

## Formulation and In Vitro Evaluation of Fast Dissolving Tablet Containing Sildenafil Citrate Nanocrystals

\*Basim Deshmukh<sup>1</sup>, Kantilal Narkhede<sup>2</sup>, Pritam Chaudhari<sup>1</sup>

1. Govindrao Nikam College of Pharmacy, Sawarde, Chiplun, Maharashtra, India.

2. Smt. BNB Swaminarayan Pharmacy College, Salvav, Vapi, Gujarat, India.

### ABSTRACT

Sildenafil citrate is a pharmacological agent which has proven useful in treatment of erectile dysfunction, pulmonary arterial hypertension as well as high altitude motion sickness. Sildenafil citrate exhibits an absolute bioavailability of about 40% and is reported to result in maximum observed plasma concentration of about 30-120 minutes following after oral administration. Sildenafil citrate exhibits low water solubility, namely 3.5mg/ml. This low water solubility with its high presystemic metabolism have contributed to its low oral bioavailability. Thus, there is a need to improve the bioavailability of sildenafil citrate. Fast dissolving tablet of sildenafil citrate were prepared with an intention to gain pre-gastric absorption that will eliminate the presystemic metabolism of drug. Attempts were also made to improve the aqueous solubility of the drug by forming its nanocrystals. The nanocrystals of sildenafil citrate were formed by nanoprecipitation technique and were evaluated for particle size and shape by scanning electron microscopy and were also subjected to DSC and FTIR analysis. This formed nanocrystals were further considered as API for the fast dissolving tablet. The formulated F3 formulation (fast dissolving tablet containing cross povidone as polymer and sildenafil citrate nanocrystals) shows rapid drug release within 2 minutes as compared to the tablet containing pure drug.

**Keywords:** Nanocrystals, Nanoprecipitation, Sildenafil citrate, Solubility

Received 16 April 2014

Received in revised form 10 May 2014

Accepted 12 May 2014

### \*Address for correspondence:

**Basim Deshmukh,**

Govindrao Nikam College of Pharmacy, Sawarde, Chiplun, Maharashtra, India.

E-mail: basim111@rediffmail.com

### INTRODUCTION

A fast dissolving system can be defined as a dosage form for oral administration, which when placed in mouth, rapidly dispersed or dissolved and can be swallowed in form of liquid. Recently fast dissolving formulation is popular as NDDS because they are easy to administer and lead to better patient compliance. Paediatric and geriatric patient have difficulty in swallowing the conventional dosage forms. Fast dissolving and fast dispersing drug delivery system may offer a solution to these problems. An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for entire duration of treatment. The FDT is also known as fast melt, fast dispersing, rapid dissolve, rapid melt, and quick disintegrating tablet. All

FDTs approved by Food and Drug Administration are classified as orally disintegrating tablets. Recently, the European pharmacopeia adopted the term orodispersible tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to gel like structure, allowing easy swallowing by patients [1].

Drug nanocrystals are pure solid drug particles with mean diameter below 1000nm. The term drug nanocrystals implies a crystalline state of discrete particles, but depending on the production method they can be partially or completely amorphous. Drug nanocrystals do not contain any matrix material. Polymeric nanocrystals, which consist of a polymeric matrix and an incorporated drug, have to be

distinguished from the Nanocrystals. The increased saturation solubility and the accelerated dissolution velocity are the most important differentiating features of drug nanocrystals. The importance for improvement of the bioavailability of poorly soluble drugs by the production of drug nanocrystals is widely accepted. The intensive research for new technologies led to many other approaches for the production of drug nanocrystals. The use of drug nanocrystals is universal formulation approach to increase the therapeutic performance of the drug in any route of drug administration. Almost any drug can be reduced to its size nanometer range [2,3].

Sildenafil citrate is a pharmacological agent which has proven useful in treatment of erectile dysfunction as well as pulmonary arterial hypertension. Sildenafil citrate exhibits an absolute bioavailability of about 40% and is reported to result in maximum observed plasma concentration of about 30-120 minutes following after oral administration. Sildenafil citrate exhibits low water solubility, namely 3.5mg/ml. This low water solubility with its high pre systemic metabolism has contributed to its low oral bioavailability. Thus, there is a need to improve the bioavailability of sildenafil citrate. Fast dissolving tablet of sildenafil citrate were prepared with a intention to gain pre gastric absorption that will eliminate the pre systemic metabolism of drug [4]. Attempts were also made to improve the aqueous solubility of the drug by forming its nanocrystals.

#### **MATERIALS AND METHODS**

Sildenafil citrate and the other materials used in the tablet formulation were obtained from Meher Chemie, Mumbai. The drug nanocrystals were synthesized by nanoprecipitation technique. Sufficient quantity of drug was added to solvent (Acetic acid). The solvent containing the drug was further added to the non solvent that is water. Sodium lauryl sulfate was added as a stabilizer. The precipitated mixture was allowed to sonicate in the ultrasonicator for about 10-15 minutes. The mixture was filtered through whatman filter paper having pore size 0.45 $\mu$ . Yield was about 90-95%. The product was dried at

90-100°C in hot air oven for about 15-20 min. The aggregate formed was triturated in mortar and pestle and the obtained powder/crystals were subjected for SEM, FTIR & DSC analysis [5].

Evaluation of Nanocrystals [6]:

FTIR analysis: The Nanocrystals were evaluated using FTIR analysis for compatibility with excipients.

DSC analysis: The obtained nanocrystals were subjected to Differential scanning calorimetry. There were no major changes observed as compared with pure drug.

SEM: The morphological analysis was done of pure drug and nanocrystals. The crystals were spherical and particle size was considerably reduced to nanometer range.

#### **Solubility determination of nanocrystals [7]**

Excess amount of sildenafil citrate was mixed with 2ml of distilled water. The vials were closed and left to be shaken at 25°C for 24 hours in water bath. Later, The suspensions were centrifuged at 5000 rpm for 10 min. Content were filtered through 0.45 $\mu$ m filter paper. The drug concentration was determined using UV.

#### **Formulation:**

The obtained nanocrystals were considered as API and were compressed into a fast dissolving tablet. Cross povidone and sodium starch glycolate were used as super disintegrant and were comparatively studied at different concentrations. The tablets were prepared by direct compression [8].

Microcrystalline cellulose was used as diluent, crosspovidone and sodium starch glycolate were used as superdisintegrants at different concentrations. Sodium saccharine was used as sweetner and mint as a flavouring agent, talc and magnesium stearate were used as a lubricant and glidant [9].

#### **Pre evaluation parameters:**

1) **Bulk density:** An accurately weighed quantity of powder, which was previously passed through sieve # 22 and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume

measure was called as the bulk volume and the bulk density is calculated by following formula;

Bulk density = Weight of powder / Bulk volume

**Table 1: Composition of tablet with different formulation batches**

Ingredients (mg/tab)	F1	F2	F3	F4
Sildenafil citrate(Nanocrystals)	50	50	50	50
Microcrystalline cellulose	88.4	88.4	88.4	88.4
Cross Povidone	1.69	-	8.9	-
Sodium Starch Glycolate	-	1.69	-	1.69
Sodium Saccharine	2.37	2.37	2.37	2.37
Mint	0.5	0.5	0.5	0.5
Magnesium stearate	1.88	1.88	1.88	1.88

**2) Tapped density:** After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (Va) and again tapped

for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb is consider as final tapped volume. The tapped density is calculated by the following formula

Tapped density = Weight of powder / Tapped volume

**3) Carr's index [Compressibility Index] and Hausner's Ratio:** Carr's index and Hausner's ratio measure the propensity of powder to be compressed and the

flowability of powder. Carr's index and Hausner's ratio can be calculated from the bulk and tapped density.

Carr's index = Tapped density - Bulk density / Tapped density X 100

**4) Hausners Ratio:** Hausners ratio is an indirect index of ease of powder flow was calculated by following formulae  
Hausner's ratio = Tapped density / Bulk density

3) The mix blend was compressed.

Post evaluation parameters:

**5) Angle of repose:** The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

**Weight variation:** 20 tablets were selected randomly from the lot and weighed individually to check for weight variation. Following is the table for Weight variation Specification as per IP.

$$\theta = \tan^{-1} h / r$$

Where, h and r are the height and radius of the powder cone, respectively.

**Hardness:** Hardness or tablet crushing strength (fc) (the force required to break a tablet in a diametric compression) was measured using Monsanto tablet hardness tester. It is expressed in kg/cm<sup>2</sup>.

**Method of preparation:**

1) All the ingredients were co ground in pestle and motor.

**Thickness:** Thickness of tablet was measured by using vernier calipers. Three tablets were selected at random from each batch. It is expressed in mm.

2) Then Talc and Magnesium stearate were added and mixed for 10 minutes.

**Friability (F):** Friability of the tablet determined using Roche friabilitor. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at height of 6 inches in each revolution.

**Table 2: Friability standards according to I. P.**

Average weight of tablets	% deviation
80mg or less	±10
More than 80mg but less than 250mg	±7.5
250mg or above	±5

Prewieghed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de-dusted

using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100$$

**Disintegration time:** The in-vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

**Wetting time:** Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W, the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$dl/dt = r \gamma \cos \theta / (4 \eta l)$$

Where I is the length of penetration, r is the capillary radius,  $\gamma$  is the surface tension,  $\eta$  is the liquid viscosity, t is the time, and  $\theta$  is the contact angle. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place. A piece of tissue paper folded double was placed in a petri dish (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

Wetting-time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

#### **Dissolution testing**

**Dissolution test:** Standard USP or IP dissolution apparatus have been used to study in vitro release profile using rotating paddle. In vitro release rate study of fast dissolving tablet of Sildenafil citrate was carried out using the apparatus 2 (Paddle apparatus) method. The dissolution test

was carried out using 900 ml of 0.01 M HCl, at  $37 \pm 0.5^\circ\text{C}$  at 50 rpm.

A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 1, 2, 5, 10, 15, 20, 30 and 45 min and withdrawn volume was replaced with fresh dissolution media. The withdrawn samples were diluted with dissolution medium and assayed at 217 nm. The % release of sildenafil citrate was calculated. The percentage release of Sildenafil citrate with respect to time for each batch, are graphically shown [10].

#### **RESULTS**

The Formulation (F3) containing crosspovidone as a polymer and drug nanocrystals shows 100% drug release within 2 minutes as compared to other formulations containing nanocrystals. The formulation of pure drug containing crosspovidone as a superdisintegrant shows 100% release rate within 10 minutes whereas, the same formulation containing drug nanocrystals shows 100% drug release within 2 minutes. This is due to the nanocrystal formation of the drug as well as due to the effect of superdisintegrant.

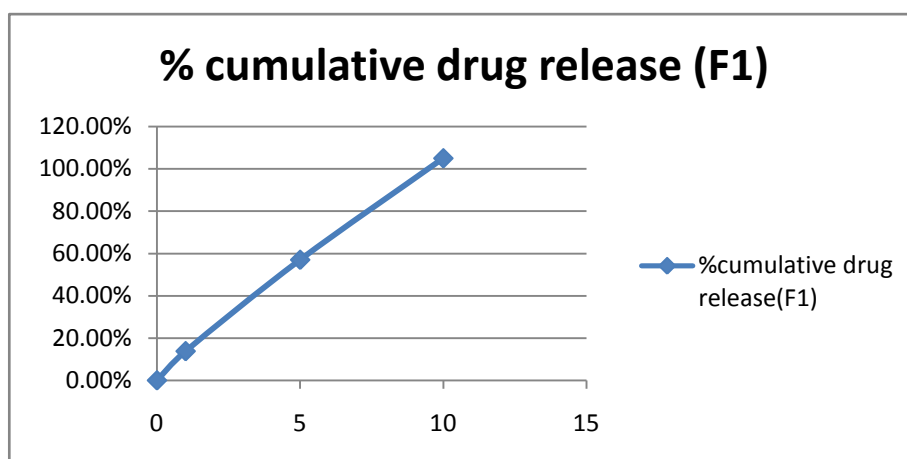
**Table 3: Pre evaluation parameters**

Batch code	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.61	0.68	33	11.47	1.11
F2	0.59	0.70	32	18.64	1.02
F3	0.62	0.75	31	17.33	1.20
F4	0.57	0.80	30	15.71	1.40

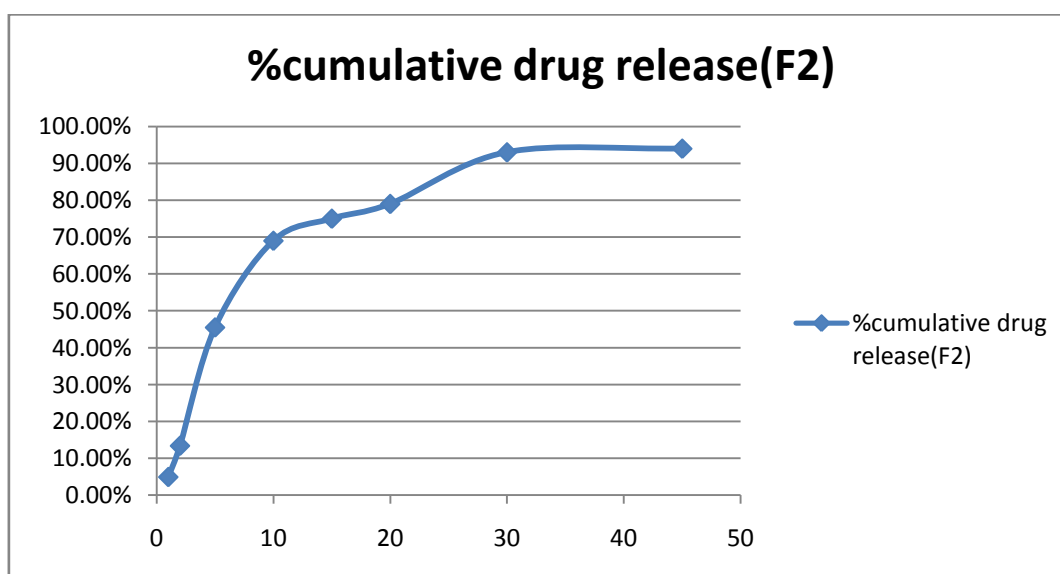
**Table 4: Post evaluation parameters**

Batch code	F1	F2	F3	F4
Weight variation	2.4%	3.5%	4.8%	2.8%
Thickness(mm)	3	3.1	3.2	3
Hardness(kg/sq.cm)	5	4.5	4.3	5.5
Friability (%)	0.60	0.71	0.72	0.68
Disintegration time(seconds)	40	35	26	35
Wetting time(seconds)	50	40	35	45
Batch code	F1	F2	F3	F4

Drug release profiles:



**Figure 1: Time in minutes versus % cumulative drug release**



**Figure 2: Time in minutes versus % cumulative drug release**

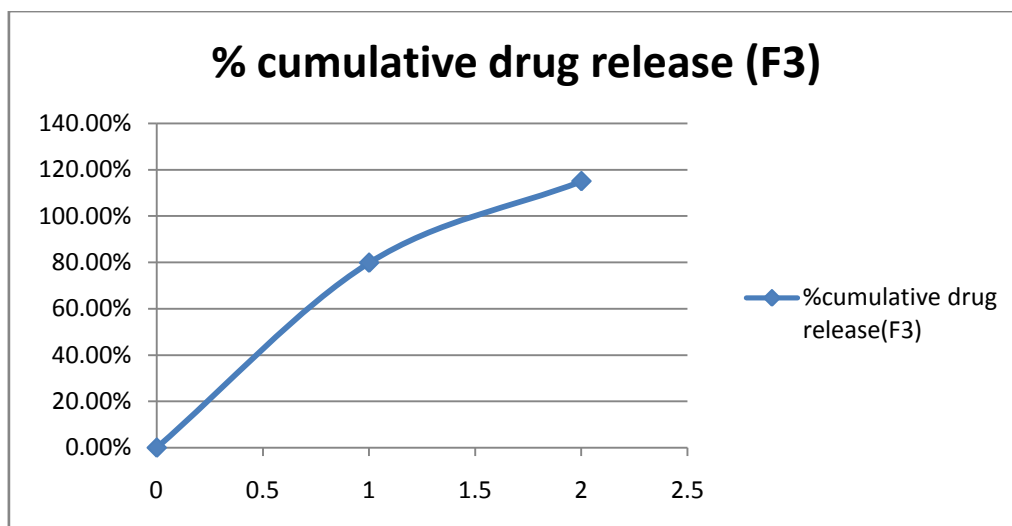


Figure 3: Time in minutes versus % cumulative drug release

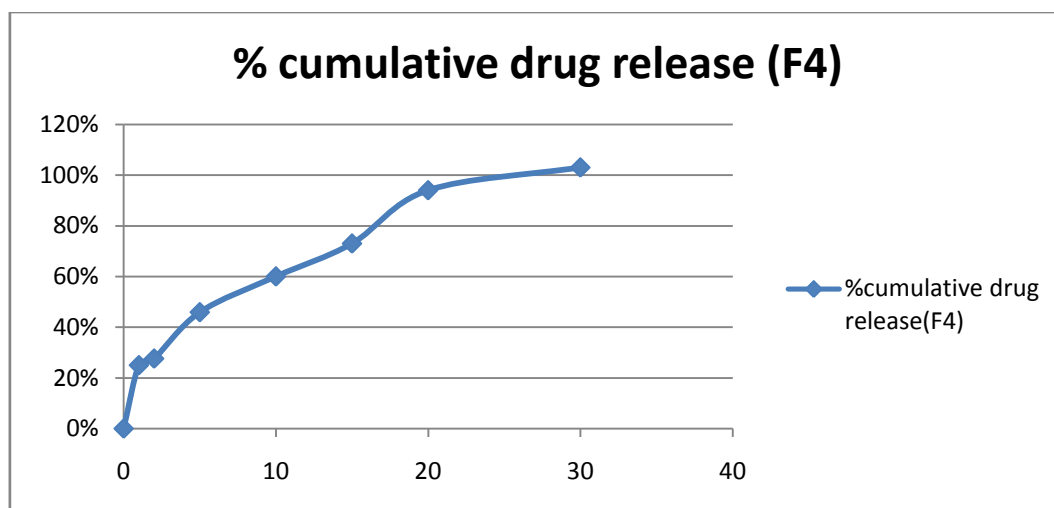


Figure 4: Time in minutes versus % cumulative drug release

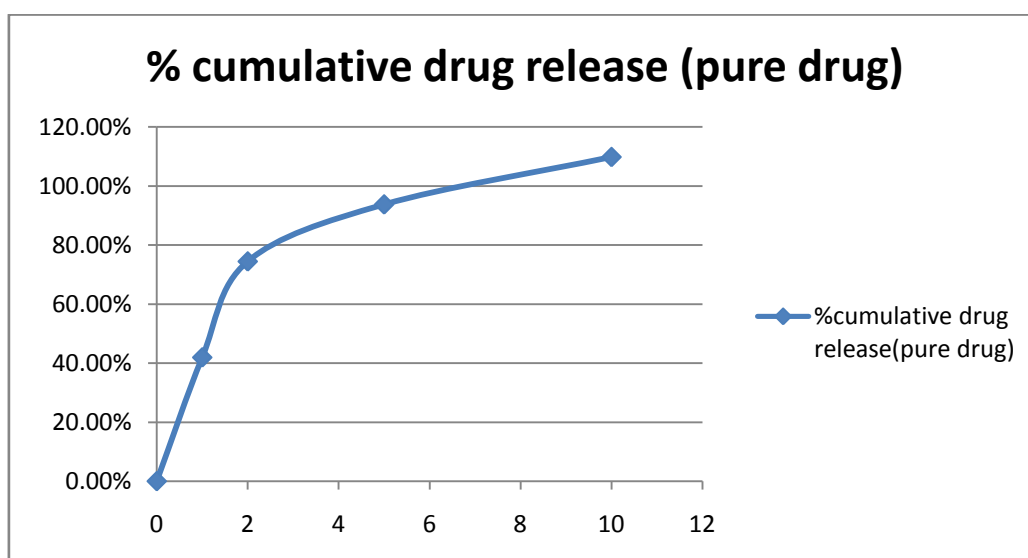


Figure 5: Time in minutes versus % cumulative drug release of tablet containing pure drug and crosspovidone as a polymer

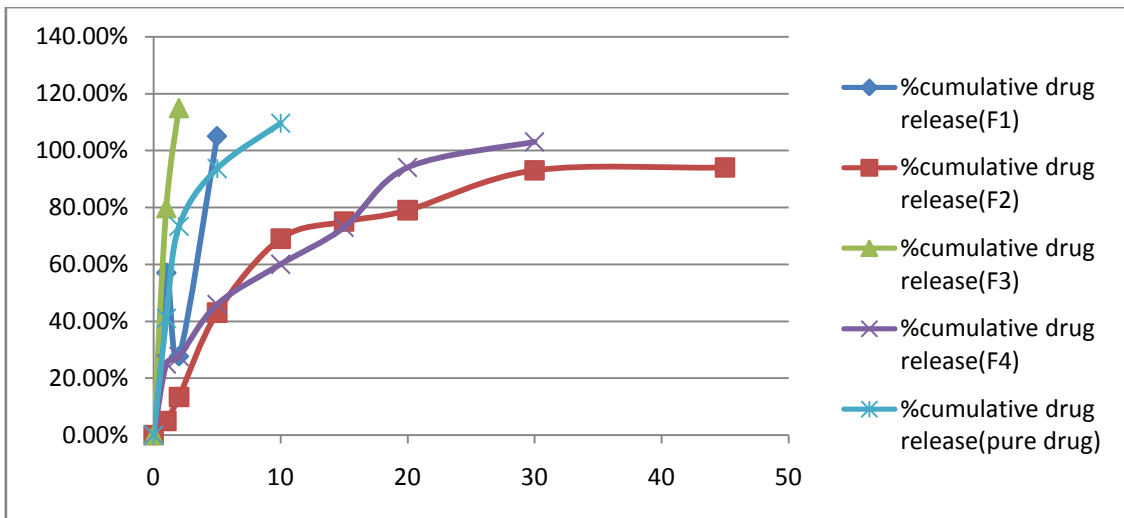


Figure 6: Comparison of dissolution profiles of different batches (f1 to f4 as well as pure drug (Time in minutes versus % cumulative drug release)

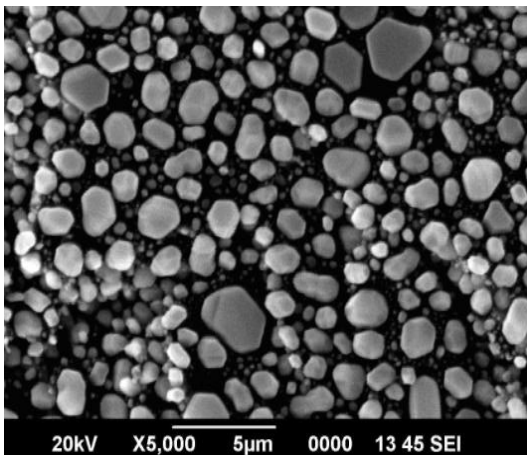


Figure 7: SEM image of sildenafil citrate nanocrystals

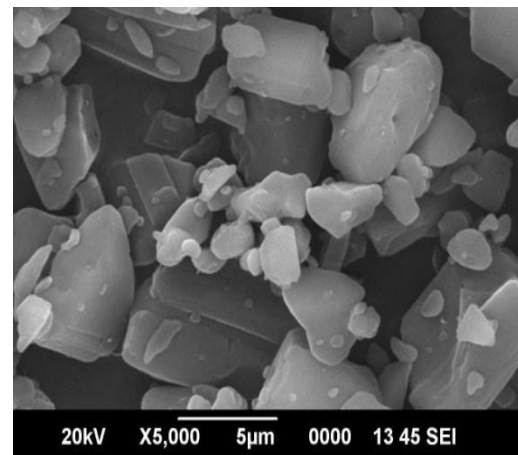


Figure 8: SEM image of sildenafil citrate pure drug

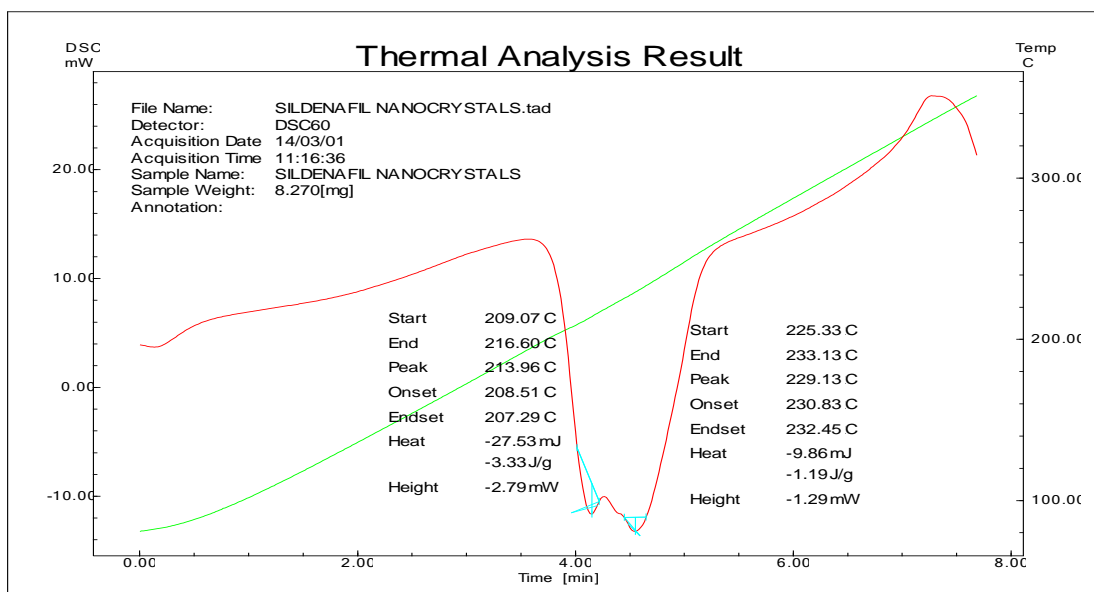


Figure 9: DSC analysis of sildenafil citrate nanocrystals

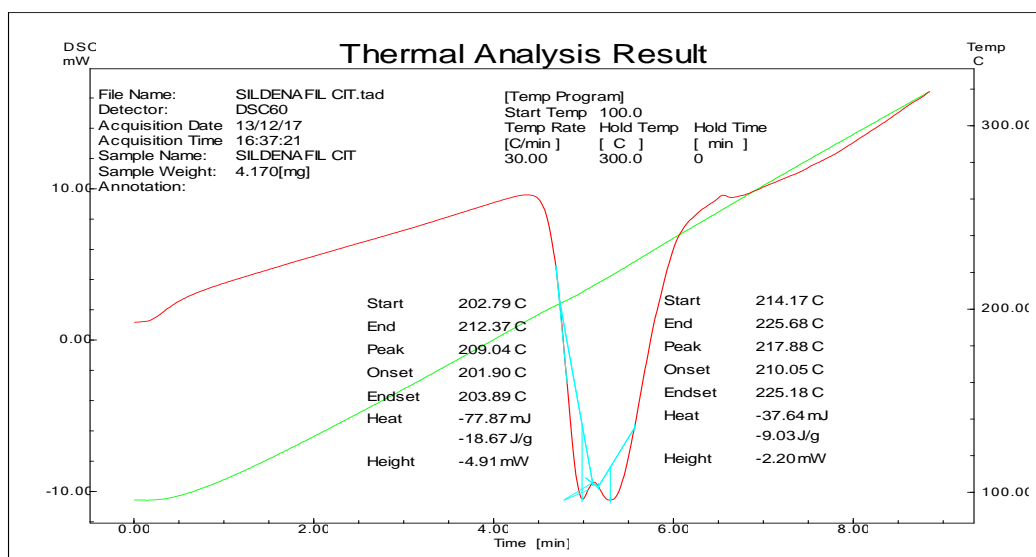


Figure 10: DSC analysis of sildenafil citrate (pure drug)

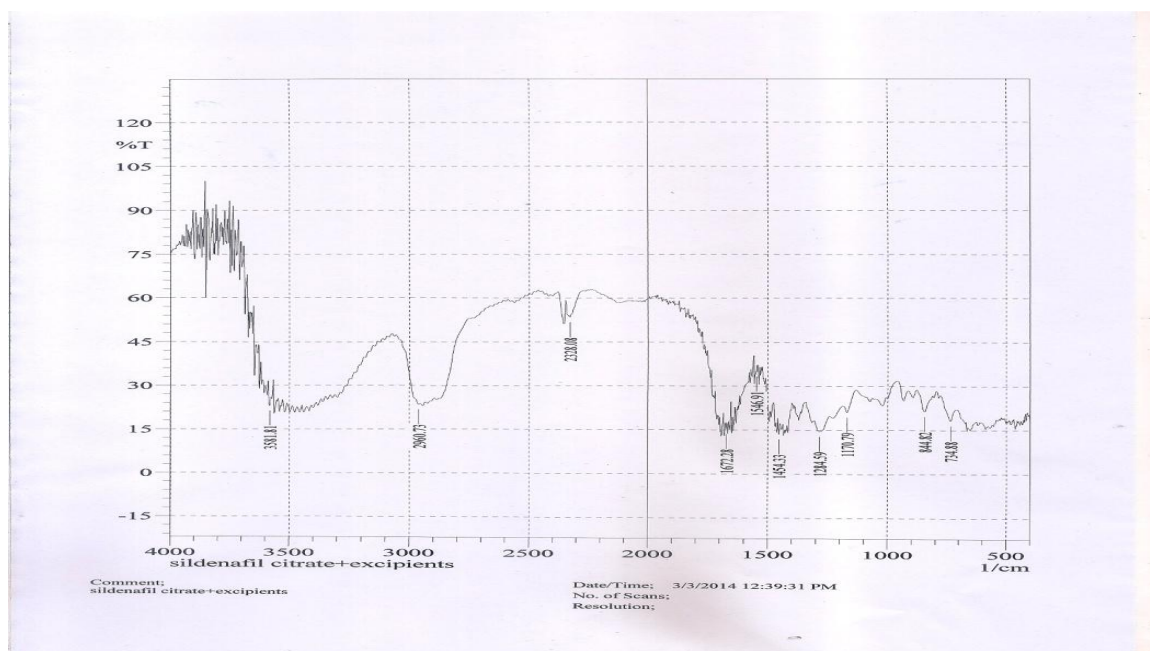


Figure 11: FTIR analysis of sildenafil nanocrystals+excipients (f3 formulation)

Solubility determinations:

	Solubility in water (mg/ml)
Sildenafil citrate	3.5
Sildenafil citrate nanocrystals	10.5

**DISCUSSION**

The fast dissolving tablet containing pure drug and cross povidone shows 100% release profile within 10 minutes. The formulation F1 shows 100% release profile within 10 minutes, whereas F2 shows 94% release profile within 45 minutes & F4 shows 100% drug release within 30 minutes. The formulation F3 shows rapid

drug release within 2 minutes .This is due to the mechanism of the superdisintegrant crosspovidone along with the nanocrystal formation which resulted in enhancement of the solubility of drug.

**CONCLUSION**

The bioavailability of sildenafil citrate can be increased by formulating drug nanocrystals into a fast dissolving delivery



system. Since, the maximum absorption of the drug will take place from the mouth, esophagus and pharyngeal regions the metabolism of the drug in the liver can be avoided & this will increase the bioavailability of sildenafil citrate. Also the side effects pertaining to the drug can be minimized. The formulated fast dissolving tablet can also be suitable for the paediatric as well as geriatric patients since it will eliminate the problem of dysphagia. The nanocrystal formation will further enhance the solubility of the drug which will increase the absorption characteristics of the drug that in turn will increase the bioavailability.

#### REFERENCES

1. Parmar R. B, Baria A,H, Tank H.M, Faldu S.D. Formulation and Evaluation of Domperidone fast dissolving tablets. International journal of Pharmtech Research 2009 July-sept Vol 1(3): 483-487.
2. Deepak Thasu, Michell deleers, Yashwant Pathak. Nanoparticulate drug delivery systems vol 166. Informa healthcare. 71-89.
3. Suman Kotteboina, USR chandrashekar.l, Balaji S. Drug Nanocrystals A novel formulation approach for poorly water soluble drugs. International journal of pharmTech Research. 2009 July-Sept. Vol 1(3) :682-694.
4. Nanostructured sildenafil base, its pharmaceutically acceptable salts and co-crystals, composition of them, process of preparation thereof and pharmaceutical composition containing them European patent 2442793A1. 2012 April 25.
5. Hansde Waard, Henderik W.Frijlink, Wouter L, J.Hinrich. Bottom up preparation techniques for nanocrystals of liophilic drugs. PharmResearch 2010 November 18. Vol 28:1220-1223.
6. Erxichi, Xinzheng, Chargshansun dichang, Tongying liang, Silingwang. Drug nanocrystals:a state of art formulation strategy for preparing the poorly water soluble drugs. Asian journal of pharmaceutical sciences, 2012 March 23. Vol 7(2):85-95.
7. Ahmed H. Elshafeey, Ehab R.Bandas and OsamaH Mohamed. Intranasal Microemulsion of sildenafil citrate: In vitro evaluation and In Vivo pharmacokinetics study in rabbits AAPS PharmsciTech. 2009 June vol 10 No:2 361-367.
8. C.P. Jain and P.S. Naruka Formulation and Evaluation of Fast Dissolving tablets of Valsartan. International Journal of Pharmacy and pharmaceutical sciences. 2009 July-September Vol 1 219-226.
9. Shailendra Kumar singh, Dinanath Mishra, Rishab Jassal, pankajson. Fast Disintegrating combination tablets of omeprazole and domperidone. Asian journal of pharmaceutical and clinical research 2009 July-September Vol 2 Issue 3:74-81.
10. Sandesh Madanlal Rathi. Formulation and Evaluation of fast dissolving tablet of sildenafil citrate with its analytical method development and validation in pure form. KLES college of pharmacy, KLE university. 2011 March 70.