

Research Article



FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF ZOLPIDEM TARTRATE BY DIRECT COMPRESSION

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ABSTRACT

The aim of this study was to compare the disintegrants efficiency of the three superdisintegrants (Ac-Di-Sol, Croscopovidone, Sodium starch glycolate) by formulating Zolpidem Tartrate immediate release tablets by direct compression method. Disintegration efficiency of powder disintegrants compared by swelling & hydration capacity of disintegrants. Nine formulations having superdisintegrants at different concentration level were prepared. While efficiency of disintegrants in tablets compared by various test like disintegration time, dissolution test, wetting time & maximal water uptake study of Zolpidem Tartrate immediate release tablets. The rapid disintegration observed for the Ac-Di-Sol containing tablets, comparing three classes of superdisintegrants represented by Ac-Di-Sol, Croscopovidone, Sodium starch glycolate (SSG). The disintegration efficiency was found in following decreasing order Ac-Di-Sol, Croscopovidone and Sodium starch glycolate.

Keywords: Immediate release tablet, swelling & hydration capacity of disintegrants.

INTRODUCTION

Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which $\geq 85\%$ of labelled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour¹. To enhance dissolution and hence bioavailability of any drug from immediate release tablets, disintegration is one of the important process. Few Super-disintegrants are available commercially as Croscarmellose sodium, Croscopovidone and SSG.

In the present investigation, we tried to judge the disintegration efficiency of disintegrants by comparing various parameters such as disintegration time, wetting time, maximal water uptake capacity and dissolution study of tablet. Disintegrants powder properties like swelling and hydration capacity was compared.

Several Technologies are available to manufacture immediate release tablets². The most common preparation methods are moulding, lyophilisation or freeze drying, direct compression, spray drying and sublimation. Direct compression, is one of the techniques that requires the incorporation of a superdisintegrant into the formulation. Direct compression does not require the use of water or heat during the formulation procedure and is very sensitive to changes in the type and proportion of excipients and the compression forces, when used to achieve tablets of suitable hardness without compromising the rapid disintegration characteristics.

Recently, immediate release tablets have gained prominence of being new drug delivery systems. Most

immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic³. The objective of this article was to investigate the comparison of different superdisintegrants in 0.01N HCl and their efficiency in promoting disintegration and dissolution of active ingredients from directly compressed tablets of Zolpidem Tartrate.

Zolpidem is a prescription medication used for the short-term treatment of insomnia, as well as some brain disorders. It is a short-acting nonbenzodiazepine hypnotic that potentiates gamma-amino butyric acid (GABA), an inhibitory neurotransmitter, by binding to gamma-amino butyric acid (GABA_A) receptors at the same location as benzodiazepines and it has a short half-life (2–3 hours)^{4,5}.

MATERIALS AND METHODS

Materials

Zolpidem Tartrate was obtained as a gift sample from Microlabs Ltd., Bangalore. Ac-Di-Sol and Croscopovidone XL were obtained from Wockhardt Research Centre (Aurangabad, India). SSG, Ludiflash and Avicel PH 102 were obtained as a gift samples from Alembic Ltd., Vadodara. Magnesium stearate and Talc were obtained from S.D.Fines (Mumbai, India).

Methods

Powder characterization

1. Swelling capacity:^{6,7,8} The swelling capacity of disintegrants was measured by taking 1 gm disintegrant. It was added to 10 ml simulated gastric fluid. The measuring cylinder was shaken vigorously for 10 minutes and allowed to stand for 24 hrs at 37 ± 1 °C. Swelling capacity was expressed as percentage and calculated according to the equation.



$$\text{Swelling capacity} = (X_v/X_i) 100$$

Where, X_v = Final volume occupied by swollen material after 24 hrs.

X_i = Initial volume of the powder in measuring cylinder.

2. Hydration capacity:^{6, 7, 8} Disintegrant (1 g) was taken in to 15 ml tarred centrifuge tube and 10 ml of simulated gastric fluid was added and allowed to stand for 10 minutes. During this time interval the content was mixed by inverting the tubes. After removal of the tubes supernatant was carefully decanted and tubes were inverted to allow drain. The tubes were then weighed in digital balance (Shimadzu) and the hydration capacity was calculated according to following formula.

Hydration capacity = weight of hydrated sample / dry sample weight

3. Drug-Excipient Interaction Study:⁹ The drug, polymer and other formulation ingredients were characterized by IR spectroscopy using a FTIR 8400S (Shimadzu, Japan). The spectra were taken by KBr discs method in the range of 4000–500 cm^{-1} .

Preparation of tablets

Zolpidem Tartrate, Ludiflash and microcrystalline cellulose (MCC) were mixed with Disintegrant for 15 minutes in porcelain mortar, passed through 60 # sieve. This blend was mixed with talc and magnesium stearate for 5 minutes and processed for direct compression by using 8 mm round flat-faced punch of rotary tablet machine (Rimek mini press-1, Karnavati Engineering Ltd, Mehsana, Gujarat). Compression force was kept constant for all formulations. The magnesium stearate level was fixed at 2 % for all formulation.

Disintegrants were used at 10, 7.5 and 5 % in tablets.

Evaluation of Powder Blend¹⁰

Bulk Density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by

$$D_b = M / V_b$$

Where, M and V_b are mass of powder and bulk volume of the powder respectively.

Tapped Density (D_t): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk

density apparatus). It is expressed in gm/ml and is given by

$$D_t = M / V_t$$

Where, M and V_t are mass of powder and tapped volume of the powder respectively.

Flow properties of blend: The flow properties of blend (before compression) were characterized in terms of angle of repose, Carr's index and Hausner ratio. For determination of angle of repose (θ), the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$$\tan \theta = (h/r)$$

Where, h = height of pile; r = radius of pile

Carr's index (or) % compressibility: It indicates powder flow properties. It is expressed in percentage and is given by

$$I = D_t - D_b / D_t \times 100$$

Where, D_t and D_b are tapped density and bulk density respectively.

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

$$\text{Hausner ratio} = D_t / D_b$$

Where, D_t and D_b are tapped density and bulk density respectively. The results were shown in the Table 2.

Evaluation of immediate release tablets¹¹

1. Weight variation, friability, hardness and thickness: Tablet weight variation, thickness and friability were measured using the USP methods and criteria. 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. Tablet friability was measured using friability tester (Roche friabilator). Thickness was measured by venire calliper and hardness of tablet was measured by Monsanto hardness tester. Weight, drug content, hardness and thickness of tablet were representing as mean \pm SD.

2. Disintegration test: Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed without disc in water at $37 \pm 0.5^\circ\text{C}$ temperature using USP Disintegration apparatus. The mean \pm SD of 6 tablets were calculated.

3. Content uniformity: It has been reported that Zolpidem Tartrate can be detected at 294 nm. Twenty tablets were powdered, and powder weight equivalent to 10 mg of Zolpidem was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml



of 0.01N HCL was added and shaken for 10 min. Then, the volume was made up to 100 ml with same solution. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 294 nm.

4. In vitro dissolution study:^{12,13} Dissolution test of Zolpidem Tartrate tablets was performed using USP dissolution testing apparatus 1 (basket method; Electrolab TDT-08L). The dissolution test was performed using 900 ml of 0.01N HCL at $37 \pm 0.5^\circ\text{C}$ and 100 rpm. Using a Shimadzu UV/Vis double beam spectrophotometer. Test sample (5 ml) was withdrawn at particular time interval (5, 10, 20, 30, 40, 50 and 60 minutes) and replaced with fresh dissolution media maintained at $37 \pm 0.5^\circ\text{C}$. The test sample was filtered (membrane filter, $0.45 \mu\text{m}$) and the concentration of drug determined using UV spectrophotometer at λ_{max} 294

nm. This test was performed on 3 tablets and mean \pm SD calculated.

4. Wetting time and water absorption ratio:¹⁴ A piece of tissue paper folded twice was placed in a small petridish (i.d. = 6.5 cm) containing 6 ml of distilled water, a tablet was put on the paper, and the time required for complete wetting was measured. The wetted tablet was then weighed. Three trials for each batch were performed and standard deviation was also determined. Water absorption ratio, R, was determined using equation.

$$R = 100 \times (W_a - W_b) / W_b$$

Where,

W_b = weight of the tablet before water absorption

W_a = weight of the tablet after water absorption

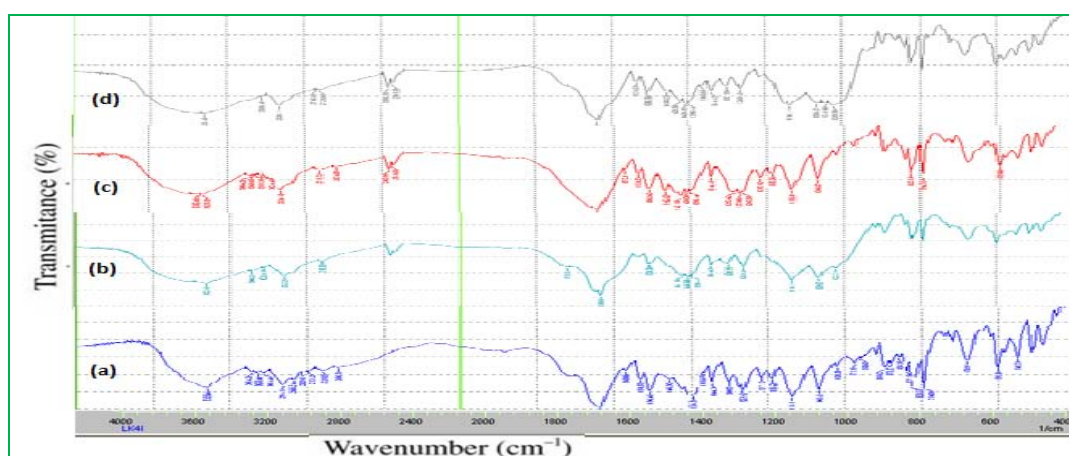


Figure 1: FT-IR spectra of pure Zolpidem Tartrate (a) and Zolpidem Tartrate and Croscarmellose sodium (b), Crospovidone (c), SSG (d).

Table 1: Different Composition of immediate release Tablets of Zolpidem Tartrate.

Batch No →	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredients ↓	Unit formula (mg per tablet)								
Zolpidem Tartrate	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Croscarmellose sodium (Ac-Di-Sol)	25	18.75	12.5	-	-	-	-	-	-
Crospovidone	-	-	-	25	18.75	12.5	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	25	18.75	12.5
Ludiflash	137	143.25	149.5	137	143.25	149.5	137	143.25	149.5
HPMC K4M	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Talc	1	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2	2

Table 2: Micromeritic properties of powder blend of immediate release tablets.

Code	Bulk Density	Tapped density	Angle of Repose (θ)	% compressibility	Hausner ratio
F1	0.41	0.47	25.78	14.28	1.16
F2	0.42	0.49	25.45	13.25	1.15
F3	0.41	0.50	27.17	18.60	1.22
F4	0.44	0.51	29.37	13.25	1.15
F5	0.44	0.50	31.10	13.41	1.15
F6	0.45	0.50	28.32	9.87	1.10
F7	0.43	0.51	28.18	15.29	1.18
F8	0.43	0.52	26.19	16.66	1.20
F9	0.43	0.51	27.38	15.47	1.18



RESULTS AND DISCUSSION

Swelling and Hydration Capacity

Swelling and hydration capacity of disintegrants are the important parameters for comparing disintegration efficiency represented in Table 3. Higher swelling and hydration capacity (capability of absorbing water) of Ac-Di-Sol leads to faster disintegration of batch F1 (35 ± 0.011 seconds). Less swelling capacity of Crospovidone XL than SSG but disintegration was found to be faster than SSG because the capillary activity of Crospovidone XL for water is responsible for its fast disintegration. SSG was found to be less swelling capacity than Ac-Di-Sol and it was found to be less effective than Crospovidone XL.

Table 3: Disintegrants Powder Properties

Disintegrant	Swelling Capacity (%)	Hydration capacity (g water/g polymer)
Croscarmellose sodium	598	8.82
Crospovidone	162	4.45
Sodium starch glycolate	555	7.88

Drug-Excipient Interaction Study

Fig. 1 demonstrates the FT-IR spectra of pure Zolpidem Tartrate (a) and Zolpidem Tartrate and Croscarmellose sodium (b), Crospovidone (c), SSG (d). The same characteristic peaks were observed for the drug-excipients mixture, indicating that no chemical reaction or interaction between the drug and excipients took place.

Table 4: Evaluation of Physical Parameters of Immediate Release Tablets of Zolpidem Tartrate

Code	Weight Variation	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Disintegration Time (sec)	Wetting Time (sec)	Water Absorption ratio
F1	249.12±0.64	3.24±0.048	3±0.0122	0.72	35±0.011	24±0.032	120±0.021
F2	251.21±0.63	3.20±0.035	3.5±0.021	0.82	40±0.034	27±0.056	122±0.032
F3	250.32±0.57	3.18±0.008	3±0.022	0.75	46±0.024	26±0.045	112±0.073
F4	249.34±0.58	3.17±0.013	3.5±0.24	0.82	42±0.054	27±0.034	129±0.023
F5	250.14±0.61	3.19±0.008	3±0.013	0.68	48±0.023	29±0.065	127±0.042
F6	250.31±0.67	3.17±0.008	3±0.014	0.70	50±0.045	30±0.036	123±0.032
F7	249.98±0.68	3.19±0.015	3.5±0.042	0.58	47±0.065	26±0.021	184±0.045
F8	248.98±0.67	3.20±0.015	3±0.021	0.67	48±0.072	32±0.035	171±0.032
F9	250.13±0.58	3.18±0.010	3.5±0.042	0.58	49±0.032	40±0.032	168±0.027

Disintegration time is very important for immediate release tablets. Which are desired to be less than 60 seconds for immediate release tablets. Disintegration time of prepared immediate release tablets was in the range of 35 to 52 seconds and the order was Ac-Di-Sol < Crospovidone < SSG. This finding is in agreement with results obtained from wetting time, since SSG swells with more gelling than Ac-Di-Sol and Crospovidone, which extend Disintegration time as a result. As the concentration of superdisintegrants in the formulations increased the disintegration time was found to decrease. Ac-Di-Sol was found to be best among all disintegrants which confirms the earlier report.

Wetting time is used as an indicator from the ease of the tablet disintegration in stomach. It was observed that wetting time of tablets was in the range of 24 to 40

Evaluation of Tablets

In the present investigation immediate release tablets of Zolpidem Tartrate were prepared by direct compression method. Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force. Values for angle of repose were found in the range of 25.45 to 31.10°. Carr's index of the prepared blends falls in the range of 9.87 to 16.60 % and this is also supported by Hausner factor values which were in the range of 1.10 to 1.22. Hence the prepared blends possessed good flow properties and these can be used for tablet manufacture (Table 2).

All the tablets were prepared under similar conditions. All the formulations exhibited white colour, odourless, flat in shape with smooth surface. The average weight of the immediate release tablet prepared by direct compression method was 248.98 to 251.21 mg. Weight variation of immediate release tablet was within 0.801 %. Hardness and friability of all formulations were within acceptable limits. Hardness of tablets prepared by direct compression was 3 ± 0.022 to 3.5 ± 0.042 kg/cm². The friability of all Formulations was found to be less than 1.0 % and hence the tablets with lower friability may not break during handling on machines and or shipping (Table 4).

seconds and type of the Disintegrant affects the wetting of the tablets. On comparing superdisintegrants, the formulation containing SSG take more wetting time than Ac-Di-Sol and Crospovidone. Wetting is related to the inner structure of the tablets and hydrophobicity of the components. This may be due to the fact that SSG is disintegrated by swelling mechanism leading to longer wetting time. Crospovidone and Ac-Di-Sol perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling. The relative ability of the various disintegrant to wick water into the tablets was studied. After contact with water the tablets containing SSG swelled, the outer edge appeared gel-like. Tablets containing Crospovidone quickly wicks water and were hydrated, but were soft as compared with tablets prepared with Ac-Di-Sol and SSG.



Higher water uptake leads to faster disintegration and dissolution of tablets. Ac-Di-Sol was found to best among all disintegrants.

In vitro dissolution studies of the prepared immediate release tablets was performed in 0.01N HCL using USP dissolution apparatus type 1. At 10% superdisintegrant level the drug release at the end of 5 minutes were found to be 27.46, 20.08 and 8.03% and at the end of 30 minutes were found to be 98.52, 97.67 and 96.90 % with Ac-Di-sol, Crospovidone and SSG respectively (Figure 2 - 4). It was observed that as the concentration of superdisintegrant increased the drug release also increased. With reference to the type of superdisintegrant, the release rate was found to follow the order: Ac-Di-sol > Crospovidone > SSG. The drug content of the prepared tablets was in the range of 9.94 to 10.11 mg per tablet.

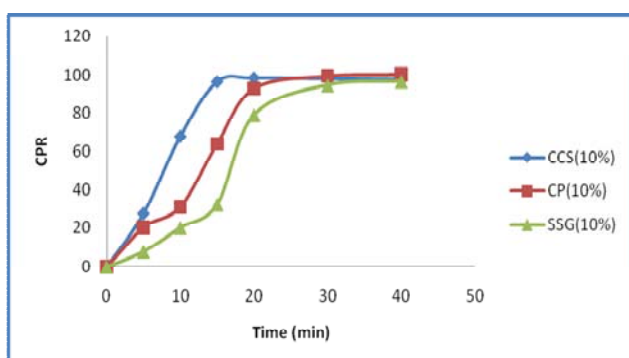


Figure 2: *In vitro* drug release profile of formulation containing 10% of superdisintegrant.

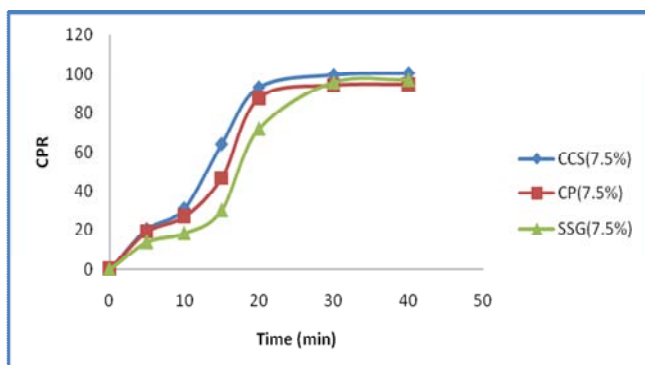


Figure 3: *In vitro* drug release profile of formulation containing 7.5% of superdisintegrant.

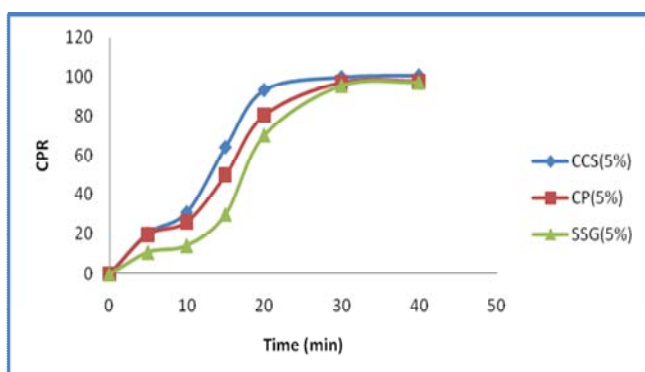


Figure 4: *In vitro* drug release profile of formulation containing 5% of superdisintegrant.

CONCLUSION

In the present study it can be concluded that among the all three disintegrants, Ac-Di-Sol was found to be more effective. High swelling capacity of Ac-Di-Sol among all disintegrants makes it more effective than all other disintegrants. It was observed that increased concentration of superdisintegrants shows increased drug release.

REFERENCES

1. Augsburger LL, Brzecko AW, Shah U, Hahm HA. Characterization and functionality of super disintegrants. Encyclopedia of Pharmaceutical Technology New York, NY: Marcel Dekker Inc; 2002; 2623-2638.
2. Available at: <http://www.pharmainfo.net>: Current status of tablet disintegration: Accessed July 2006.
3. Zhao N, Augasburger LL. The Influence of Swelling Capacity of Superdisintegrants in Different pH Media on the Dissolution of Hydrochlorothiazide from Directly Compressed Tablets. AAPS pharmscitech 2005;6:E120-E126.
4. Kenneth C. Waterman*, Michael B. Fergione P res-coating of immediate release powders onto coated controlled release tablets with adhesives. Journal of Controlled Release 89 (2003) 387–395.
5. Zolpidem-Wikipedia, the free encyclopaedia.
6. Jain G, Goswami J, Studies on formulation and evaluation of new superdisintegrants for dispersible tablets. International journal of pharmaceutical excipients 2005;37-43.
7. Bussemmera T, Peppasb N, Bodmeiera R. Evaluation of the swelling, hydration and rupturing pulsatile drug delivery system. European journal of pharmaceutics and bio pharmaceutics 2006;56:261-270.
8. B.G.Shiyani*, R.B.Dholakiya1, B.V.Akbari1, D.J.Lodhiya1, G.K.Ramani2 Development and evaluation of novel immediate release tablets of Metoclopramide HCl by direct compression using treated gellan gum as a disintegration-accelerating agent. Journal of Pharmacy Research 2009, 2(9), 1460-1464.
9. P. W. Heng, and L. W. Chah. Drug substance and excipients characterization. In D. M. Parikh (ed.), Handbook of Pharmaceutical Granulation Technology, 81: Decker, New York, 1997, pp. 52–55.
10. S.R. Shahi, G.R. Agrawal, N.V. Shinde, S.A. Shaikh, S.S. Shaik, V.G. Somani, P.B. Shamkuvarand M.A. Kale:Formulation And In Vitro Evaluation Of Oro-Dispersible Tablets Of Etoricoxib With Emphasis On



- Comparative Functionality Evaluation Of Three Classes Of Superdisintegrants: *Rasayan J. Chem* Vol.1, No.2 (2008), 292-300.
11. Raguia Ali Shoukri, Iman Saad Ahmed b, Rehab N. Shamma: In vitro and in vivo evaluation of nimesulide lyophilized orally disintegrating tablets: *European Journal of Pharmaceutics and Biopharmaceutics* 73 (2009) 162–171.
 12. VOLUME ONE, *Second Edition*, Handbook of Pharmaceutical Manufacturing Formulations *Compressed Solid Products*. Page 98.
 14. K.S. Patil; Y.V. Pore and S.B. Bhise: Spectrophotometric Estimation of Zolpidem in Tablets *J. Pharm. Sci. & Res. Vol.2(1), 2010, 1-4*.
 15. C.P. Jain, and P.J. Naruka: Formulation and evaluation of fast dissolving tablets of valsartan: *International Journal of Pharmacy and Pharmaceutical Sciences*, Vol. 1, Issue 1, July-Sep.2009

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