. B., Patil, S. R., Paschapur, M. S. Formulation evaluation of mouth dissolving tablets of fenofibrate using sublimation technique. *Int. J .Chem. Tech. Res.* **2009**, *1* (4), 840-850.
6. Kumar, R., Patil, M. B., Patil, S. R., Paschapur, M. S., Mahalaxmi, R. Development and characterization of orodispersible tablets of aceclofenac by sublimation technique. *Int. J .Chem. Tech. Res.* **2009**, *1* (2), 210-214.
7. Rahane, R. D., Rachh, P. R. A review on fast dissolving tablet. *J. Drug Deliv. Therp.* **2018**, *8* (5), 50-55.
8. Vidyadhara, S., Sasidhar, R. L. C., Balakrishna, T., Vikas, S., Bhaskar, M. Design and evaluation of fast

dissolving tablets for rizatriptan benzoate. *Der Pharmacia Lett.* **2015**, *7* (11), 80-85.
9. Elbary, A. A., Ali, A. A., Aboud, H. M. Enhanced dissolution of meloxicam from orodispersible tablets prepared by different methods. *Bull. Fac. Pharm. Cairo Univ.* **2012**, *50* (2), 89-97.
10. Koizumi, K. I., Watanabe, Y., Morita, K., Utoguchi, N., Matsumoto, M. New method of preparing high-porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material. *Int. J. Pharma.* **1997**, *152* (1), 127-131.
11. Kaushik, D., Dureja, H., Saini, T. R. Mouth dissolving tablets: A review. *Indian Drugs-Bombay.* **2004**, *41* (4), 187-193.
12. Pahwa, R., Piplani, M., Sharma, P. C., Kaushik, D., Nanda, S. Orally disintegrating tablets-Friendly to pediatrics and geriatrics. *Arch. Appl. Sci. Res*. **2010**, *2* (2), 35-48.
13. Thapliyal, S., Bhatt, G., Kandpal, G. Orodispersible Tablets: A Review. *World J. Pharm. Res.* **2018**, *7* (13), 146-162.
14. Abdel Halim, S. A. Formulation of new sildenafil citrate-caffeine orally disintegrating tablets: in vitro and in vivo evaluation. *J. Pharm. Res. Open.* **2013**, *3* (8), 46-63.
15. Saurí, J., Zachariah, M., Macovez, R., Tamarit, J. L., Millán, D., Suñé-Pou, M., Suñé-Negre, J. M. Formulation and characterization of mucoadhesive controlled release matrix tablets of captopril. *J. Drug. Deliv. Sci. Tech.* **2017**, *42*, 215-226.
16. Giron, D. Applications of thermal analysis and coupled techniques in pharmaceutical industry. *J. Therm. Anal. Calorim.* **2002,** *68* (2), 335-357.
17. Wael, A., Alia, A. B., Mahmoud, A. M., Hanan, M. E. Formulation and Evaluation of Carbamazepine 200 mg Controlled Release Tablets Using Different HPMC Grades. *Br. J. Pharm. Res.* **2013,** *3* (4), 632-647.
18. Sasidhar, R. C., Vidyadhara, S., Deepti, B., Nagaraju, R., Satish, K. R..Formulation and optimization of orodispersible tablets containing an antidepressant. *Der. Pharm. Lett.* **2014,** *6* (2), 156-164.
19. Kumar, R., Patil, S., Patil, M. B., Patil, S. R., Paschapur, M. S. Formulation evaluation of mouth dissolving tablets of fenofibrate using sublimation technique. *Int. J. Chem. Tech. Res.* **2009**, *1* (4), 840-850.
20. Aher, S., Saudagar, R., Chaudhari, D. Formulation and evaluation of taste masked fast dissolving tablet of prazosin hydrochloride. *J. Drug Deliv. Therp.* **2018**, *8* (4), 263-271.
21. Bikshapathi, D., Saikrishna, K., KUMAR, U., Sabitha, G., Saikumar, B. Fast dissolving tablets: An update. *Int. Res. J .Pharm.* **2011,** *2* (3), 45-53.
22. Wagner-Hattler, L., Wyss, K., Schoelkopf, J., Huwyler, J., Puchkov, M. In vitro characterization and mouth feel study of functionalized calcium carbonate in orally disintegrating tablets. *Int. J. Pharm.* **2017,** *534(1-2)*, 50-59.
23. Abdelbary, G., Prinderre, P., Eouani, C., Joachim, J., Reynier, J. P., Piccerelle, P. H. The preparation of orally disintegrating tablets using a hydrophilic waxy binder. *Int. J. Pharm.* **2004,** *278* (2), 423-433.
24. Bhowmik, D., Jayakar, B., Kumar, K. S. Design and characterization of fast dissolving tablet of telmisartan. *Int. J. Pharm. Recent Res.* **2009,** *1* (1), 31-40.
25. Reddy, M. S., Kore, N., Haq, S. M. F. U. Formulation and evaluation of diltiazem HCl fast dissolving tablets using different co-processed excipients by direct compression method. *Int. J. Pharm. Sci. Res.* **2017,** *8* (7), 2853-2861.
26. Ghorab, M. M., Yasser, S., Makky, A. A., Badr-Eldin, S. M. *Int. J. Pharm.* **2013**, *3* (1), 28-39.
27. Okhuelegbe, E. S., Osayande, E. P., Amara, I. M. Optimization of disintegrant blends using Box Behnken design in the formulation of fast disintegrating tablets of diclofenac sodium. *Nigerian J. Pharm. Appl. Sci. Res.* **2017,** *6* (2), 1-7.
28. Chawla, M., Srinivasan, G. Evaluation of galen IQ polymer in Tramadol Hydrochloride orally disintegrating tablet. *Int. J. Drug. Deliv.* **2011,** *3* (3), 439-455.
29. Adchitre Vaishali, B., Khadbadi, S., Patil, P. R., Shaikh, M. Fast Dissolving Tablets–A Novel Approach to Drug Delivery. *Am. J. Pharm. Res.* **2016**, *6* (4), 5009-5023.
30. Verma, A. K., Sachan, A. K. A review on fast dissolving tablet as an efficient technique for oral drug delivery. *J. Chem. Pharm. Sci.* **2013**, *6* (1), 29-34.
31. United States Pharmacopeia 40 NF 35, **2017**.
32. Kuno, Y., Kojima, M., Nakagami, H., Yonemochi, E., Terada, K. Effect of the type of lubricant on the characteristics of orally disintegrating tablets manufactured using the phase transition of sugar alcohol. *Eur. J. Pharm. Biopharm.* **2008,** *69* (3), 986-992.
33. Ahmed, T. A., Khalid, M., Mahmoud, M. F., Samy, A. M., Badawi, A. A. Miconazole nitrate oral disintegrating tablets: *in-vivo* performance and stability study. *AAPS Pharm. Sci. Tech.* **2012**, *13* (3), 760-771.
34. Hajare, A. A., Kale, S. N., Powar, T. A. Freeze Dried Fenugreek Seed Mucilage as disintegrant for Fast Dissolving Tablets of Valsartan. *Res. J. Pharm. Tech.* **2018**, *11* (1), 328-336.
35. Prateek, S., Ramdayal, G., Kumar, S. U., Ashwani, C., Ashwini, G., Mansi, S. Fast dissolving tablets: a

new venture in drug delivery. *Am. J. Pharm. Tech. Res.* **2012**, *2* (4), 252-279.
36. Gohel, M., Patel, M., Amin, A., Agrawal, R., Dave, R., Bariya, N. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. *AAPs Pharm. Sci. Tech.* **2004**, *5* (3), 10-15.
37. Gunda, R. K., Kumar, J. N. S. Formulation Development and Evaluation of Amisulpride Fast Dissolving Tablets. *FABAD J. Pharm. Sci.* **2018,** *43* (2), 15-25.
38. GhartiKul, P., Bidur, S., Laxman, B. *J. Chem. Pharm. Res.* **2015,** *7* (4), 792-799.
39. USFDA dissolution methods data base (online); Available from: https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_getallData.cfm. Accessed on 27 March **2018.**
40. Natarajan, R., Abirami, M., Murugananthan, G. Design and Evaluation of Atorvastatin Calcium Extended Release Tablets. *World J. Pharm. Pharm. Res.* **2017,** *6* (10), 1411-1423.
41. Frunza, L., Zgura, I., Nicolaie, I., Dittmar, A., Kosslick, H., Fricke, R. Embedding Jacobsen manganese (III) salen complex into nanoporous molecular sieves: Spectroscopic characterisation of host-guest interactions. *J. Optoelectron. Adv. Mat.* **2005**, *7* (4), 2141-2148.
42. Realpe, A., Velázquez, C. Growth kinetics and mechanism of wet granulation in a laboratory-scale high shear mixer: Effect of initial polydispersity of particle size. *Chem. Eng. Sci.* **2008,** *63* (6), 1602-1611.
43. Bala, R., Khanna, S., Pawar, P. Polymers in fast disintegrating tablets–a review. *Asian J. Pharm. Clin. Res.* **2012**, *5* (2), 8-14.
44. Bhatt, P. Mouth Dissolving Tablets Challenges, Preparation Strategies with a Special Emphasis on Losartan Potassium–A Review. *World J. Pharm. Pharm. Sci.* **2018**, *7* (9), 271-287.
45. Sheskey, P. J., Cook, W. G., & Gable, C. G. (Eds.). *Handbook of Pharmaceutical excipients* 6^{th}. APhA/Pharmaceutical Press, London, UK, **2017**.
46. Zhao, N., Augsburger, L. L. The influence of swelling capacity of superdisintegrants in different pH media on the dissolution of hydrochlorothiazide from directly compressed tablets. *AAPS Pharm. Sci. Tech.* **2005,** *6* (1), 120-126.
47. Koester, L. S., Xavier, C. R., Mayorga, P., Bassani, V. L. Influence of β-cyclodextrincomplexation on carbamazepine release from hydroxypropyl methylcellulose matrix tablets. *Eur. J. Pharm. Biopharm.* **2003**, *55* (1), 85-91.