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FORMULATION AND COMPARITIVE IN-VITRO EVALUATION OF ZOLPIDEM TARTRATE SOLID DISPERSION SUBLINGUAL TABLET

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ABSTRACT

The present study is an attempt to increase solubility of an anti-psychotic drug Zolpidem tartrate by designing it as solid dispersion-sublingual (SDSL) tablets to maintain the desired plasma concentration of the drug. The solid dispersion and physical mixtures of Zolpidem Tartrate in PEG-6000, PEG-4000 and Poloxamer-188 with different ratios were prepared by solvent evaporation method and melting method. The pre- compression and post-compression parameters and release profiles of Zolpidem Tartrate with polymers are carried out to select the optimized formulation, among which Zolpidem Tartrate in Poloxamer-188 (ratio 1:5) by solvent evaporation method resulted in highest increase in dissolution rate and optimum rate of release of the drug. The SDSL tablets was prepared by direct compression technique using Crospovidone, Sodium starch glycolate, crosscarmellose sodium as superdisintegrant, directly compressible Mannitol as diluent, MCC as diluent, tablet disintegrant, Magnesium stearate as lubricant and Aspartame as sweetening agent. The disintegration efficiency was found to be better for Croscarmellose sodium when compared to Crospovidone and Sodium starch glycolate. FTIR spectrum of pure drug and the mixture of drug-polymers revealed no chemical interaction**.** The pre-compression study indicated good flow properties of bulk powder which is within an acceptable range. In-vitro drug release from the formulations was studied using buffer pH 6.8. From the entire formulations, the best in vitro disintegration time, in vitro drug release was obtained with the optimized formulation F6 containing 5% of Croscarmellose sodium. The tablets of formulation F6 have a hardness 3.3±0.5 kg/cm^2,

disintegration time of 14.00±1.41 seconds and % drug release of 99.87±0.42% in 30mins. The optimized formulations were also found to be stable during stability studies conducted for 3 months as per ICH guidelines.

KEYWORDS: ZolpidemTartrate, Poloxamer-188, Solid dispersion, Croscarmellose sodium, Crospovidone, Sodium Starch Glycolate, Dissolution, Sublingual tablet.

INTRODUCTION

Sublingual route is one of the oral mucosal drug delivery systems in which the drug solutes are rapidly absorbed into the reticulated vein which lies underneath the oral mucosa, and transported through the facial veins, internal jugular vein, and brachiocephalic vein and then drained into systemic circulation.[1] The drug bypasses the hepatic first-pass metabolic processes.[2-4] Zolpidem tartrate[5-7] is used for the short term treatment of insomnia which comes under Class I drug in BCS classification system with a pKa value is 6.2, onset of action is within 15 minutes, half life is 2-3 hours, rate of absorption is more in empty stomach and have 70%[8] oral bioavailability. It has low solubility in water but is easily soluble in aqueous buffer solution (pH 6.8), HCL, and H2SO4. Presently EDLUAR (5 and 10mg) and INTERMEZZO (1.75 and 3.5mg) is the Zolpidem Tartrate marketed products for the treatment of insomnia as a sublingual tablet.[9] In the present study, an attempt has been made to select the best suitable method of preparation of solid dispersions to enhance the solubility of Zolpidem tartrate and subsequently formulating sublingual tablets of the best batch of the prepared SD's for fast dissolution and absorption which result in rapid onset of action and enhanced oral bioavailability.

MATERIALS AND METHODS

Materials

Zolpidem Tartrate, gift sample from Medreich, Bengaluru, India, Crospovidone, Crosscarmellose sodium, Microcrystalline Cellulose, Poloxamer 188, PEG 4000 & 6000 and Aspartame was purchased from Sigma-Aldrich Corporation, Bengaluru, India. All other chemicals used were of analytical grade.

Methods

Fourier Transform Infrared Spectroscopy Studies (FT-IR)[10]

This was carried out to find out the compatibility between the drug Zolpidem tartrate and the polymers such as Crospovidone, Croscarmellose sodium, Sodium starch glycolate,

Microcrystalline cellulose, Poloxamer, Aspartame. The spectra obtained were compared and interpreted for the functional group peaks.

Preparation of solid dispersions of Zolpidem Tartrate[11-13]

Solid dispersions are prepared by hot melt method and solvent evaporation methods. The preliminary solubility study indicated that carriers like PEG 6000, PEG 4000, Polaxomer-188, can be tried in preparation of solid dispersions for solubility and dissolution enhancement. Hence Solid dispersions are prepared in order to improve the solubility using carriers like PEG 6000, PEG 4000, and Polaxomer-188 as shown in Table No. 01.

Table No. 01: Formulations of solid dispersions

Formulation		Components	Ratio
Code for Melting Method	Code for Solvent Evaporation Method		
SD 1	SD 4	Drug : PEG 6000	1:1
SD 2	SD 5	Drug : PEG 6000	1:3
SD 3	SD 6	Drug : PEG 6000	1:5
SD 7	SD 10	Drug : PEG 4000	1:1
SD 8	SD 11	Drug : PEG 4000	1:3
SD 9	SD 12	Drug : PEG 4000	1:5
SD 13	SD 16	Drug : Poloxamer-188	1:1
SD 14	SD 17	Drug : Poloxamer-188	1:3
SD 15	SD 18	Drug : Poloxamer-188	1:5

Preparation of physical mixtures

Co-ground the solid dispersions of Zolpidem Tartrate and varying amounts of carriers until a homogenous mixture is obtained and sieved in #44 and pulverized and stored in desiccators at room temperature. The formula for the preparation of physical mixtures is shown in Table No. 02.

Table No. 02: Formulation of Physical Mixture

Formulation Code	Components	Ratio
PM 1	Drug : PEG 6000	1:1
PM 2	Drug : PEG 6000	1:3
PM 3	Drug : PEG 6000	1:5
PM 4	Drug : PEG 4000	1:1
PM 5	Drug : PEG 4000	1:3
PM 6	Drug : PEG 4000	1:5
PM 7	Drug : Poloxamer-188	1:1
PM 8	Drug : Poloxamer-188	1:3
PM 9	Drug : Poloxamer-188	1:5

Evaluation of Zolpidem Tartrate solid dispersions

Calculation of percentage practical yield of solid dispersion

$$\% \text{ practical yield} = \frac{\text{practical mass (SolidDispersion)}}{\text{theoretical mass}} \times 100$$

Drug content estimation

Solid dispersions of Zolpidem Tartrate equivalent to 50 mg are weighed and dissolved in little amount of phosphate buffer (6.8pH) in volumetric flask and volume is made upto 100ml with the buffer pH 6.8 and subsequent dilutions are made and absorbance is measured at 241nm and drug content is calculated using standard curve. Each test is performed in triplicate.

$$\% \text{ drug content} = \frac{\text{actual drug content in solid dispersion}}{\text{theoretical amount of drug in solid dispersion}} \times 100$$

***In-vitro* dissolution studies**

The dissolution testing is carried out at a temperature of 37°C at 50 RPM in 900ml 6.8pH phosphate buffer as a dissolution medium using USP dissolution test apparatus type I. one capsule (containing Solid Dispersion/and physical mixtures) is placed in the basket, basket is then immersed in dissolution medium. The cumulative percentage release of Zolpidem Tatrate is calculated. The studies are carried out in triplicate. The cumulative percentage release v/s time (minutes) are plotted and the dissolution profile of Zolpidem Tartrate solid dispersions and physicals mixtures are compared.

Preparation of Zolpidem tartrate solid dispersions sublingual tablets by Direct compression.

The best formulation of Zolpidem Tartrate solid dispersions were compressed with the different concentrations of excipients mentioned in the Table No. 03 were directly compressed. The tablets were prepared using 6 mm Flat Faced Bevel Edged (FFBE) punches. The total weight of the tablet was made up to 100mg.

Table No. 03: Formulation of Zolpidem Tartrate solid dispersion sublingual tablets.

S.No	Name of the ingredient	Formulation code								
		FS1	FS 2	FS 3	FS 4	FS 5	FS 6	FS 7	FS 8	FS 9
1.	Zolpidem Tartrate-SD (~5mg)	30	30	30	30	30	30	30	30	30
2.	Crospovidone	3	4	5	-	-	-	-	-	-
3.	Croscarmellose sodium	-	-	-	3	4	5	-	-	-
4.	Sodium Starch glycolate	-	-	-	-	-	-	3	4	5
5.	Aspartame	2	2	2	2	2	2	2	2	2
6.	MCC	45	45	45	45	45	45	45	45	45
7.	Mannitol	18	17	16	18	17	16	18	17	16
8.	Magnesium stearate	2	2	2	2	2	2	2	2	2
Total tablet weight(mg)		100	100	100	100	100	100	100	100	100

Evaluation of Zolpidem tartrate compressed tablet

Pre Compression parameters:[14-17]

Pre-compression parameters Bulk Density (Db), Tapped Density (Dt), Compressibility index (Carr's Index) (CCI), Hausner's Ratio and Angle of Repose were carried out.

Post Compression Parameters:[18-21]

Thickness of prepared tablets

The thickness and diameter of the tablet were measured using Vernier calipers. It is measured in mm.

Friability (F)

The friability was determined by using Roche friabilator. The percentage friability was calculated for each batch by using the following formula

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

Where,

$W_{initial}$ = initial weight of the tablets

W_{final} = Final weight of tables

Weight variation test

20 tablets were selected at random from a lot, weighed individually, and the average weight was determined. The percent deviation of each tablet weight against the average weight was calculated. The test requirements are met; if not more than two of the individual weight deviates from the average weight of not more than existing 5%.

Uniformity of drug content

The prepared tablets were tested for their drug content. 20 tablets of each formulation were finely powdered; weight equivalent to 100 mg of powder was accurately weighed, and the drug Zolpidem tartrate was completely extracted with methanol and the solution was filtered. 1 ml of the filtrate was suitably diluted using phosphate buffer of pH 6.8 and analyzed for Zolpidem tartrate content by a UV spectrophotometer at 241nm.

Wetting time

The tablets wetting time was measured by a procedure modified from that reported by Bi *et al*. The tablet was placed at the center of two layers of absorbent paper fitted into a dish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablets was then recorded using a stopwatch.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish Containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio (R), was determined using the following equation.

$$R = 100 \times Wa–W_b/Wa$$

Where,

Wa = Weight of tablet after water absorption.

W_b = Weight of tablet before water absorption.

***In-vitro* disintegration time**

In-vitro disintegration study of Zolpidem Tartrate was carried out by using Disintegration Tester (USP) ED2L model. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless steel screen (mesh no. 10) was immersed in a water bath at 37±2°C. The time required for the complete disintegration of the tablet in each tube was determined.

***In vitro* drug release studies**

The in vitro dissolution studies were carried out for the formulations using USP apparatus type II. The dissolution medium used was 900 ml of phosphate buffer of pH 6.8 for 30 mins, temperature at $37^oC \pm 0.5^oC$ and stirring rate 50rpm.

Stability Studies

The selected formulations were packed in the strip packaging Alu-Alu, which were placed in the card board box and labeled. They were then stored at 40 ^{o}C / 75% RH and kept for three months and evaluated for their Hardness, drug content and drug release at specific intervals of time as per ICH Guidelines.

RESULTS AND DISCUSSION

Pre-formulation studies

Organoleptic properties of zolpidem tartrate were found to be normal.

FTIR studies

Based on the results of FTIR analysis majority of the excipients were found to be compatible with the drug and was characterized by no newly developed peaks were observed in the IR spectra of physical mixture of drug and excipients. It shows that there were no changes in the chemical integrity of the drug.

Drug Content

The drug content analysis of different formulations was done according to the procedure. The percentage drug content of all formulations is shown below. Physical mixture (PM 1- PM 9) of Zolpidem Tartrate with carriers showed lower rate of dissolution rate compared to that of solid dispersions (SD1 – SD18). In case of all the solid dispersions (SD1-SD18) which was prepared by using PEG 6000, PEG 4000 and Polaxomer-188 prepared by solvent evaporation method and melting method in the ratios of 1:1, 1:3, 1:5. Zolpidem tartrate with Poloxamer-188 in the ratio of (1:5) prepared by solvent evaporation method showed best drug release of 66.23±0.60% in 30 minutes as shown in Table No. 04.

Table No. 04: Drug content of Zolpidem tartrate in solid dispersions (SD) and physical mixtures (PM).

Formulation code	% Drug content of SD	Formulation code	% Drug content of SD	Formulation code	% Drug content of PM
SD 1	95.52±0.11	SD 10	98.75±0.10	PM 1	98.20±0.11
SD 2	97.03±0.10	SD 11	96.86±0.09	PM 2	98.25±0.10
SD 3	97.25±0.11	SD 12	98.89±0.11	PM 3	98.56±0.09
SD 4	96.25±0.10	SD 13	96.69±0.08	PM 4	97.44±0.09
SD 5	97.58±0.11	SD 14	97.15±0.10	PM 5	98.74±0.10
SD 6	98.29±0.11	SD 15	99.00±0.09	PM 6	98.13±0.07
SD 7	96.36±0.10	SD 16	98.57±0.11	PM 7	97.70±0.11
SD 8	96.95±0.10	SD 17	97.45±0.11	PM 8	98.71±0.11

mean ± SD (n=3)

***In-vitro* drug release**

From the dissolution study it was found that solid dispersions of Zolpidem Tartrate showed more solublity of drug for the formulation (SD-18) (Table No. 05 to 10 and Figure No. 01 to 06) prepared by solvent evaporation method in the ratio of (1:5) compared to all other SD's and physical mixture formulations (Table No. 11 to 13 and Figure No. 07 to 09). In comparison for the formulations prepared by solvent evaporation technique and melting method, solvent evaporation method showed good dissolution profile. The formulation with PEG-4000 and PEG-6000 showed less drug release when compared to Pol-188 (66.23±0.60%) in 30mins at 6.8pH buffer. The solubility enhancement of Zolpidem Tartrate with various carriers was found to be in the order of Poloxamer-188 > PEG-6000 > PEG-4000. This might be due to the higher solubility of PEG in acid media and POL-188 in basic media which increases the wettability of the drug.

Table No. 05: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:1) (Melting Method)

S. No	Time (min)	% Drug Released*		
		SD 1	SD 7	SD 13
1	0	0	0	0
2	5	22.56±0.87	21.06±0.67	23.34±0.65
3	10	25.67±0.63	22.63±0.41	25.00±0.68
4	15	27.03±0.61	26.25±0.87	28.67±0.85
5	20	30.05±0.45	30.11±0.16	32.45±0.40
6	25	33.00±0.9	32.98±0.48	36.89±0.80
7	30	38.44±0.46	34.27±0.26	39.66±0.86

*Mean± SD (n=3)

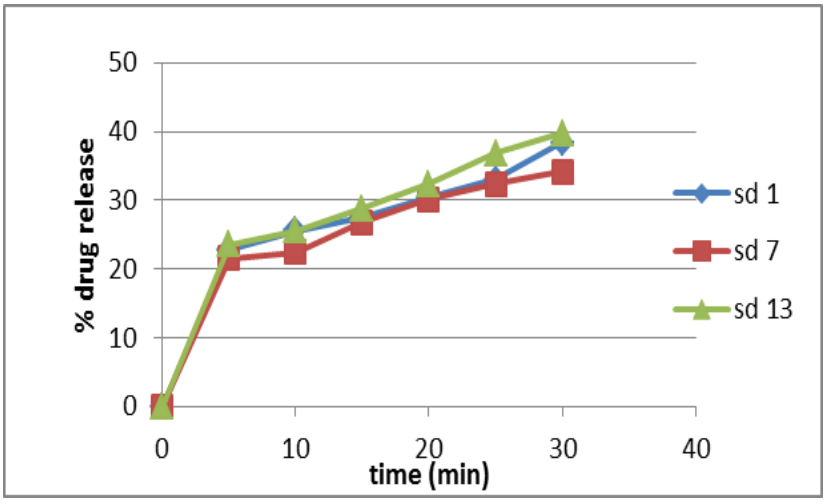

Figure No. 01: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:1) (Melting Method)

Table No. 06: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:3) (Melting Method)

S.No	Time (min)	% Drug Released*		
		SD 2	SD 8	SD 14
1	0	0	0	0
2	5	25.77±0.48	23.46±0.67	26.00±0.09
3	10	28.12±0.20	25.89±0.09	29.87±0.20
4	15	32.87±0.16	28.45±0.14	32.13±0.46
5	20	36.34±0.85	31.32±0.68	35.02±0.67
6	25	40.94±0.49	34.87±0.40	43.00±0.85
7	30	43.23±0.80	37.11±0.20	47.09±0.20

*Mean± SD (n=3)

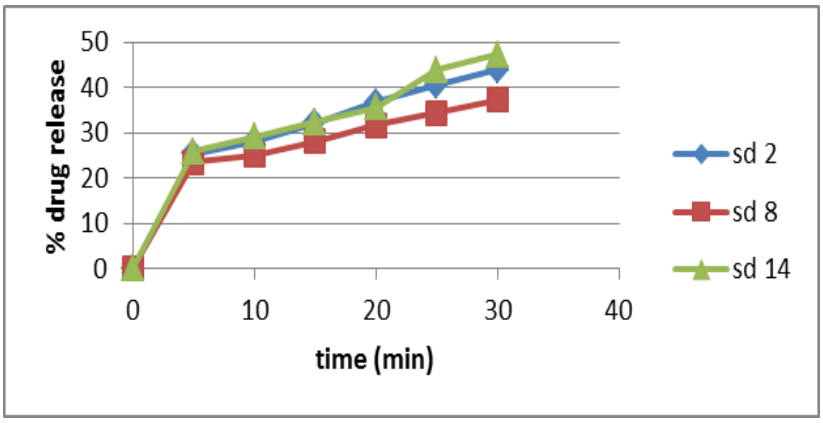

Figure No. 02: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:3) (Melting Method)

Table No. 07: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:5) (Melting Method)

S.No	Time (min)	% Drug Released*		
		SD 3	SD 9	SD 15
1	0	0	0	0
2	5	36.88±0.89	22.00±0.89	34.00±0.61
3	10	39.56±0.48	28.01±0.40	40.87±0.43
4	15	43.00±0.87	33.95±0.69	43.12±0.40
5	20	45.66±0.06	39.87±0.48	46.67±0.25
6	25	46.01±0.48	40.34±0.41	49.00±0.21
7	30	49.00±0.07	43.89±0.80	51.45±0.24

*Mean± SD (n=3)

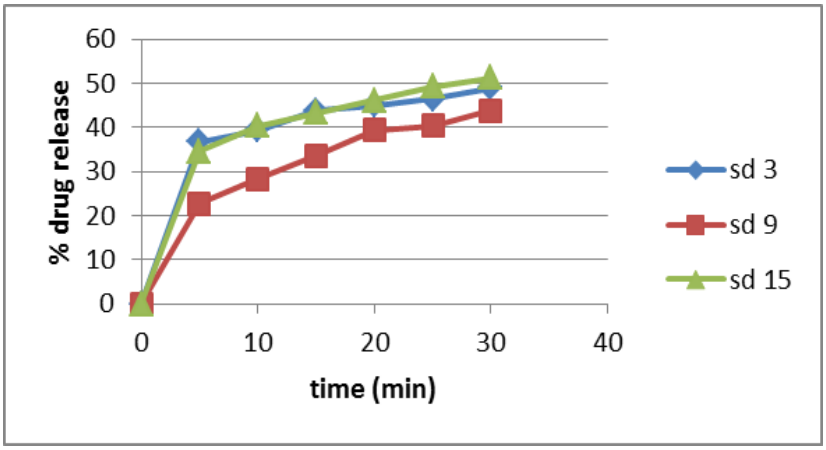

Figure No. 03: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:5) (Melting Method)

Table No. 08: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:1) (Solvent evaporation Method)

S.No	Time (min)	% Drug Released*		
		SD 4	SD 10	SD 16
1	0	0	0	0
2	5	22.16±0.27	22.34±0.80	25.00±0.45
3	10	25.87±0.07	25.85±0.29	27.56±0.07
4	15	28.55±0.24	26.89±0.06	32.44±0.40
5	20	32.54±0.46	30.96±0.22	37.04±0.24
6	25	35.00±0.49	31.39±0.02	40.09±0.47
7	30	39.23±0.40	32.15±0.44	44.00±0.87

*Mean± SD (n=3)

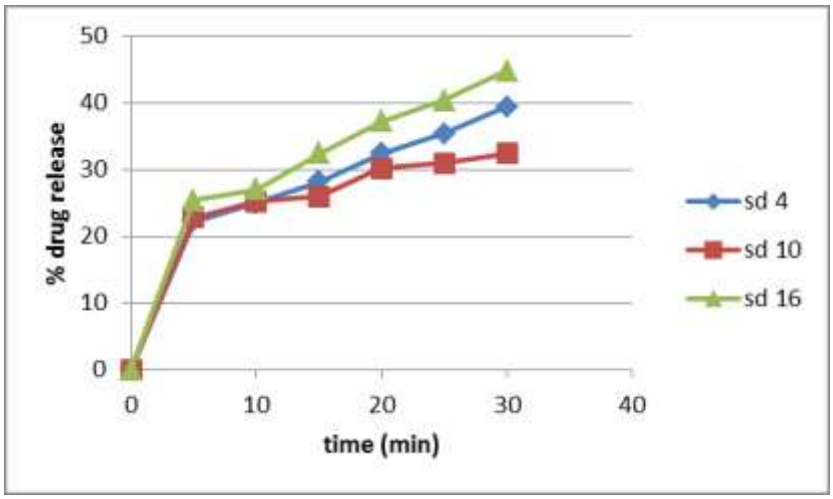

Figure No. 04: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:1) (Solvent evaporation Method)

Table No. 09: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:3) (Solvent evaporation Method)

S.No	Time (min)	% Drug Released*		
		SD 5	SD 11	SD 17
1	0	0	0	0
2	5	23.12±0.80	27.78±0.05	28.45±0.25
3	10	28.12±0.22	29.67±0.86	32.89±0.26
4	15	32.00±0.43	36.34±0.27	36.56±0.45
5	20	36.65±0.49	39.56±0.47	40.44±0.45
6	25	41.00±0.07	40.66±0.47	45.00±0.21
7	30	45.76±0.09	43.23±0.05	51.09±0.09

*Mean± SD (n=3)

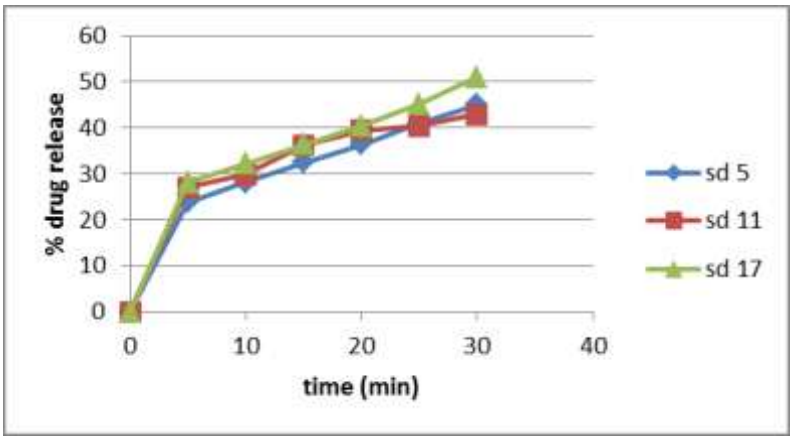

Figure No. 05: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:3) (Solvent evaporation Method).

Table No. 10: *In-Vitro* Dissolution Profile of solid dispersions (Ratio – 1:5) (Solvent evaporation Method).

S.No	Time (min)	% Drug Released*		
		SD 6	SD 12	SD 18
1	0	0	0	0
2	5	36.88±0.49	27.12±0.61	37.00±0.20
3	10	39.09±0.24	30.56±0.25	40.66±0.48
4	15	41.45±0.24	38.45±0.65	48.67±0.41
5	20	43.56±0.89	41.12±0.23	58.00±0.64
6	25	47.34±0.09	45.34±0.06	62.00±0.03
7	30	50.88±0.44	47.12±0.08	66.23±0.60

*Mean± SD (n=3)

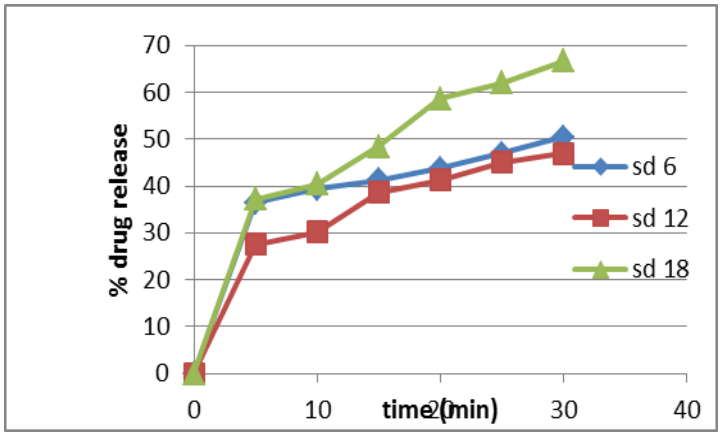

Figure No. 06: *In-Vitro* release studies of solid dispersions (Ratio – 1:5) (Solvent evaporation Method).

Table No. 11: *In-Vitro* Dissolution Profile of Physical mixtures PEG-6000 (Ratio 1:1, 1:3, 1:5).

S.No	Time (min)	% Drug Released*		
		PM 1 (1:1)	PM 2 (1:3)	PM 3 (1:5)
1	0	0	0	0
2	5	21.60±0.21	23.82±0.32	34.21±0.43
3	10	24.44±0.45	26.86±0.46	36.84±0.72
4	15	26.00±0.11	30.43±0.72	41.00±0.32
5	20	27.00±0.74	34.88±0.39	43.67±0.01
6	25	29.23±0.33	38.85±0.49	45.65±0.83
7	30	36.87±0.54	40.42±0.41	50.23±0.07

*Mean± SD (n=3)

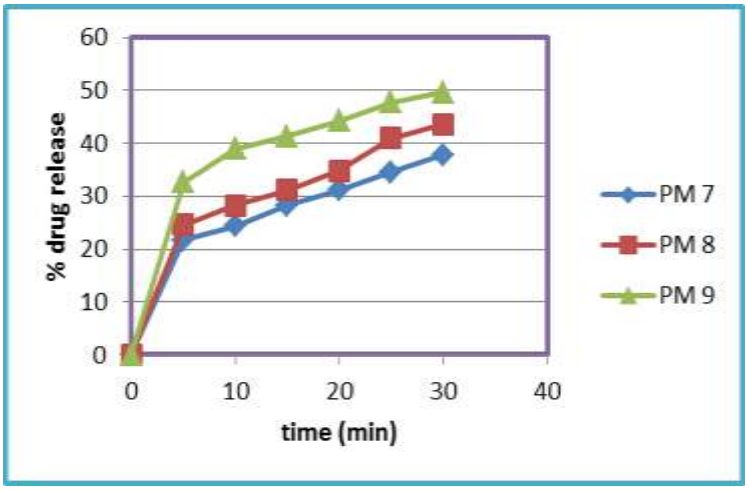

Figure No. 07: *In-Vitro* release studies of physical mixtures PEG-6000 (Ratio 1:1, 1:3, 1:5).

Table No. 12: *In-Vitro* Dissolution Profile of Physical mixtures PEG-4000 (Ratio 1:1, 1:3, 1:5).

S.No	Time (min)	% Drug Released*		
		PM 4 (1:1)	PM 5 (1:3)	PM 6 (1:5)
1	0	0	0	0
2	5	21.65±0.35	23.65±0.55	24.65±0.11
3	10	22.81±0.22	25.24±0.65	28.00±0.43
4	15	24.43±0.56	27.43±0.54	30.23±0.19
5	20	25.80±0.23	30.43±0.71	32.61±0.61
6	25	28.25±0.76	34.00±0.12	36.69±0.41
7	30	32.45±0.21	36.61±0.29	40.00±0.11

*Mean± SD (n=3)

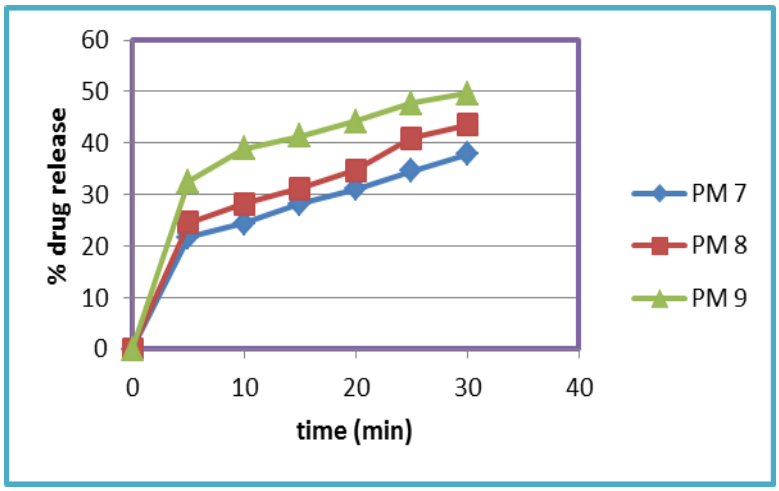

Figure No. 08: *In-Vitro* release studies of physical mixtures PEG-4000 (Ratio 1:1, 1:3, 1:5).

Table No. 13: *In-Vitro* Dissolution Profile of Physical mixtures Poloxamer-188 Ratio (1:1, 1:3, 1:5).

S.No	Time (min)	% Drug Released*		
		PM 7 (1:1)	PM 8 (1:3)	PM 9 (1:5)
1	0	0	0	0
2	5	21.71±0.14	24.61±0.73	32.67±0.21
3	10	24.45±0.85	28.21±0.97	39.00±0.11
4	15	28.21±0.71	31.26±0.64	41.45±0.55
5	20	31.14±0.41	34.89±0.45	44.21±0.66
6	25	34.61±0.62	41.00±0.87	47.89±0.27
7	30	37.89±0.22	43.67±0.11	49.61±0.18

*Mean± SD (n=3)

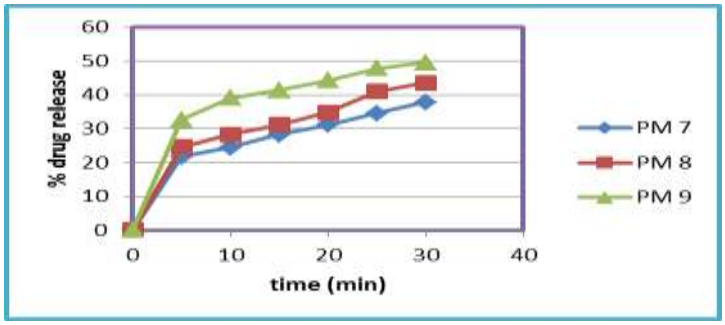

Figure No. 09: *In-Vitro* release studies of physical mixtures Poloxamer-188 (Ratio 1:1, 1:3, 1:5).

Evaluation of pre-compression parameters for Zolpidem Tartrate SD- tablets

Pre-compression parameters of all formulations were in acceptable range as per the specification. The results like, Bulk density ranges from 0.314±0.06 to 0.399±0.05 gm/cc, Tapped density ranges from 0.351±0.01 to 0.431±0.06 gm/cc, Compressibility or Carr's index ranges from 5.22±0.05 % to 10.54±0.02 %, Hausner's ratio ranges from 1.05±0.06 to 1.11±0.01 and angle of repose ranges from 22.13±0.13 ° to 25.33±0.13°. Hence, it concludes that all the prepared formulations fall under excellent flow property as given in the Table No. 14.

Table No. 14: Evaluation of pre-compression parameters of formulations F1-F9.

S.No	Formulations	Bulk density (gm/cc)	Tapped Density (gm/cc)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (θ)
1	F1	0.375±0.02	0.407±0.01	7.86±0.02	1.08±0.02	24.13±0.11
2	F2	0.352±0.03	0.377±0.03	6.63±0.03	1.07±0.01	25.26±0.09
3	F3	0.399±0.05	0.421±0.05	5.22±0.05	1.05±0.06	24.38±0.02
4	F4	0.395±0.02	0.431±0.06	8.35±0.05	1.09±0.02	24.57±0.06
5	F5	0.349±0.04	0.377±0.03	7.42±0.02	1.08±0.03	24.00±0.06
6	F6	0.369±0.02	0.398±0.06	7.28±0.06	1.07±0.01	22.82±0.11
7	F7	0.314±0.06	0.351±0.01	10.54±0.02	1.11±0.01	22.13±0.13
8	F8	0.384±0.05	0.414±0.05	7.24±0.06	1.07±0.02	24.6±0.06
9	F9	0.360±0.02	0.385±0.02	6.49±0.02	1.06±0.02	25.33±0.13

*Mean± SD (n=3)

Evaluation of Post-Compression Parameters

The results for Hardness (3.2-3.4 kg/cm$^{2)}$, Friability (Not more than 1%), Average weight (Range is 90-110 mg), Weight variation (±5 % from the average weight) and content uniformity (90-110 %). All these parameters of formulation F1-F9 are given in Table No. 15. All the formulations are within the prescribed ranges as specified by the pharmacopeia. Hence, all prepared formulations pass the post-compression studies.

Table No. 15: Post-Compression Parameters of for Zolpidem Tartrate SD- tablets F1 – F9

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)*	2.9±0.0	2.7±0.0	2.9±0.0	3.0±0.0	3.1±0.0	3.3±0.0	2.5±0.0	2.8±0.0	3.0±0.0
Hardness (kg/cm2)	3.3±0.1	3.3±0.12	3.2±0.11	3.4±0.1	3.4±0.1	3.3±0.1	3.2±0.1	3.2±0.1	3.3±0.1
Friability* (%)*	0.11	0.12	0.10	0.09	0.11	0.09	0.10	0.12	0.10
Average Weight* (mg)	100±0.5	98±0.2	105±0.8	102±0.2	110±0.5	100±0.5	98±0.2	105±0.7	100±0.4
Weight Variation*	2.5%	2.6%	2.1%	2%	2.10%	2.5%	2.1%	2.6%	2.10%
Assay* 0f Zolpidem Tartrate	94.20±0.5	96.50±0.5	97.60±0.7	94.20±0.5	98.60±0.6	99.30±0.4	97.78±0.5	96.72±0.7	97.7±0.5

*Mean± SD (n=3)

Evaluations from wetting time, water absorption ratio and disintegration time: The evaluation of prepared all formulations for wetting time ranges from 8.22±0.58 s to 28.00±1.00 s, water absorption ratio ranges from 32.03±0.75 % to 48.00±1.46 % and disintegration time ranges from 14±1.16 s to 31±1.15 as shown in the Table No. 16 and Figure No. No. xx. The formulation F1 showed less disintegration time since the concentration is less. F2 contains 4% and it showed good precompression parameters and the disintegration time was 21 seconds and the drug release was found to be less than F1.

Table No. 16: Evaluations for Wetting Time, Water Absorption Ratio and Disintegration Time of Formulations F1-F9.

Formulation	Wetting time(seconds) AM±SD	Water absorption ratio (%) AM±SD	Disintegration time(seconds)
F1	26.00 ± 2.00	32.03±0.75	25.0±1.15
F2	23.67±1.53	34.69±1.33	21.0±1.12
F3	19.00±1.00	40.11±1.17	20.0±1.23
F4	16.33±0.58	39.94±1.12	18.0±1.23
F5	11.12±0.59	45.00±1.46	16.0±1.16
F6	8.22±0.58	48.50±1.08	14.0±1.41
F7	28.00±1.00	35.03±0.8	28±1.0
F8	26.67±2.50	36.69±1.33	25±1.1
F9	25.06±0.02	41.10±0.02	23±1.4

*Mean± SD (n=3)

It was observed that as the concentration of Crosspovidone was increase tablet showed minimal disintegration time. F5 and F6 were formulated using 4% and 5% Croscarmellose sodium which showed rapid disintegration time of 16 sec and 14 sec respectively Hence, it was concluded that formulation F6 was the best among F1 to F9..

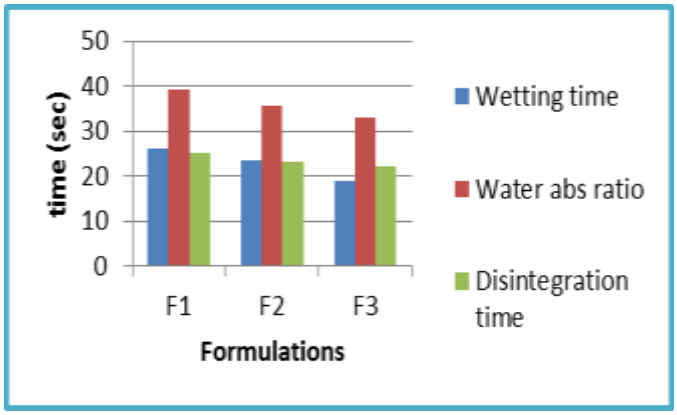

Figure No. 10: Wetting time, Water absorption ratio and Disintegration time of formulationsF1 to F3

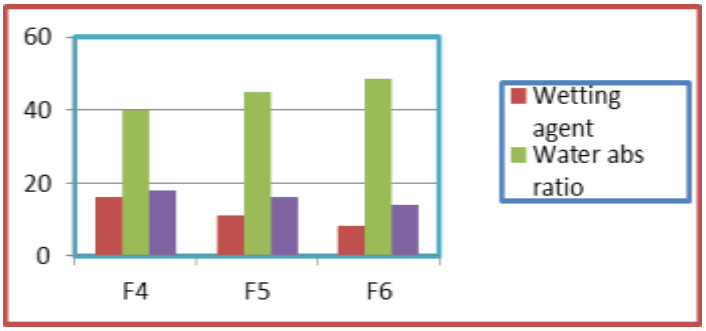

Figure No. 11: Wetting time, Water absorption ratio and Disintegration time of formulations F4 to F6.

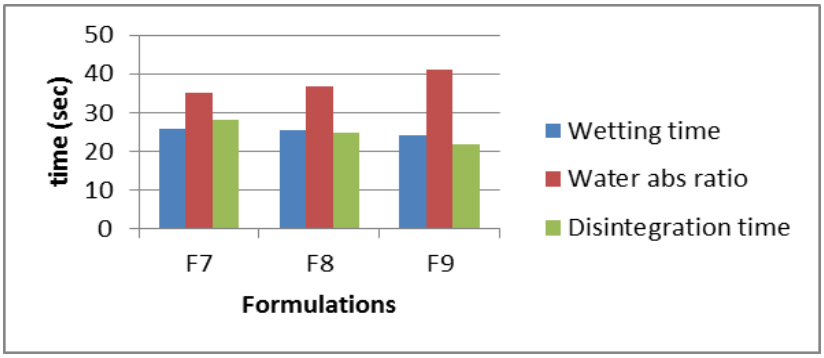

Figure No. 12: Wetting time, Water absorption ratio and Disintegration time of formulations F7 to F9.

***In-vitro* dissolution profiles of sublingual tablets of Zolpidem Tartrate SD tablets**

The *in-vitro* drug release of sublingual tablets of F1 to F9 were in the range from 38.23±0.2% to 99.87±0.8 as shown in the Table No. 17 and Figure No. 13 to 15. The % in vitro drug release of F3 was found to be less compared to F1 and F2. F5 and F6 were formulated using 4% and 5% Croscarmellose sodium which released 96.54% and 99.87% and hence F6 was considered to be the best among all the formulations prepared by using 5% Croscarmellose sodium.

Table No. 17: *In-vitro* release studies of Formulations F1 to F9

Time (min)	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
0	0	0	0	0	0	0	0	0	0
5	38.23±0.2	40.45±0.8	35.48±0.6	41.11±0.2	40.78±0.8	45.12±0.0	40.28±.0	40.89±0.4	43.65±0.6
10	44.58±0.4	46.87±0.2	38.41±0.8	62.45±0.8	54.28±0.2	60.84±0.8	45.65±0.0	47.62±0.0	53.85±0.8
15	53.50±0.4	54.23±0.4	46.12±0.6	65.56±0.0	69.56±0.6	66.65±0.6	51.54±0.1	53.39±0.8	61.47±0.0
20	62.00±0.0	58.13±0.2	56.32±0.4	80.48±0.6	81.15±0.4	82.65±0.6	58.75±0.8	61.78±0.0	66.85±0.6
25	77.87±0.2	70.45±0.8	62.95±0.8	89.87±0.0	92.36±0.6	97.28±0.2	64.85±0.4	73.58±0.6	75.64±0.6
30	81.23±0.2	73.57±0.2	68.56±0.8	93.25±0.8	96.54±0.4	99.87±0.8	73.28±0.2	78.28±0.2	84.95±0.0

*Mean± SD (n=3)

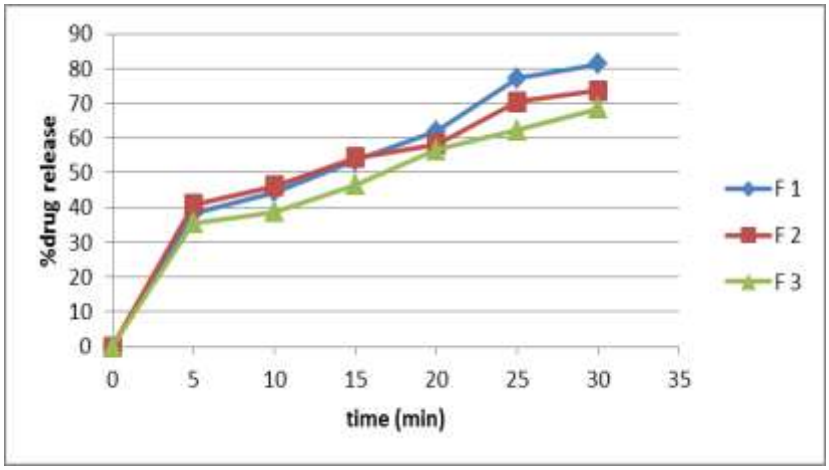

Figure No. 13: *In-vitro* release of Formulations F1 to F3

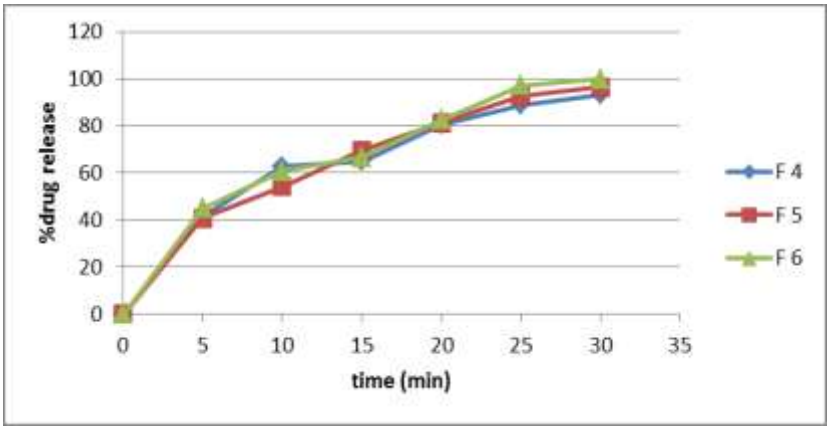

Figure No. 14: *In-vitro* release of Formulations F4 to F6

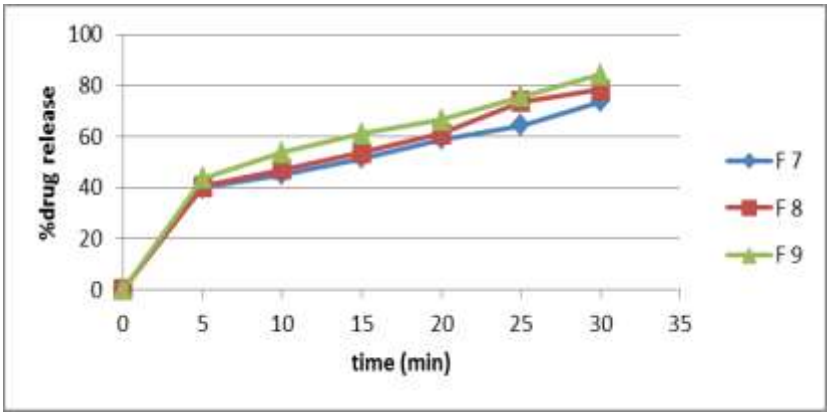

Figure No. 15: *In-vitro* release of Formulations F7 - F9

Stability study

The accelerated stability study of selected formulation F6 results are given in table 13 and table 14 respectively, and it concludes that all the parameters were within the acceptable ranges and there is no alteration in the physical appearance of formulation.

Table 28: Stability studies of Sublingual tablets of Zolpidem tartrate at 40 °C/75% RH of Formulation (F6)

Test	Formulation at 40^0C/75%RH			
	Initial	**1-month**	**2-Months**	**3-Months**
Hardness	3.3 kg/cm²	3.2 kg/cm²	3.1 kg/cm²	3.0 kg/cm²
Assay	99.30%	98.15%	97.72%	97.07%
In-vitro disintegration time	16.00 min	16.32 min	18.00 min	18.00 min
Dissolution				
Time	% drug release			
5	45.00±0.0	43.36±0.3	40.58±0.0	38.19±0.2
10	60.82±0.8	58.75±0.1	55.89±0.1	51.13±0.1
15	66.65±0.6	64.54±0.0	61.78±0.3	59.37±0.8
20	82.68±0.6	80.52±0.4	77.85±0.5	75.23±0.9
25	97.23±0.2	94.15±0.2	92.00±0.0	89.45±0.7
30	99.87±0.8	97.78±0.6	94.76±0.8	92.88±0.3

*Mean± SD (n=3).

CONCLUSION

Solid dispersion-immediate release tablets of anti-psychotic drug, Zolpidem tartrate for the treatment of short term insomnia was prepared and evaluated. Among nine formulations, F6 containing 5% Croscarmellose sodium showed less wetting time and disintegration time also the dissolution study that has been carried out was found to be faster when compared with that of other formulations. Various physicochemical parameters tested for the formulation F6 have shown good results. It was concluded that this lowered dose of sublingual tablets of Zolpidem Tartrate-SD tablets (5mg) prepared by direct compression technique has enough efficacy and can be used efficiently as an alternative to other marketed formulations of Zolpidem Tartrate-SD tablets for short term treatment of insomnia.

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CONFLICT OF INTEREST

No.

REFERENCES

1. Neha N and Jyoti S. Sublingual mucosa as a route for systemic drug delivery. Int J Pharm Pharm Sci., 2011; 3(2): 18-22.
2. Birudaraj R, Berner B, Shen S and Li X. Buccal permeation of buspirone: mechanistic studies on transport pathways. J Pharm Sci., 2005; 94: 70-78.
3. Ishikawa T, Koizumi N, Mukai B, Utoguchi N, Fujii M, Matsumoto M, et al. Pharmacokinetics of acetaminophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PH-M-06) and spherical sugar granules. Chem Pharm Bull., 2001; 49: 230-32.
4. Price TM, Blauer KL, Hansen M, Stanczyk F, Lobo R and Bates GW. Single dose pharmacokinetics of sublingual versus oral administration of micronized 17 Beta-estradiol. Obstet Gynecol, 1997; 89: 340-45.
5. Meda Pharmaceuticals Inc. US Patent 6761910. Reference ID-3295869.
6. Introduction to Psychotropic substances. http://shodhganga.inflibnet.ac.in/.
7. http://www.drugbank.ca/drugs/DB00425.
8. Karthikeyan M, Arunachalam A, Ravikiran N, Ashutosh kumar S, Eswaramma P and Manidipa S. Formulation And Evaluation of Zolpidem Tartrate Extended Release Matrix Tablets. International Journal of Pharmaceutical & Biological Archives, 2010; 1(5): 421–428.
9. Manjula Talluri, Shakti Saha and Sachin Basavaraj Adahalli Development and evaluation of sublingual tablet of zolpidem tartrate an antipsychotic drug. International Journal of Pharmacy and Pharmaceutical Sciences, 2016; 8(3): 179-187.
10. Kimura S, Imai T and Otagiri M. Pharmaceutical evaluation of Ibuprofen syrup containing low molecular weight gelatin. J. Pharm. Sci., 1992; 81: 141-144.
11. Dhirendra K, Lewis S, Udapa N et al. Solid dispersions. Pak J Pharm Sci., 2009; 22(2): 234-46.
12. Mooter GV, Augustijns P, Blaton N and Kinget R. Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. Int. J. Pharm., 1998; 164: 67-80.
13. Ahuja N, Katare OP, Singh B. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. Eur. J. Pharm. Biopharm, 2007; 65: 26-38.
14. Allen L.V and Wang B. Method of making a rapidly dissolving tablet. US Patent, 1997; 5(635): 210.

15. Bhowmik D, Chiranjib B, Pankaj K and Chandira RM. Fast Dissolving Tablet: An Overview. Journal of Chemical and Pharmaceutical Research, 2009; 1(1): 163-77.
16. YX Bi, Sunanda M, Yonezana Y and K Daujo. Evaluation of Rapidly Disintegrating Tablets Prepared by a Direct Compression Method. Drug. Dev. Ind. Pharm., 1999; 25(8): 571- 581.
17. Avasi NG and Bhalakar M. Indian Drugs, 2004; 4(1): 19-23.
18. United States Pharmacopeia XXIV-NR XIX, Asian Edition, VSP Convention Inc., 2001; 1941–1943.
19. Vaja Diveyesh Kumar N and Patel Maulik M, Joshi Ujjwal T and Patel Jaykishan M., J. Chem. Pharm. Res., 2010; 2(5): 307-352.
20. Meyers GL, Battist GE, Fuisz RC. Process and apparatus for making rapidly dissolving dosage units and product there from. PCT Patent W/C 95/34293-A1, 1995.
21. Cherukuri SR, Myers GL, Battist GE, Fuisz RC. Process for forming quickly dispersing comestible unit and product there from. US Patent 5587172, 1996.