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Development of Non-Bitter Zolpidem Tartrate Mouth Dissolving Tablet

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ABSTRACT

Purpose: Zolpidem tartrate is a centrally acting potent hypnotic agent. It is slightly bitter in taste. In the present study an attempt has been made to prepare bitterless mouth dissolving tablets of Zolpidem tartrate using ion exchange resin Tulsion 335 as a taste masking agent. Method: Ion exchange resinates and tasteless granules were prepared with Tulsion 335 in weight ratio of 1:3. Resinates and granules were evaluated for its taste sensation in human volunteers. Prepared complex was further examined through IR, DSC and XRD curves. The mouth dissolving tablets of both resinates and granules were prepared with two superdisintegrants e.g. crosscarmellose sodium and crospovidone in different concentration. The blend was examined for their flow properties. The tablets were evaluated for physiochemical properties. Pure drug and tablets were also evaluated loss of righting reflux in albino Mice.Results: The tasteless blends having good flow properties. The prepared zero defect mouth dissolving tablets were passed all the official and non-official parameters. The disintegration time was also tested and was found to be less than one minute. A tablet having resinates shows less time for onset of action of drug due to enhanced and fast release of Zolpidem Tartrate. Conclusion: It was concluded that tablets prepared by addition of superdisintegrant crospovidone has less disintegration time, fast and more dug release than those prepared by crosscarmelose sodium; which was also further founded in the in-vivo investigation.

Keywords: Zolpidem tartrate, Resinate, Mouth dissolving Tablet, Bitterless

INTRODUCTION

Taste of a pharmaceutical product is an important parameter for governing compliance. Thus, taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment especially in pediatrics. More than 50 percent of pharmaceutical products are orally administered having undesirable taste is one of the important formulation problem encountered with oral products. Therefore, formulation of taste masked products is a challenge to the pharmacists[1-2]. Taste masking of the active ingredients can be achieved by various techniques. Two approaches are commonly utilized to overcome the bitter taste of the drugs. The first includes reduction of drug solubility in saliva, where it's reduced solubility and bioavailability. Another approach is to alter the ability of the drug to interact with taste receptor by forming a complex with other compatible and non pharmacological materials[3-4]. Zolpidem tartrate is a potent hypnotic, used in treatment of insomnia, as well as some brain disorders. It is a very bitter drug and having very less solublility [5-6]. The main objective of the present work is to formulate taste masked mouth dissolving tablets of Zolpidem tartrate (ZP). The bitterless complex (resinate and granules) were prepared by using Ion Exchange Resin (IER) Tulsion 335. These taste masked granules or resinates was further formulated into the mouth-dissolving tablet by direct compression method using crosscarmellose sodium (Ac-Di-Sol) and crospovidone as the superdisintegrants. Enhanced release and fast onset of action was achieved by these formulations resulted in increased bioavailability. Such taste-masked formulations have been found to improve the quality of treatment in patients which have difficulty in swallowing.

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MATERIALS AND METHODS

Materials

Zolpidem tartrate was a gift sample from Symbiosis Pharmaceutical Pvt Ltd.Baddi. Tulsion 335 was procured from Thermax Ltd. Pune, India. Lactopress (lactose monohydrate), Avicel PH 102 (Microcrystalline cellulose), Crosspovidone and Ac-Di-Sol were a gift sample from Signet Chemicals (Mumbai). Sucrose, Magnesium stearate and Talc purchased from S. D. Fine Chemicals Ltd. (Mumbai). All other reagent and solvent used were of analytical grade. Deionized water was freshly prepared whenever in use.

Methods

Preparation of Non Bitter Drug-Resinate Complex

Activation of Resin

Ion exchange resins Tulsion-335 was swelled with deionised water for an hour and then washed with 1N HCl and 1N NaOH in order to remove impurities (alkali and acidic impurities). The treated resin was washed several times with freshly prepared deionized water to remove the traces of acid or alkali. This treated resin was kept in oven for 12h at 50^0C. The dried activated resin was kept in desiccator until in use [7].

Resinate formation

The activated resins were swelled in deionized water (100mL) for an

hour with homogenous continuous stirring on magnetic stirrer at 100 rpm. After swelling of activated resin (15g) the Zolpidem tartrate (5g) was added to this solution on weight basis and stirred on magnetic stirrer at 50 rpm for a period of 4h using deionized water. The obtained resinate was separated by filtration and dried in vacuum desiccators [8].

Preparation of Non Bitter Drug-Resin Granules

Drug was mixed with Tulsion 335 and Avicel Ph 102 with the help of mortar and pestle. Then 10% ethanol was added to mixture. Then dump mass was prepared which was converted into the taste-masked granules by passing through sieve no. 24. After granule formation the dump granules were dried at 50^{0}C in tray drier.

Evaluation of Drug Resinate and Granules

Thermal analysis

Thermal analysis was carried out with the help of DSC equipment (DSC821e Mettler Toledo) calibrated using indium as a standard with a melting point of 156.63°C and a calibration energy of 28.89 J/g. The temperature was increased from 25°C to 300°C at a heating rate of 10°C/min under a flow of nitrogen (80 ml/min). From each stressed sample approximately 5 mg of the sample was weighed and subjected to DSC.

X-Ray Diffractometry

The Powder XRD patterns of Zolpidem Tartrate, Zolpidem tartrate resinate and Zolpidem Granules were recorded using Philips XPERT PRO X-Ray diffractometer having X'Celerator Detector. Samples were irradiated with monochromatized Cu Ká radiation (1.5406 Å) after passing through Nickel filters and were analyzed between 40° and 2° (2è) with scan step size 0.0167 in spinning condition and number of scan steps was 2274. The voltage and current applied were 45 KV and 40 mA, respectively.

Fourier-Transform Infrared Spectrophotometry

Infrared spectra of Zolpidem Tartrate, Zolpidem resinate and Zolpidem granules were obtained using FTIR spectrophotometer, Model- Spectrum One of Perkin Elmer Instruments. The pellets were prepared on KBr press, and the spectra were recorded over the wave number 4000 to 400 cm^{-1}.

Drug Loading

The prepared resinate and granule was crushed and dissolved in Sorensen's buffer pH 6.8. The solution was filtered using 0.45µm nylon filters. The filtrates were analyzed by UV-VIS spectrophotometer for its drug content at 295nm. The test was performed in triplicates.

***In Vivo* Taste Evaluation**

Taste evaluation of the drug resin complex was performed by consensus of trained taste panel of seven healthy volunteers in the age groups of 25 to 30 years. The 5mg equivalent to Zolpidem Tartrate, Zolpidem Tartrate Resinate and Zolpidem tartrate granules were held in mouth for 60s by each volunteer, and the bitterness level was recorded using a numerical scale. After 60sec, complex was spitted out and the mouth was rinsed thoroughly with mineral water. A numerical scale was used with the following values: 1=tasteless, 2=slightly bitter, 3=bitter, 4=very bitter [9].

Flowability of Resinate and Granules

The bulk density and tapped density of the mixed powders before compression was studies for determining the Hausener's ratio (H) and Carr's index (I %) from a known weight of sample using a measuring cylinder and following formula [10-12].

$$I\% = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

$$HR = \frac{\rho_t}{\rho_b}$$

Where, ρ_t = Tapped density

ρ_b = Bulk density

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

Tan ? = h/r; Therefore; ? = Tan^{-1}[h/r]

Where, ? is Angle of Repose; h is height of cone; r is radius of cone.

Determination of in vitro drug release

The release of drug from resinate was carried out from USP 24 dissolution apparatus II, paddle (USP 24, 2000). Three different dissolution media (900 mL) used were simulated oral media (Sorenson's Buffer pH 6.8), simulated gastric fluid (0.1N HCl pH 1.2) and simulated intestinal fluid (Phosphate Buffer pH 7.4) at 37±0.5^{0}C. Rotation speed was 50 rpm. An accurate weight of granules and resinate equal to 5mg of zolpidem was added in dissolution media while the solution was agitated using the paddle. A 5 mL of sample was collected and replaced with fresh medium at appropriate interval. An absorbance of collected sample was measured by UV-VIS spectrophotometer at 295 nm.

Preparation and Evaluation of Blends

All the ingredients (shown in Table 1) were passed through mesh number 20, and they were co-ground and mixed properly together in a pestle motor for 15 minutes. Talc and Magnesium stearate were mixed at the end of the process. These blends were evaluated for mass-volume relationship (Bulk Density, Tapped Density, Hausners Ratio and Compressibility Index) and flow properties (Angle of Repose).

Compression of Tablets

The mixed blend of excipients were compressed using a single punch tablet punching machine (Cadmach, Ahmedabad) to produce flat faced tablets weighing 100 mg each with 7 mm diameter. A minimum of 100 tablets were prepared for each batch.

Evaluation of the Prepared Tablets

After compression of powder, the tablets were evaluated for organoleptic and physical characteristics like color, odor, taste, diameter, thickness, Weight variation, Hardness, Friability, *In vitro* Disintegration time, Wetting time and *In vitro* Dispersion time. *In vitro* dissolution studies of fast dissolving tablet were carried using 900-mL sorenson's buffer (pH 6.8) as the dissolution media [13].

Tablet Thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by suing filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using digital micrometer (Mitutoyo, Japan).

Weight Variation

I.P. 1996 procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance (Shimadzu, Japan). The average weight of one tablet was determined from the collective weight.

Hardness

The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was measured using a Monsanto hardness tester (Tab-Machines Ltd., India). The test was performed on 10 tablets and the average was calculated.

Friability

Friability of the tablets was determined using Roche friabilator (Electrolab, India) at 25 rpm for 4 minutes. Preweighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula

$F\% = [1-W_0/W]X100$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test.

***In vitro* Disintegration Test**

Disintegration of fast disintegrating tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* conditions. A modified version of the simple but novel method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10-mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve (Figure 1). To determine disintegration time, 6ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4ml of the media was below the sieve and 2ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined [14].

Wetting Time

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (i. d. = 6.5 cm) containing 6 ml of Sorenson's buffer (pH 6.8). A tablet was placed on the paper, and the time for the complete wetting was measured. The test was carried out on triplicate and the mean value was considered [15].

***In vitro* Dispersion Time**

Tablet was added to 10ml of Sorenson's buffer solution (pH 6.8) and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed [16].

Dissolution studies

For the dissolution studies, an IP paddle type dissolution apparatus I with six basket (Lab India) was used. One tablet was placed in each basket, which rotated at 50 rpm in 900 ml of the dissolution medium (Sorenson buffer, pH 6.8) at 37^0C. The experiment was run for 10 minutes, during which samples were withdrawn at suitable time intervals and replaced by an equal volume of dissolution medium kept at 37^0C. Samples were assayed by uv- spectrophotometer at 295 nm [18].

Pharmacological Studies

Male *Lacca* mices weighing 25–30 g were kept under a 12h light–dark cycle at a temperature of 23±2°C and 65% humidity. Upon arrival at the animal facilities there was a minimum of 7 days of acclimatization during which the animals had free access to food and water. Mices (?ve for each experimental group) received by an appropriate needle an intragastric administration of the ZP, resinate, granules and tablet suspension (F2 and F6, respectively) given in equimolar doses (10 mg/kg of animal) as solutions in 5 ml of water. As controls were administered ZP suspended in water, ZP suspended in water containing little quantity of gum acacia per 5 ml, and an resinate of ZP and Tulsion 335 vortexed and immediately administered. This last was an opalescent mixture. Rats were observed for the following 90 min and the time of ataxic induction, which was de?ned as the time from drug administration to the status of profound sedation characterized by motor inco-ordination of all four legs, was recorded.

RESULT AND DISCUSSION

Evaluation of Drug Resinate and Granules

The DSC trace of Zolpidem tarterate shows one endothermic peak at 296.94, which is associated with it's melting point. In the DSC of Zolpidem tartrate in it's resinate with Tulsion 335, the changes in the endothermic peak of the Zolpidem tartrate were well preserved with little change in sharpening, broadening or shifting towards a lower temperature (Figure 2). These slight changes in the melting endotherm of the drug may be attributed to the mixing process, which lowers the purity of each component in the mixture, thus resulting in slightly broader and lower melting points, but not truly representing any incompatibility.

The x-ray diffractograms of Zolpidem tartrate confirmed its crystalline nature, as evidenced from the number of sharp and intense peaks. The diffractograms of Tulsion 335 showed diffused peaks, indicating its amorphous nature while the diffraction pattern of resinate represents complete disappearance of crystalline peaks of drug. These findings suggested that the drug was completely entrapped in the resin polymer matrix (Figure 3).

IR spectra of Zolpidem tartrate, Tulsion 335 and resinate are presented in Figure 4. Pure Zolpidem tartrate spectra showed sharp characteristic peaks. All the above characteristic peaks appear in the spectra of all binary systems at same wave number indicating no modification or interaction between the drug and carrier.

Drug loading for prepared resinates and granules were found 57.13% and 99.43% respectively. According to these results resinates and granules were calculated equivalent to 5 mg of Zolpidem and incorporated in tablets formulation.

In Vivo Taste Evaluation

For taste evaluation time intensity method is used. Panel of healthy human volunteers of seven was used. The satisfactory taste masking of Zolpidem tartrate was done as shown in the table 2. Granules shows low degree of bitterness than pure zolpidem tartrate, while resinate did not show any bitter taste when these are held in the mouth which shows excellent taste masking effect of the resins.

Detemination of in vitro drug release

Release of Zolpidem tartrate from granules and resinate in three different pH media is shown in figure 5.

Table 1 Formulation and Evaluation Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Drug granules with Tulsion 335 equivalent to 5 mg of zolpidem tartrate(1:3)	20 mg	20 mg	20 mg	20 mg	-	-	-	-
Drug resonates equivalent to 5mg of zolpidem tartrate	-	-	-	-	35 mg	35 mg	35 mg	35 mg
Crosspovidone (mg)	3	4	-	-	3	4	-	-
Ac-di-sol (mg)	-	-	3	4	-	-	3	4
MCC (mg)	26	26	26	26	26	26	26	26
Dextrose (mg)	15	15	15	15	15	15	15	15
Lactopress (mg)	15	15	15	15	15	15	15	15
Mg. stearate (mg)	2	2	2	2	2	2	2	2
Talc (mg)	2	2	2	2	2	2	2	2
Bulk Density (gm/cm^3)	0.633±0.005	0.574±0.012	0.628±0.006	0.574±0.006	0.584±0.009	0.625±0.007	0.611±0.006	0.627±0.006
Tapped Density (gm/cm^3)	0.715±0.011	0.649±0.003	0.717±0.009	0.648±0.009	0.666±0.007	0.718±0.008	0.71±0.010	0.714±0.011
Compressibilty Index (%)	11.44±0.015	11.49±0.004	12.44±0.013	11.31±0.004	12.21±0.005	12.95±0.005	14.0±0.010	12.22±0.004
Hausners Ratio	1.129±1.233	1.117±0.782	1.126±0.908	1.122±0.556	1.126±0.392	1.134±0.544	1.13±0.765	1.112±0.795
Angle of Repose	23.28±0.754	24.23±0.725	23.40±0.445	24.06±0.337	22.71±0.953	22.931±0.26	23.18±0.553	23.756±0.434
Thickness(mm)	2.334±0.092	2.291±0.024	2.361±0.061	2.295±0.066	2.313±0.022	2.076±0.121	2.329±0.089	2.415±0.025
Weight (mg)	98.366±1.167	98.900±2.38	97.233±0.60	97.733±0.32	99.133±0.66	98.466±0.73	99.4±0.264	100.833±1.45
Hardness (kg/cm^3)	2.766±0.152	2.993±0.221	2.800±0.191	2.990±0.101	2.713±0.156	2.913±0.200	3.043±0.150	3.003±0.090
Friability (%)	0.590±0.081	0.656±0.077	0.653±0.081	0.856±0.041	0.823±0.051	0.64±0.05	0.536±0.030	0.626±0.045
In vitro Disintegration Time (sec.)	57.00±4.58	23.33±2.51	66.33±3.05	41.66±1.52	51.66±2.51	20.66±2.08	62.66±2.516	38.00±3.00
Wetting time (sec.)	51.33±3.05	21.00±2.00	55.66±6.11	38.33±2.08	47.33±6.02	18.66±2.51	57.66±3.51	32.33±3.51
In vitro Dispersion.. Time (sec.)	63.66±3.05	31.00±2.00	68.66±2.08	46.00±2.64	57.33±1.52	26.33±2.08	68.33±2.08	46.33±2.51

Table 2 Taste Evaluation of Drug, Granules and Resinates

Volunteers no	Taste Evaluation		
	Drug	Granules	Resinate
1	4	2	1
2	4	3	1
3	4	1	1
4	4	1	1
5	4	2	1
6	3	2	1
7	4	1	1

1) Tasteless 2) Slightly bitter 3) Bitter 4) very bitter

Table 3 Flow Properties of Granules and Resinate

Parameters	Resinate	Granules
Bulk Density (gm/cm^3)	0.611	0.628
Tapped Density (gm/cm^3)	0.702	0.694
Compressibilty Index (%)	12.962	9.523
Hausners Ratio	1.148	1.105
Angle of Repose	23.64	21.817

Flowability of Resinate and Granules

Table 4 Sedation Time of Different Formulation

Zolpidem Formulations	Sedation Time (min)
Pure drug suspended in water using gum acacia	6.2±1.4
Granules	17.7±2.5
Resinate	12.3±2.3
F2 suspension	19.4±2.8
F6 suspension	11.4±1.7

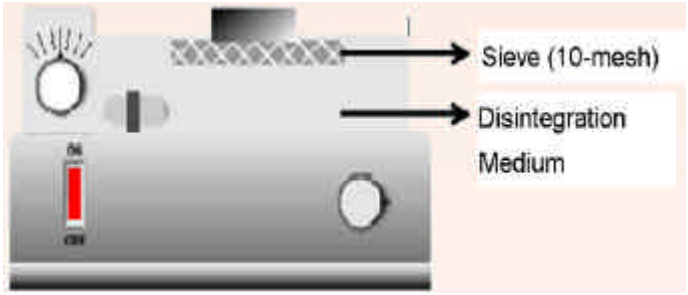

Figure 1: Device Used to Determine the Disintegration Time of Fast Disintegrating Tablets

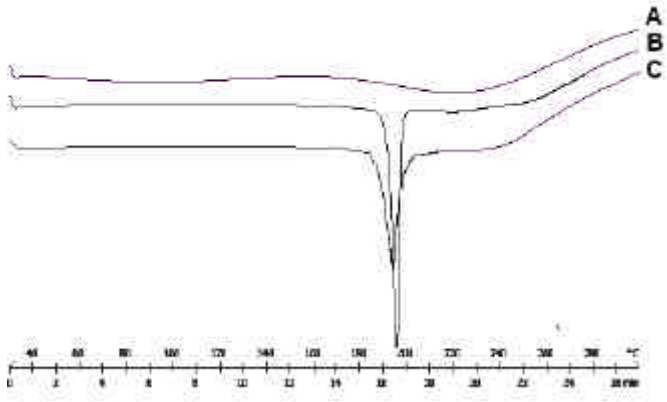

Figure 2: DSC Thermograms of Tulsion335 (A), Zolpidem Tarterate (B) and Resinate(C)

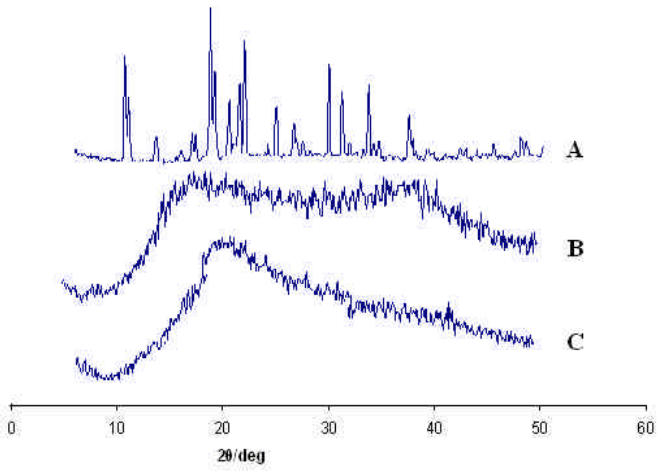

Figure 3: X-ray diffraction patterns of Zolpidem tartrate (A), Tulsion 335 (B) and Resinate(C)

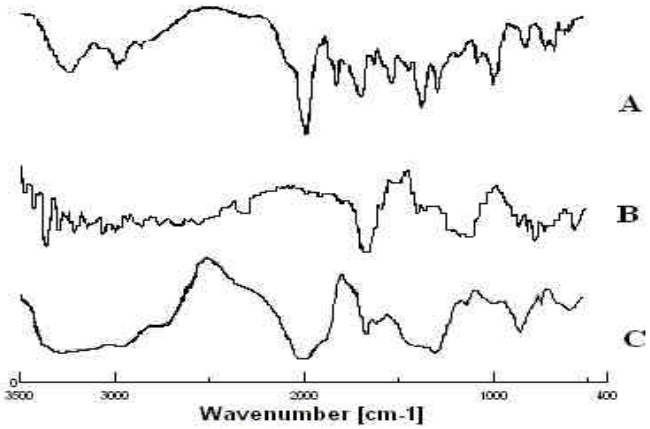

Figure 4: FT-IR Spectra of Zolpidem tartrate (A), Tulsion 335 (B) and Resinate(C)

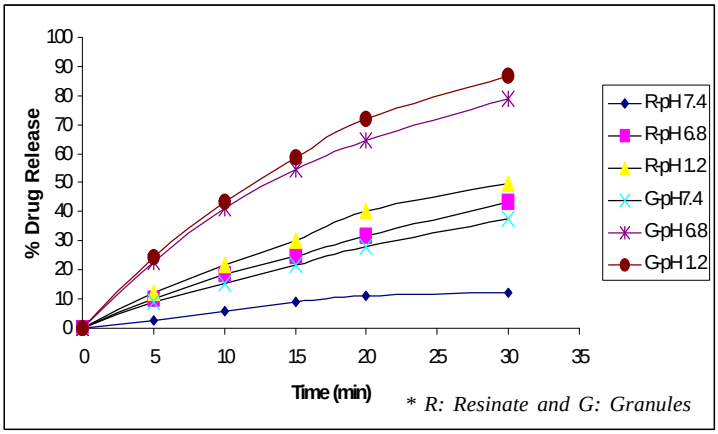

Figure 5: Dissolution Profile of Drug from Granules and Resinate in different pH medium

Evaluation of Blends

For each formulation blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. Bulk density was found in the range of 0.574-0.633 g/cm^3 and tapped density between 0.648-0.718 g/cm^3 as shown in Table 1. Using these two densities data compressibility index and hausner's ratio was calculated. The powder blends of all the formulations had compressibility index between 11.316 and 14.051 which indicating good flowability of the powder blend. Hausner's ratio for all formulation was less than 1.2, indicated good flowability. The good flowability of the blend was also evidenced with angle of repose which is between 22.713 and 24.02. The results are shown in Table 1.

Evaluation of the Prepared Tablets

All the formulations were prepared by direct compression technique (Table 1). The data obtained for post-compression parameters such as uniformity of thickness, weight variation, hardness, friability test, *in vitro* disintegration time, wetting time and *in vitro* dispersion, are shown in the Table 1. The tablets diameters were almost uniform for all formulations and thickness range was very well within ±5% of the standard value.

All the tablets passed weight variation test, as % weight variation was within the pharmacopoeial limits i.e., ±10%. The measured average hardness of the tablets was between 2.712 - 3.043 Kg/cm^2, this ensures good handling characteristics of both formulations. The percentage friability was less than 1% for all formulations, ensuring that the tablets were mechanically stable.

The *in- vivo* disintegration time, wetting time, *in vitro* dispersion time was observed to be very fast for formulation containing crosspovidone when compared to formulation containing Ac-Di-Sol. Formulation containing resinate show less *in- vivo* disintegration time, wetting time, *in vitro* dispersion time as compared to formulation containing granules of drug and resin. F2 and F6 disintegrate in 23 and 20 second, which were fulfilling our purpose.

To detect possible correlations between dissolution rates observed with resinates, granules and their tablets, and pharmacological effects, we investigated on sedation time in mice by administration of the following formulations: ZP drug alone, granules, resinate, F2 and F6 given in equimolar doses (10 mg/kg). Sedation time of following the intragastric administration of each formulation were recorded and the results are summarized in Table 4. In these experiments, rats displayed a marked sedation and ataxia, characterized by motor incoordination involving all four legs; however, no loss of the righting re?ex was observed if the animals were laid on their back. As illustrated in Table 4, sedation times subsequent to intragastric administration of ZP as suspensions of tablets were longer than that observed when administrating the corresponding resonates and granules. The differences observed in sedation time are therefore very significant. Since the intensity of the pharmacological effect of any drug orally administered essentially depends on its concentration in the plasma which, in turn, results from both the dissolution in GI ?uids and intestinal membrane permeability, it follows that in the presence of Tulsion 335 the intestinal membrane permeability may be the rate-limiting factor in the gastrointestinal absorption process.

CONCLUSION

In the present investigation, a complex of Zolpidem tartrate was successfully formulated using Tulsion 335 resin, which was confirmed using FTIR, XRD and DSC. The volunteers rated the resinate as tasteless and agreeable complex. The methods designed for drug resinate complexation and tablet formulation is simple, rapid, cost effective and highly efficient.

It was concluded that mouth dissolving tablet of resinate can be successfully prepared by super disintegrant addition and was found to be disintegrate less than 1 minute, which provide faster effect and better patient compliance.

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