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FORMULATION AND EVALUATION OF TASTE MASKED FAST DISSOLVING TABLET OF ZOLPIDEM TARTRATE BY DIRECT COMPRESSION METHOD

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ABSTRACT

Zolpidem Tartrate is a centrally acting potent sedative hypnotic agent used in the treatment of insomnia as well as in brain disorders. It is slightly bitter in taste and slightly soluble in water. In the present work an attempt has been made to prepare fast dissolving tablet of Zolpidem Tartrate with an view to enhance the patient compliance, and provide a quick onset of action, increasing the solubility and masking its bitter taste. Taste masking and solubility was enhanced by complexing Zolpidem Tartrate with Hydroxyl Propyl Beta Cyclodextrin (HPβCD) in 1:1 molar ratio by solvent evaporation method. Prepared complex was further examined through FTIR, DSC. The studies showed that the drug and carrier were compatible. These complexes were compressed into tablets by direct compression using different superdisintegrant like Crospovidone (Polyplasdone XL-10), Croscarmellose, Sodium Stach Glycolate (Explotab) in different concentration such as 3%, 4%, 5%, using aspartame as a sweetener and aerosol as lubricant. It was than evaluated for precompression parameters such as bulk density, tapped density, Hausner's ratio, compressibility, angle of repose etc. The prepared tablets were evaluated for hardness, friability, content uniformity, mouth feel, *in vitro* disintegration time, in vitro dissolution studies and bioavailability studies. The results were satisfactory. The drug release from tablets increased with increase in the concentration of superdisintegrants, the drug release was found to be highest with formulation F6 containing 5% Crospovidone which was consider to be the best formulation that released drug up to 98.49% in 12 min. *In-vivo* studies revealed that FDDT of formulation (F6) showed good bioavailability compared to conventional tablet. Thus results conclusively demonstrated rapid disintegration of the formulated tablet in oral cavity with masked bitter taste and good mouth feel.

Keywords: Zolpidem Tartrate, HPβCD Complex, Superdisintegrants, FDDT, Mouth Feel.

INTRODUCTION

From various current methods for treating illness and diseases, chemotherapy (treatment with drugs) is the most frequently used technique. It has the broad range of applications over the greatest variety of disease states and is frequently the preferred treatment method[1]. For many decades, treatment of acute disease or chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectbales as drug carriers[2, 3]. Despite phenomenal advances in the inhalable, injectable, Transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred route. There are of course many applications and large markets for non-oral products and the technologies that deliver them. However, if it is a viable option, oral drug delivery will be chosen in all but the most exceptional circumstances. Moreover, if the oral route is not immediately viable, pharmaceutical companies will often invest resources in making it viable, rather than plumping for an alternative delivery system[4]. Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms and is the most convenient and preferred route for systemic effects due to its ease of dosing administration, pain avoidance, accurate dosage, patient compliance and flexibility in formulation[5, 6]. The oral drug delivery market is the largest segment of the drug delivery market and there's no sign that it is slowing down. With pharmaceutical companies increasingly turning to drug delivery to extend the revenue-earning lifetime of their biggest products, and seeking to tap into the growing elderly population that requires products with a level of ease- of-use and cost benefit, it's no surprise that the oral delivery drug market is a $35 billion industry and expected to grows much as ten percent per year. Oral delivery provides the definitive break down of the market for oral delivery drug markets[7]. Amongst drugs that are administered orally; solid oral dosage forms i.e. tablets and capsules, represent the preferred class of products[7, 8]. Out of the two oral solid dosage forms, the tablets are the preferred ones. Tablets have number of advantages over other dosage forms. Recent advances in novel drug-delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a

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dosage form being convenient for the administration. Difficulty in swallowing (i.e., dysphagia) is experienced by patients such as pediatrics, geriatric, bedridden, disabled, mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of noncompliance and ineffective therapy[9] In order to solve this problem and improve patient acceptance and compliance, the development of solid dosage forms that disintegrate rapidly or dissolve even when taken orally without water is being undertaken. Oral fast-disintegrating dosage forms (tablet or a capsule) are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form[10] into a solution or suspension in the mouth without the need for water[11]. The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 s after administration[12]. The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect. Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing[13]. Orally disintegrating tablets are also called as Orodispersible tablets, quick-disintegrating tablets, mouth-dissolving tablets, fast-disintegrating tablets, fast dissolving tablets, rapid-dissolving tablets, porous tablets, and rapid melts. However, of all the above terms, the United States Pharmacopoeia (USP) approved these dosage forms as Orodispersible tablets (ODTs). Recently, the European Pharmacopoeia has used the term Orodispersible tablets for tablets that disperse readily and within 3 min in the mouth before swallowing. The United States Food and Drug Administration define ODT as "a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute[14]. Other advantages of ODTs that have been investigated are their potential to increase the bioavailability of poorly water soluble drug through enhancing the dissolution profile of the drug[15]. Moreover, pharmaceutical companies also have commercial reasons for formulating ODTs. As a drug reaches the end of its patent, the development and formulation of the drug into new dosage forms allow pharmaceutical companies to extend the patent life and "market exclusivity"[16]. The ODTs could be prepared using various techniques such as tablet moulding, spray drying, sublimation, lyophilization, solid dispersion, or addition of disintegrants[9-13]. The basic approach to the development of ODTs is the use of superdisintegrants such as Croscarmellose sodium and sodium starch glycolate. Another approach used in developing ODTs is maximizing the pore structure of the tablet matrix. Freeze drying and vacuum drying techniques have been tried by researchers to maximize the pore structure of the tablet matrix[14–16]. However, freeze drying is cumbersome and yields a fragile and hygroscopic product. Vacuum drying along with the sublimation of volatilizable ingredient has been employed to increase tablet porosity. While in designing dispersible tablets, it is possible to achieve effective taste masking as well as a pleasant feel in the mouth. The main criterion for ODTs is the ability to disintegrate or dissolve rapidly in saliva of the oral cavity in 15 to 60 s and have a pleasant mouth feel[17].To improve the quality of life and treatment compliance, great efforts have been made to develop fast-disintegrating tablets (FDTs) in the oral cavity, using jelly, water-absorbing, and swelling-gelated materials or water-soluble polymers[18]. The fundamental principle used in the development of the Fast Disintegrating tablets is to maximize its pore structure. Researchers have evaluated spray dried materials[21] and plastic materials[22] for development of such tablets. Vacuum-drying[23-28] and freeze- drying[29-32] techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and yields a fragile and hygroscopic product. Therefore, a vacuum drying technique was adopted in the present investigation after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly[33-39]. In the present study, an attempt was made to develop taste masked fast disintegrants tablets of Zolpidem Tartrate, to investigate the effect of superdisintegrants concentration on the release profile of the drug in the tablets.

MATERIAL

Zolpidem Tartrate was chosen as an active ingredient, a gift sample by Symbiosis Pharmaceutical Pvt Ltd, Baddi. HP-β-Cyclodextrin was purchased from S.D. Fine Chem. Ltd., Mumbai. Microcrystalline Cellulose (Avicel) was gift sample from Sanofi Aventis Pvt. Ltd., Goa. Crospovidone (polyplasdone XL-10), Croscarmellose Sodium (Ac-di-sol) and Sodium Starch Glycolate was a gift sample from Sanofi Aventis Pvt. Ltd., Goa. Spray Dried Lactose (KMV Enterprises, Hyderabad), Aspartame (Kawarlal & Sons, Chennai) were used. All other reagents were of analytical grade.

METHOD OF FORMULATION

Zolpidem Tartrate taste masked fast disintegrating tablets were formulated by using direct compression method. The drug and all other excipients were sifted through #30 sieves and mixed thoroughly. The above blend was pre lubricated with aerosil and lubricated with magnesium stearate. The above lubricated blend was compressed using 8.5mm Flat punch at a tablet weight of 100mg.

CHARACTERIZATION OF FAST DISINTEGRATING TABLETS

The prepared tablets were evaluated for different Pre Compressional and Post Compressional properties like Angle of Repose, Bulk Density, Tapped Density, % Compressibility, Hausner's Ratio, Weight Variation Test, Friability, Hardness, Thickness, Disintegration Time,

Wetting Time, Drug Content, Invitro Dispersion Time, Mouth Feel effect and In vitro Dissolution Studies.

Angle of Repose[38 – 41]

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the following formula.

$\tan\theta = h/r$

Bulk Density[38 - 41]**:**

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

$\rho b = Vb / M$

Tapped Density[38 - 41]**:**

The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tapings). The minimum volume (Vt) occupied in the cylinder and weight of the blend was measured. The tapped density (ρt) was calculated using following formula,

$\rho t = Vt/M$

Compressibility Index[38 - 41]**:**

The simplest method of measurement of free flow of powder is compressibility, an indication of the ease with which material can be induced to flow and is given by compressibility index (I) which is calculated as follows,

$I = \{(\rho t - \rho b) / \rho t\} * 100$

The value below 15% indicates a powder which usually gives rise to excellent flow characteristics, whereas above 25% indicate poor flow ability.

Hausner's Ratio (H) [38 - 41]**:**

This is an indirect index of ease of powder flow. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25). It is calculated by the following formula,

$H = \rho t / \rho b$

WEIGHT VARIATION[42-45]**:**

20 tablets were selected at random, and then the average weight was determined. All the 20 tablets were weighed individually and compared with the average weight the tablets meet USP specifications. No more than 2 tablets should be outside the percentage limit, and no tablet differs by more than 2 times the percentage limit.

FRABILITY[42-45]**:**

The friability test was performed for all the formulated fast dissolving tablets of Zolpidem Tartrate. Twenty tablets were taken and their weight was determined. Then they were placed in the Roche friabilator and allowed to make 100 revolutions. The tablets were then de-dusted and reweighed. The percentage weight loss was calculated. Percentage Friability was calculated as follows:

Percentage Friability = $(W_1 - W_2) \times 100/W_1$

Where, W1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 1% are generally acceptable.

HARDNESS[42-45]**:**

Monsanto hardness tester was used for measuring the hardness of the formulated Zolpidem Tartrate fast dissolving tablets. From each batch, five tablets were taken and subjected to test. The mean of the five tablets were calculated. The breaking strength (in kg) of each tablet was tested using a Stokes-Monsanto hardness tester (DT Stokes, Bristol, PA). The formulated tablets were circular and flat. After the dial on the tester was set to zero, a tablet was placed between the two jaws. The breaking point was determined by gradually increasing the force on the tester. Breaking strength is the force applied (in kg) to break the tablet radially into two halves.

WETTING TIME[42-45]**:**

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a Petridish containing 10.0 ml 0f water containing Eosin blue. A tablet was carefully placed on the surface of tissue paper. The time required for develop blue color on the upper surface of the tablet was noted as the wetting time.

THICKNESS OF TABLETS[42-45]**:**

Thickness is measured by using instrument called digital "vernier calipers". Randomly 10 tablets were taken and thickness was measured for each tablet by placing between two anvils and rotating sliding knob until the tablet was tightly fitted and the reading was noted on the digital scale.

***IN- VITRO* DISPERSION TIME**[46]**:**

In vitro dispersion time was measured by dropping a tablet in 20ml of Simulated Salivary Fluid (Phosphate Buffer of pH – 6.8) in a beaker. The time for the tablet to completely disintegrate into fine particles was noted. Three tablets from each batch were randomly selected and *in vitro* dispersion time was performed.

DRUG CONTENT[46]:

10 tablets were taken, powdered well and a quantity of powder equivalent to 100mg of Zolpidem Tartrate was accurately weighed and dissolved in 100ml of Simulated Salivary Fluid (Phosphate Buffer of pH – 6.8) and filtered. The absorbance of the solution was measured at 254nm against blank Simulated Salivary Fluid (Phosphate Buffer of pH – 6.8). The concentration of the sample was calculated using standard graph.

MOUTH FEEL EVALUATION[46]**:**

A panel of 6 volunteers was employed to assess the mouth feeling of prepared Zolpidem Tartrate taste masked fast disintegration tablets. The human test was performed according to the guidelines of WMA Helsinki declaration[28]. The comments of the panel members were recorded.

FTIR[46]**:**

The FTIR spectrums of pure drug and formulation were determined. A FTIR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 and 400 cm^{-1} resolution.

***IN-VITRO* DRUG RELEASE**[47]

In vitro dissolution studies for all the formulated tablets was carried out using USP paddle method at 50 rpm in 500ml of Simulated Salivary Fluid (Phosphate

Buffer of pH – 6.8) as dissolution media, maintained at 37±0.5°C. 5 ml aliquot was withdrawn at the specified time intervals, filtered through wattmann filter paper and assayed spectrophotometrically at 254nm. An equal volume of fresh medium, which was pre-warmed at 37°C, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test.

STABILITY STUDY[48]:

The fast disintegrating tablets of batch F_6 were wrapped in an aluminum foil and placed in a stability chamber controlled at 40 ± 2°C/75 ± 5°C relative humidity for a period of 3 months. At the end of 3rd month the formulation F_6 was evaluated for its Drug Content, Hardness, Friability, Invitro Dispersion Test, Wetting Time, Invitro Disintegration Time.

STATISTICAL ANALYSIS[49-50]:

The results were analyzed by two tailed Student's t-test using the Graph Pad Instat Software (GPIS; Version: 1.13).

RESULTS AND DISCUSSION

Pre-Compressional Parameters:

Table-2 shows the results obtained for angle of repose of all the formulations. The values were found to be in the range of 26°.64' to 29°.69'. All formulations showed the angle of repose within 30°, which indicates a good flow property of the granules. Both loose bulk density (LBD) and tapped bulk density results are shown in Table-2. The loose bulk density and tapped bulk density for all the formulations varied from 0.50 gm/cm^3 to 0.59 gm/cm^3 and 0.70 gm/cm^3 to 0.73gm/cm^3 respectively. This result helps in calculating the % compressibility of the powder. Table-2 shows the result obtained for Hausner's ratio of all formulations. The values were found to be in the range of 1.09 - 1.21. All formulations showed the Hausner's ratio within the range, which indicates a good flow property of the granules. This percent compressibility of powder mix was determined by Carr's Index. Table-2 shows the results obtained for percentage compressibility. The percent compressibility for all the nine formulations lies within the range of 15.49 to 17.69. All formulations are showing good compressibility.

Hardness: Table-3 shows results of hardness and hardness was found to be within 3.20±0.11 kg/cm^2 to 3.70 ± 0.21 kg/cm^2 and the results indicate that the all tablets possess good mechanical strength with sufficient hardness.

Friability: The study results are tabulated in Table-3. Formulation F1 to F9 possesses good mechanical strength. The low values of friability indicate that tablets were mechanically hard enough.

Thickness: As shown in Table-3, thickness of tablets ranged from 2.23 ± 0.02 mm to 2.52 ± 0.03 mm.

Weight Variation Test: The percentage weight variation for all the formulation was tabulated in Table-3. It was found to be from 99.0±1.02 to 102.0±1.02 mg. The weight of all the tablets was found to be uniform.

Water Absorption Ratio: Water absorption ratio, which is an important criterion for understanding the capacity of disintegrants to swell in presence of little amount of water, was calculated. It was found to be in the range of 42.39 ± 0.671 to 61.04 ± 1.236. The Water absorption ratio increased with increase in the concentration of superdisintegrant from 3-5%. This increase in was due water up take ability of the Superdisintegrants. The results are shown in Table-3.

Disintegration Time: Internal structure of the tablets that is pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration. The results are in the range of 10.38±2.19 to 25.63±2.13 shown in Table-3. Among the three superdisintegrants used, Crospovidone showed less disintegrating time followed by Croscarmellose Sodium and Sodium Starch Glycolate.

Wetting Time: The result of the wetting time is shown in Table-3. All formulation showed quick wetting in the range of 21.21±1.43 to 39.20±1.29. This may be due to ability of swelling and also capacity of absorption of water. All superdisintegrants have high water absorption capacity and cause swelling.

Drug Content of Tablets: The content uniformity was performed for all the nine formulations and results are shown in Table-3. The drug content of the tablets were found between 96±0.08 mg to 101±0.021 mg of Zolpidem Tartrate. The results indicated that in all the formulations the drug content was uniform.

***In Vitro* Dispersion Time:** In vitro dispersion time gives direct information regarding the nature of super-disintegrating agent used in the formulations. In vitro dispersion time is measured by observing the time taken by the tablets to undergo uniform dispersion in pH 6.8 buffer. Rapid dispersion of the tablets was observed in all the formulations. This indicate that the efficiency of superdisintegrants was in the order Crospovidone > Croscarmellose > Sodium Starch Glycolate. The values obtained are recorded in Table-3.

Mouth Feel Evaluation: Table-3 shows formulations using taste masking agent, Aspartame. The tablets were prepared by compressing under 8.5mm flat punch and each tablet weight is adjusted to 100mg which were evaluated for taste and mouths feel in 6 volunteers. The formulations with Aspartame scored various acceptability results. Among them formulation (F6) showed good acceptability. In the formulation aspartame was used as a sweetner to mask the taste and improve the mouth feel and taste of Zolpidem Tartrate tablet. Volunteers felt that the tablets had a good taste and a good palatable mouth feel.

Fourier Transform Infrared Spectroscopy (FTIR): Figures 1 to 6 shows all similar spectrum peak points of functional groups as pure drug Zolpidem Tartrate in all the formulations. This clearly indicates that there is no drug excipient interaction.

Invitro – Dissolution Studies:

All the nine formulations were subjected for the in vitro dissolution studies using tablet dissolution tester. The samples were withdrawn at different time intervals and analyzed at 254 nm. The plots of cumulative % drug

release V/s. time are shown in Figure 7 to 9. The dissolution rate was found to increase linearly with increasing concentration of superdisintegrant. Formulations F1, F2 and F3 which contained increasing concentrations of Croscarmellose Sodium from 3%w/w to 5%w/w, have recorded drug release 88.27%, 92.56% and 96.22% respectively, at the end of 12 minutes. Formulations F4, F5 and F6 which contained increasing concentrations of crospovidone from 3%w/w to 5%w/w, have recorded drug release 90.81%, 94.92% and 98.49% respectively, at the end of 12 minutes. Formulations F7, F8 and F9 which contained increasing concentrations of sodium starch glycolate from 3%w/w to 5%w/w, have recorded drug release 87.60%, 91.02% and 92.81% respectively, at the end of 12 minutes. In all the formulations the drug release was near to 100% within 12 minutes. The relative efficiency of different superdisintegrants to improve the dissolution rate of tablets was in order, Crospovidone > Croscarmellose Sodium > Sodium starch glycolate. In comparative study of the formulations F3, F6 and F9 showed 96.52%, 98.49% and 92.87% drug release respectively at the end of 12 minutes, graphical representation is shown in Figure -10.

Stability Studies:

The formulations F3, F6, F9 were selected for stability studies on the basis of their high cumulative % drug release and also results of *in vitro* disintegration time, wetting time, and *in vitro* dispersion studies. The stability studies were carried out at 40^0C/75% RH for all the selected formulations up to 180 days. For every 30 days time interval the tablets were analyzed for drug content uniformity, hardness, *in vitro* disintegration time, friability and wetting time up to 180 days. These formulations showed not much variation in any parameter. The results obtained are tabulated in Table-4. From these results it was concluded that, formulations F3, F6, F9 are stable and retained their original properties.

CONCLUSION

The fast dissolving tablets of Zolpidem Tartrate were prepared by direct compression method using different superdisintegrants such as Crospovidone, Croscarmellose Sodium, and Sodium Starch Glycolate in different concentration. Disintegration time decreased with the increase in the concentration of superdisintegrants from 3% w/w to 5% w/w. Among all formulation, formulation containing Crospovidone as superdisintegrants is fulfilling all the parameters satisfactorily. It has shown excellent In vitro Disintegration, In Vitro Dispersion Time, compared to other superdisintegrants. The relative efficiency of these superdisintegrants to improve the disintegration and dissolution rates of tablets was in order. Crospovidone> Croscarmellose Sodium> Sodium Starch Glycolate. In vitro release studies revealed that almost 90% drug was released from all the formulation were within 12 min. Formulation F3, F6 and F9 showed faster drug release in comparison to other formulation. The mouth feel revealed that tablet had a good palatable taste and the bitter taste has been masked with HPβCD. *In Vitro* studies revealed that FDT of formulation (F6) showed good bioavailability. Stability studies were conducted for formulations F3, F6 and F9 at 40^0C/75% RH for 180 days. Various parameters like hardness, friability, drug content uniformity, *In vitro* disintegration, wetting time were analyzed at a time interval of 30 days till a period of 180 days. Not much variation or change was observed in any parameters throughout the study period. Best selected formulations F3, F6 and F9 found to be stable. The prepared fast dissolving tablets disintegrate in seconds without need of water and enhance the absorption; this leads to increase in the bioavailability of Zolpidem Tartrate.

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Table 1: Formulae used in the preparation of tablets containing different Concentrations of Superdisintegrants.

Ingredients (mg/tablet)	Formulation Code (Quantity in mg for one tablet)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Inclusion Complex of Drug	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose (Avicel101)	42	42	42	42	42	42	42	42	42
Lactose	40	39	38	40	39	38	40	39	38
Croscarmellose Sodium (Ac-di-sol)	3	4	5	-	-	-	-	-	-
Crospovidone (polyplasdone XL-10)	-	-	-	3	4	5	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	-	3	4	5
Aspartame	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Aerosil	1	1	1	1	1	1	1	1	1
Total	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

*Each value represents mean ± S.D (n=3).

Table 2: Pre – Compressional Parameters Angle of Repose, Bulk Density, % Compressibility of different Tablet formulations

Formulation	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Density (g/ml)	% Compressibility	Hausner's Ratio
F_1	27.17±0.13	0.72±0.02	0.72±0.02	15.49±0.04	1.09±0.01
F_2	27.91±0.16	0.52±0.01	0.71±0.01	17.41±0.15	1.10±0.02
F_3	28.01±0.19	0.51±.0.02	0.70±0.04	17.99±0.11	1.20±0.02
F_4	29.18±0.21	0.52±0.00	0.72±0.01	17.23±0.05	1.22±0.02
F_5	29.69±0.28	0.59±0.02	0.71±0.04	17.20±0.13	1.11±0.01
F_6	29.41±0.08	0.57±0.02	0.75±0.01	16.49±0.14	1.2±0.01
F_7	29.53±0.21	0.50±0.02	0.70±0.02	17.17±0.04	1.20± 0.01
F_8	26.96±0.25	0.51±0.01	0.70±0.01	17.94±0.13	1.21±0.02
F_9	26.64±0.23	0.52±0.04	0.73±0.02	15.64±0.76	1.12±0.14

*Each value represents mean ± S.D (n=3).

Table 3: Post – Compressional Parameters, Disintegration Time, Wetting Time, Drug Content & Dissolution Time & Mouth Feel Effect of different Tablet Formulations

Formulation	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Avg. Weight (mg)	Content Uniformity (%)	Wetting Time (sec)	In vitro Dispersion Time (sec)	Water Absorption Ratio (%)	Disintegration Time (Sec)	Mouth Feel
F1	3.67±0.19	2.37±0.01	0.37±0.05	100.0±1.032	100±0.011	34.01 ± 0.37	23.30 ± 1.69	54.64 ± 1.163	22.30 ± 1.69	+
F2	3.40±0.13	2.52±0.03	0.48±0.05	99.5±2.151	100±0.011	32.74 ± 1.55	17.43 ± 0.65	55.26 ± 1.712	21.43 ± 0.65	+
F3	3.70±0.21	2.41±0.05	0.44±0.04	99.3±2.163	97±0.012	27.53 ± 1.57	15.21 ± 1.43	51.41 ± 2.531	19.21 ± 1.43	+
F4	3.26±0.29	2.23±0.02	0.38±0.12	101.7±2.88	96±0.008	31.60 ± 0.76	21.68 ± 1.53	49.45 ± 2.144	22.68 ± 1.53	+
F5	3.30±0.23	2.37±0.01	0.22±0.04	102.0±1.021	99±0.021	25.28 ± 1.25	16.64 ± 1.15	42.74 ± 0.671	15.64 ± 1.15	+
F6	3.41±0.21	2.33±0.04	0.34±0.05	99.0±1.021	100±0.015	21.21 ± 1.43	13.38 ± 2.19	43.31 ± 1.121	10.38 ± 2.19	+
F7	3.46±0.14	2.39±0.03	0.36±0.06	97.9±2.171	98±0.011	39.20 ± 1.29	25.63 ± 2.13	42.39 ± 1.183	25.63 ± 2.13	+
F8	3.20±0.11	2.27±0.02	0.22±0.06	100.3±2.045	100±0.046	32.66 ± 0.71	22.54 ± 1.36	60.31 ± 1.965	21.54 ± 1.36	+
F9	3.66±0.20	2.25±0.01	0.36±0.08	99.5±2.194	101±0.021	35.41 ± 1.59	24.12 ± 1.14	61.04 ± 1.236	22.12 ± 1.14	+

*Each value represents mean ± S.D (n=3); '+' Good palatable mouth feel, '-' Poor palatable mouth feel

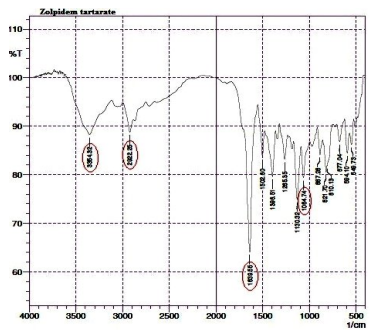

Fig.1: IR spectrum of Zolpidem Tartrate

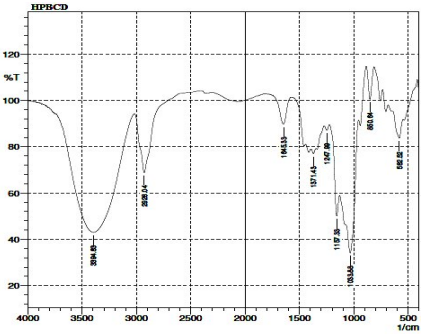

Fig.2: IR Spectrum of HPβCD.

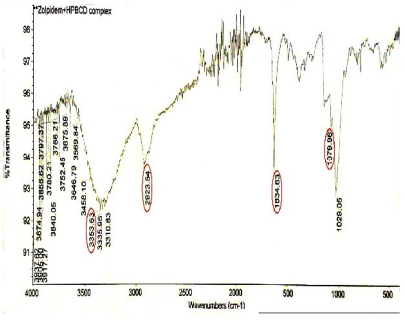

Fig.3: IR spectrum of Zolpidem Tartrate +HPβCD complex.

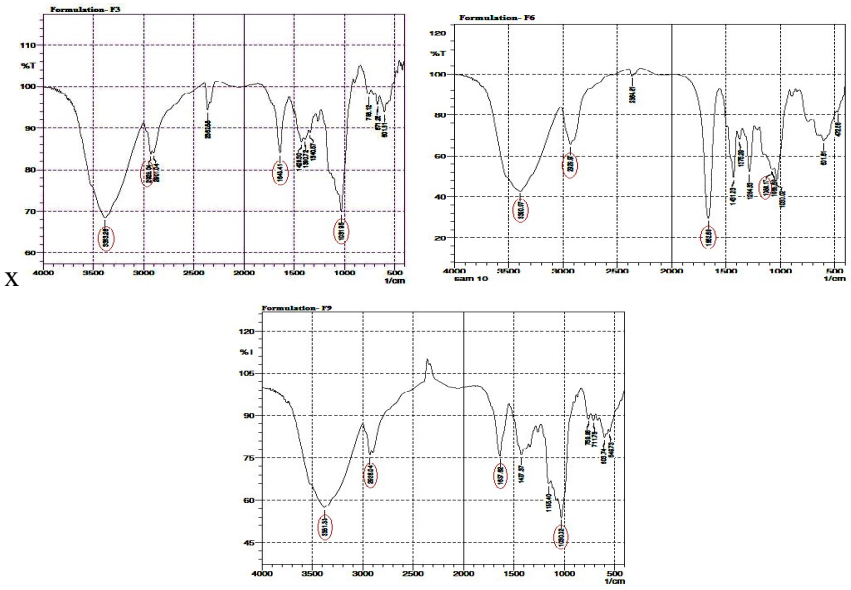

Fig.4: IR Spectrum of Formulation F3 **Fig.5:** IR Spectrum of Formulation F6 **Fig.6:** IR Spectrum of Formulation F9

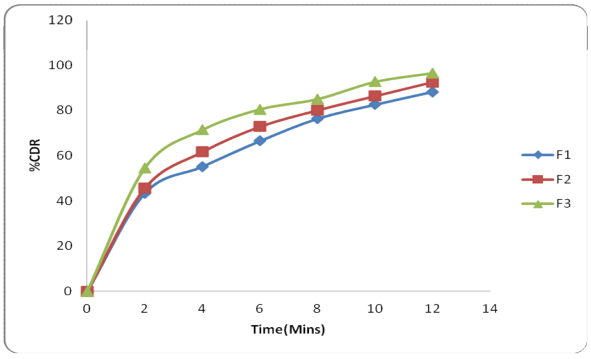

Fig.7: Comparative In Vitro Release Profile of Zolpidem Tartrate from Formulation F1, F2 and F3.

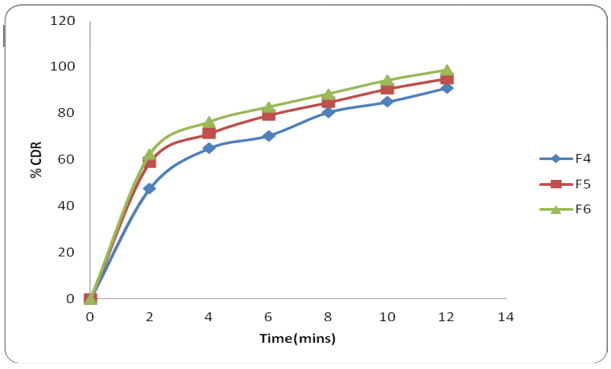

Fig.8: Comparative In Vitro Release Profile of Zolpidem Tartrate from Formulation F4, F5 and F6.

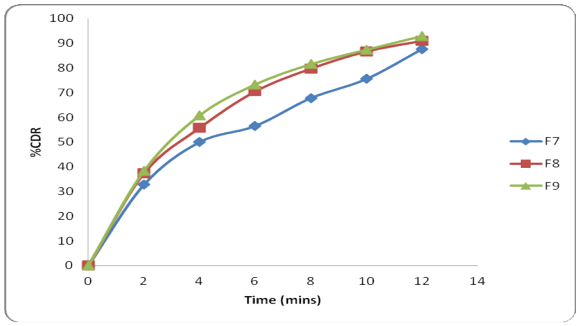

Fig.9: Comparative In Vitro Release Profile of Zolpidem Tartrate from Formulation F7, F8 and F9.

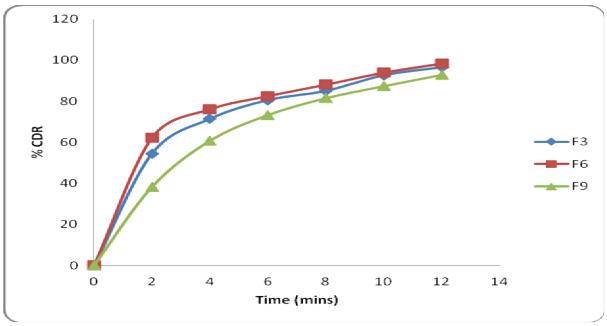

Fig.10: Comparative In Vitro Release Profile of Zolpidem Tartrate from Formulation F3, F6 and F9.

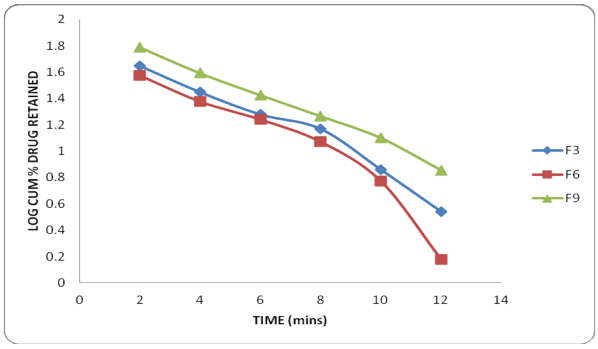

Fig.11: *In Vitro* Log Cumulative % Drug Retained V/s Time of Zolpidem Tartrate according to First Order Kinetics for Formulation F3, F6 & F9.

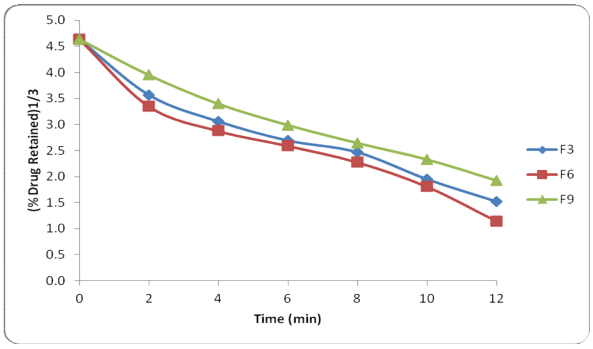

Fig.12: *In Vitro* (% Drug Retained)$^{1/3}$ V/s. Time (Hixson Crowell) from Formulation F3, F6 and F9

Table 4: Stability studies of Formulations F3, F6 and F9 stored at 40^{0}C/75% RH

Formulation Code	Tested After Time (in days)	Hardness (kg/cm^2)	Disintegration Time (sec)	Wetting Time (sec)	Drug Content (n=3)	Friability % *(n=3)*
		Mean ± SD (n=3)				
F3	30	4.31±0.21	16.21±1.43	28.31±1.57	99±0.021	0.3493±0.03
	60	4.29±0.20	16.15±1.41	28.16±1.56	100±0.015	0.3459±0.07
	90	4.25±0.19	16.11±1.41	28.05±1.51	98±0.011	0.3421±0.04
F6	30	4.22±0.21	13.38±2.19	20.22±1.43	100±0.046	0.2451±0.06
	60	4.29±0.19	13.31±2.20	20.17±1.43	101±0.021	0.2439±0.06
	90	4.11±0.15	13.19±2.21	20.13±1.47	100±0.011	0.2431±0.07
F9	30	4.30±0.20	22.12±1.14	37.39±1.59	100±0.011	0.2683±0.04
	60	4.21±0.15	22.11±1.13	37.42±1.51	97±0.012	0.2673±0.05
	90	4.31±0.15	22.01±1.10	37.25±1.39	96±0.008	0.2656±0.03

REFRENCES

1. Banker G S. Drug products: Their role in the treatment of disease, their quality, and their status and future as drug-delivery systems. In: Banker GS, Rhodes CT, editors. Modern Pharmaceutics. 2nd edition. Marcel Dekker. New York: Madison Avenue; 1990:1-21.
2. Manjula A, Selvam P, Nirmal R and ShakilabanuS. In vitro evaluation studies of crosslinked chitosan microspheres containing rabeprazole sodium. Int J Pharm Sci Res 2011; 2(6):1513-7.
3. Chein YW, editor. Novel Drug Delivery Systems. 2nd edition. Marcel Dekker. New York: Madison Avenue; 1992:139-96.
4. Furness G. Introduction. In: Oral Drug Delivery When You Find the Holy Grail. UK: ONdrug Delivery Ltd; 2007:3.
5. Dahiya A, Rohilla A, Rohilla S and Khan MU. Gastroretentive dosage forms: Review on floating drug delivery systems. Int Res J Pharm 2011; 2(5):72-8.
6. Sharma A, Jain A, Purohit A, Jatav R and Sheorey RV. Formulation and evaluation of aceclofenac fast dissolving tablets. Int J Pharm & Life Sci 2011;2 (4):681-6.
7. Sampath Kumar K P, Bhowmik D, Chiranjib, Chadira M and Tripathi K K. Innovations in sustained release drug delivery system and its market opportunities. J Chem Pharm Res 2010; 2 (1):349-60.
8. Rawlins E A. Bentley's text book of pharmaceutics. 8th ed. London: Bailliere Tindall; 1992:269.
9. Mishra DN, Bindal M, Singh SK, Kumar SGV. Spray dried excipient base: A novel technique for the formulation of orally disintegrating tablets, Chem Pharm Bull, 2006, 54(1), 99– 102.
10. Seager H. Drug delivery products and the Zydis fast dissolving dosage forms. J Pharm. Pharmacol, 1998, 50,375–82.
11. Ciper M, Bodmeier R. Modified conventional hard gelatin capsules as fast disintegrating dosage form in the oral cavity, Eur J Pharm Biopharm., 2006, 62(2), 178–84.
12. Suresh B, Rajendar KM, Ramesh G, Yamsani MR. Orodispersible tablets: an overview. Asian J Pharm, 2008, 2, 2–11.
13. Dobetti L. Fast-melting tablets: developments and technologies, Pharma Tech. 2001, (Suppl.), 44–50.
14. Koizumi K, Watanabe Y, Monita K, Utosuchi N. New method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material. Int J Pharm., 1997, 152,127–31.

15. FuY,Yang S, Jeong Sh,Kimura S, ParkK.Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. Crit Rev Ther Drug Carrier Sys., 2004,21,433–76.
16. Ahmed IS, Aboul-Einien MH. In vitro and in vivo evaluation of a fast-disintegrating lyophilized dry emulsion tablet containing griseofulvin. Eur J Pharm Sci., 2007, 32(1),58–68.
17. Biradar SS, Bhagavati ST, Kuppasad IJ. Fast dissolving drug delivery systems: a brief Overview, Internet J Pharmacol, 2006, 4(2). 21-27.
18. Omaima AS, Mohammed AH, Nagia AM, Ahmed SZ. Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion. AAPS PharmSciTech. 2006,7,55 - 58.Renon, J.P., Corveleyn, S., Freeze-dried rapidly disintegrating tablets, US Patent No. 6,010,719, 2000.
19. Patel M, Patel N, Patel M. Fast-dissolving rofecoxib tablets: formulation development & optimization using factorial design. Drug Del Technol., 2007,7,33–8.
20. Ahmed IS, Fatahalla FA. Pilot study of relative bioavailability of two oral formulations of ketoprofen in healthy subjects, a fast dissolving lyophilized tablet as compared to immediate release tablet. Drug Develop Ind Pharm., 2007, 33,505–11.
21. 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 PharmSci-Tech., 2004,5,36.
22. Ahmed IS, Nafadi MM, Fatahalla FA. Formulation of fast dissolving ketoprofen tablet using freeze-drying in blister technique. Drug Develop Ind Pharm., 2006, 32,437–42.
23. Indurwade NH, Rajyaguru TH, Nahat PD. Novel approach in fast dissolving tablets. Indian Drugs. 2002,39(8),405–9.
24. Shu T, Suzuki H, Hironaka K, Ito K.. Studies of rapidly disintegrating tablets in the oral cavity using co-ground mixtures of mannitol with crospovidone. Chem. Pharm Bull,, 2002, 50(2),193–8.
25. The Merck index, 14th Edn. 2006; 281.
26. Sweetman SC. Martindale: The complete drug reference, pharmaceutical press, 33rd Edn. London: The Pharmaceutical Press; 2002; 907.
27. Drug today, Vol. I, April-June 2006; 155.
28. Omaima AS, Mohammed AH, Nagia AM, Ahmed SZ. Formulation and optimization of mouth dissolve tablets containing Rofecoxib solid dispersion. AAPS Pharm.Sci.Tech. 2006; 7:55.
29. 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; 5:36.
30. Suresh S, Pandit V, Joshi HP. Preparation and evaluation of mouth dissolving tablets of Salbutamol sulphate. Indian J Pharm. Sci. 2007; 69:467-9.
31. Heinemann H, Rothe W. Preparation of porous tablets. US patent 3 885 026. May 20, 1975.
32. Knistch A, Hagen E, Munz HD. Production of porous tablets. US patent 4 134 843. January 16, 1979.
33. Roser BJ, Blair J. Rapidly soluble oral dosage forms, methods of making the same and composition thereof. US patent 5 762 961, June 9, 1998.
34. Ahmed IS, Fatahalla FA. Pilot study of relative bioavailability of two oral formulations of Ketoprofen in healthy subjects, a fast dissolving lyophilized tablet as compared to immediate release tablet. Drug. Develop. Ind. Pharm. 2007; 33:505-11.
35. Ahmed IS, Nafadi MM, Fatahalla FA. Formulation of fast dissolving Ketoprofen tablet using freeze-drying in blister technique. Drug Develop Ind. Pharm. 2006; 32:437-42.
36. Corveleyn S, Remon JP. Formulation and production of rapidly disintegrating tablets by lyophilization using Hydrochlorothiazide as a model drug. Int. J Pharm. 1997; 152:215-25.
37. Remon JP, Corveleyn S. Freeze-dried rapidly disintegrating tablets. US patent 6 010 719, January 4, 2000.
38. Allen, L.V, Wang, B., Method of making a rapidly dissolving tablet. US Patent No. 5,635,210, 1997.
39. Bhowmik D, Chiranjib B, Pankaj K, Chandira RM. Fast Dissolving Tablet: An Overview. Journal of Chemical and Pharmaceutical Research 2009; 1(1): 163-77.
40. YX Bi, M Sunanda, Y Yonezana, K Daujo. Drug. Dev. Ind. Pharm. 1999; 25(8): 571- 581.
41. NG Avasi, M Bhalakar. Indian Drugs. 2004; 4(1): 19-23.
42. United States Pharmacopeia XXIV-NR XIX, Asian Edition, VSP Convention Inc., 2001, 1941 – 1943.
43. N Vaja Diveyesh Kumar, M Patel Maulik, T Joshi Ujjwal, M Patel Jaykishan., J. Chem. Pharm. Res., 2010; 2(5): 307 -352.
44. 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.
45. Cherukuri SR, Myers GL, Battist GE, Fuisz RC. Process for forming quickly dispersing comestible unit and product there from. US Patent 5587172, 1996.
46. Fuisz R. Ulcer prevention method using a melt-spun hydrogel. US Patent 5622717; 1997.
47. S. Kimura, T. Imai and M. Otagiri, Pharmaceutical evaluation of Ibuprofen syrup containing low

molecular weight gelatin. J. Pharm. Sci. 1992; 81: 141-144.
48. Ashiqul Islam, Syed Shabbir Haider and Md. Selim Reza. Formulation and Evaluation of Orodispersible tablet of Domperidone. Dhaka Univ. J. Pharm. Sci. 2011; 10 (2): 117-122.
49. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Adopted in the 18th WMA General Assembly and subsequent amendments, 1964.
50. J. Wells, Pharmaceutical preformulation, the physicochemical properties of drug substances, in Pharmaceutics – the Science of Dosage Form Design, 2nd ed. (Ed. M. E. Aulton), Churchill Livingstone, London 2002, pp. 113–138.

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