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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLET OF TOLVAPTAN

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ABSTRACT

Tolvaptan is relatively a new chemical and pharmacologic class of drug known as aquaretic sorvaptans. which is a selective, competitive vasopressin receptor$_2$ antagonist used to treat hyponatremia associated with congestive heart failure, cirrhosis and syndrome of inappropriate anti diuretic hormone (SIADH). Tolvaptan block the vasopressin V_2 receptor located on the basolateral aspect of collecting duct cells of the renal tubule, thereby lowering osmolarity, inducing a water diuresis (aquaresis) and raising serum osmolalility and sodium concentration. In the present work an attempt has been made to prepare fast dissolving tablet of Tolvaptan with an view to enhance the solubility by micronization of drug, to increase patient compliance and to provide a quick onset of action. Solubility of drug was enhanced by micronizing Tolvaptan by jet mill. Tolvaptan granules were prepared by wet granulation technique with Hydroxyl Propyl methyl cellulose. The granules were compressed into tablets by using different superdisintegrant like Crospovidone, Croscarmellose, Sodium Stach Glycolate in different concentration such as 4%, 6%, 8%, using Magnesium Stearate as lubricant. Prepared tablets were further examined through FTIR, DSC. The studies showed that the drug was stable. 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, water absorption ratio, wetting time, *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 F_9 containing 8% Crospovidone which was consider to be the best formulation that released drug up to 98.49% in 30 min. *In-vitro* studies revealed that FDDT of formulation (F_9) showed good bioavailability compared to conventional tablet.

Key Words: Tolvaptan, Micronization, Superdisintegrants, FDDT, Hyponatremia.

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].

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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[6, 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 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[23-28]. Vacuum-drying and freeze- drying techniques[29-32] 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 fast disintegrants tablets of Tovaptan, to investigate the effect of superdisintegrants concentration on the release profile of the drug in the tablets.

MATERIAL:

Tolvaptan was chosen as an active ingredient, a gift sample by MSN Pharmaceuticals Pvt Ltd, Hyderabad. HPMC was purchased from Dow chemical International Pvt.Ltd, Mumbai.. Microcrystalline Cellulose (Avicel) was gift sample from Sanofi Aventis Pvt. Ltd., Goa. Crospovidone, Croscarmellose Sodium and Sodium Starch Glycolate was a gift sample from Sanofi Aventis Pvt. Ltd., Goa. All other reagents were of analytical grade.

METHOD OF FORMULATION

Tolvaptan solubility was enhanced by micronization technique, subjecting drug to jet milling. Fast disintegrating tablets were formulated by wet granulation technique using HPMC as binding agent. Accurately weighed required quantity of Tolvaptan, Lactose Monohydrate, Microcrystalline Cellulose pH101, Maize Starch, Sodium Starch Glycolate/Croscarmellose Sodium/Crosspovidone were passed through sieve # 40 (Pore size 420µ) and then all are mixed in polybag for 5min. Binder was prepared by using Hydroxy propyl methyl cellulose (5cps) with SLS in quantity sufficient purified water and subjected to stirring for 15min. Ingredients were mixed by using RMG (Rapid Mixer Granulator) for 900 seconds and below variables were maintained during mixing. Cycle type-dry mixing, Manual cycle time-900sec, Main impeller-200rpm, Chopper-nil. To obtain the granules, chopper (for cutting) was maintained on the speed of 1000 RPM. The obtained granules was subjected to drying by using fluid bed drier (FBD) and during the drying process the percentage of moisture content (% MC) was determined by using Metlor Tolado Moisture analyzer. Extra granular part lubricating agent sifted through sieve ≠ 60(pore size 250µ) then mixed with intra granular part by using octagonal blender at 15 rpm for 10min. The lubricated blend was compressed into tablets by using 7mm punch, after completion of the pre-compression parameters.

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, Water Absorption Ratio, FTIR Studies, Stability Studies, Statistical Analysis (Graph Pad Instat Software (GPIS; Version: 1.13)) and In vitro Dissolution Studies[38 - 50].

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 $25^0.64'$ to $30^0.5'$. All formulations showed the angle of repose within 30^0, 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 0.44 gm/cm^3 to 0.50 gm/cm^3 and 0.52 gm/cm^3 to 0.59gm/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 1.18 - 1.22. 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 14.8 to 17.54. All formulations are showing good compressibility.

Hardness: Table-3 shows results of hardness and hardness was found to be within 3.08±0.02 kg/cm^2 to 3.26 ± 0.02 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 2.9 ± 0.02 mm to 3.3 ± 0.02 mm.

Weight Variation Test: The percentage weight variation for all the formulation was tabulated in Table-3. It was found to be from 177.57±0.03 to 180.12±0.01 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 83.4 ± 0.02 to 115.0 ± 0.02. 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 40.0±0.01 to 105.0±0.01 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 26.0±0.02 to 80.0±0.02. 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: 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 96.67±0.02 mg to 99.75±0.02 mg of Tolvaptan. The results indicated that in all the formulations the drug content was uniform.

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

***In vitro* – 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 268 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 Sodium Starch Glycolate from 4%w/w to 8%w/w, have recorded drug release 85.7%, 89.6% and 93.5% respectively, at the end of 60 minutes. Formulations F4, F5 and F6 which contained increasing concentrations of Croscarmellose Sodium from 4%w/w to 8%w/w, have recorded drug release 88.6%, 90.4% and 96.5% respectively, at the end of 60 minutes. Formulations F7, F8 and F9 which contained increasing concentrations of crospovidone from 4%w/w to 8%w/w, have recorded drug release 90.2%, 95.4% and 98.6% respectively, at the end of 30 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 88.7%, 92.4% and 98.6% drug release respectively at the end of 30 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.

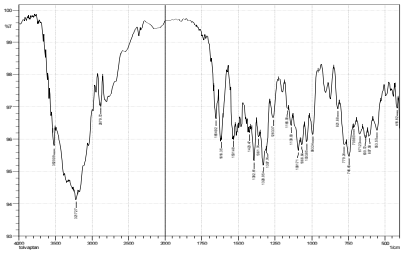

Fig:1 IR spectrum of Tolvaptan with Croscarmellose Sodium

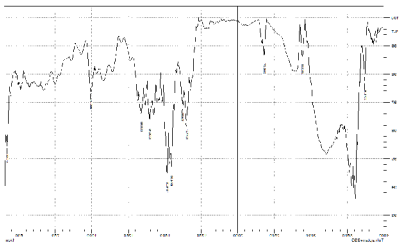

Fig.2: IR Spectrum of Tolvaptan + SSG.

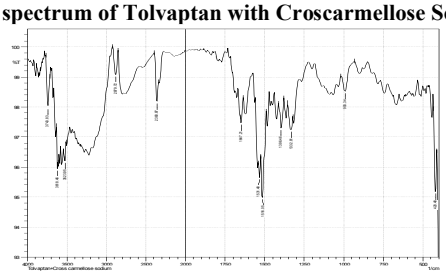

Fig.3: IR spectrum of Tolvaptan+Croscarmellose Sodium

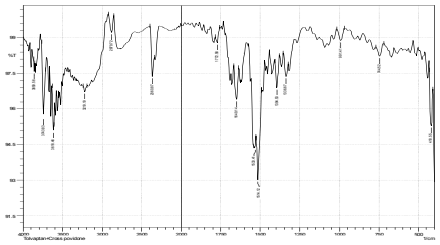

Fig.4: FTIR Spectrum of Tolvaptan: Crosspovidone.

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

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tolvaptan	30	30	30	30	30	30	30	30	30
Lactose monohydrate	86.4	84.0	81.3	86.4	84.0	81.3	86.4	84.0	81.3
M.C.C. pH 101	42.5	40.3	38.6	42.5	40.3	38.6	42.5	40.3	38.6
Maize starch	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0
Sodium starch glycolate	7.2	10.8	14.4	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	7.2	10.8	14.4	-	-	-
Crosspovidone	-	-	-	-	-	-	7.2	10.8	14.4
HPMC(5 cps)	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
Sodium lauryl sulphate	1.8	2.8	3.6	1.8	2.8	3.6	1.8	2.8	3.6
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight (mg)	180	180	180	180	180	180	180	180	180

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	30.5±0.01	0.45±0.02	0.54±0.01	16.6±0.03	1.2±0.02
F_2	27.9±0.02	0.46±0.01	0.55±0.02	16.36±0.01	1.19±0.01
F_3	26.5±0.01	0.44±0.03	0.52±0.02	15.38±0.02	1.18±0,03
F_4	26.5±0.01	0.47±0.01	0.56±0.01	16.07±0.03	1.19±0.02
F_5	27.47±0.02	0.493±0.02	0.58±0.03	15.5±0.01	1.18±0.03
F_6	26.10±0.01	0.48±0.01	0.57±0.01	15.7±0.03	1.18±0.02
F_7	25.64±0.01	0.46±0.03	0.54±0.02	14.8±0.01	1.17±0.01
F_8	29.6±0.02	0.47±0.01	0.57±0.01	17.54±0.01	1.22±0.01
F_9	27.02±0.01	0.50±0.01	0.59±0.01	15.2±0.02	1.18±0.03

*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)	Water Absorption Ratio (%)	Disintegration Time (Sec)
F1	3.08±0.02	3.1±0.01	0.84±0.02	180.12±0.01	98.18±0.01	80 ±0.02	72.5±0.01	105±0.01
F2	3.16±0.03	3.0±0.01	0.79±0.01	179.30±0.02	97.25±0.02	65±0.01	89.4±0.03	87±0.02
F3	3.24±0.02	2.9±0.02	0.64±0.02	177.57±0.03	98.23±0.01	40 ±0.02	104.5±0.01	68 ±0.01
F4	3.13±0.01	3.2±0.01	0.82±0.01	178.90±0.02	96.76±0.03	70 ±0.01	83.4±0.02	90±0.03
F5	3.1±0.03	3.3±0.02	0.7±0.03	179.57±0.01	97.89±0.02	50±0.02	92.4±0.01	75 ±0.02
F6	3.25±0.02	3.1±0.01	0.65±0.01	177.96±0.02	98.28±0.01	33±0.01	110.4±0.01	56±0.01
F7	3.12±0.01	3.2±0.03	0.86±0.02	178.90±0.01	96.67±0.02	60±0.02	93.6±0.02	78 ±0.02
F8	3.14±0.02	3.1±0.01	078±0.03	177.80±0.02	97.54±0.02	38±0.03	100.4±0.01	60±0.03
F9	3.26±0.02	3.0±0.02	0.66±0.01	180.03±0.01	99.75±0.02	26±0.02	115 ±0.02	40±0.01

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

Table-4: Stability studies of Formulations F3, F6 and F9 stored at 40^0C/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

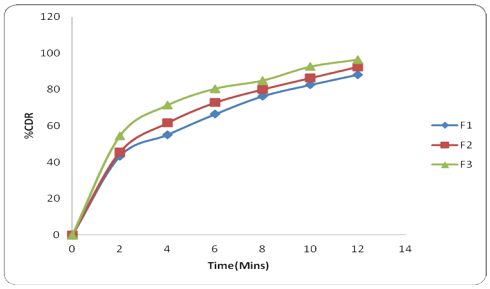

Fig.5: Comparative *In Vitro* Release Profile of Zolpidem Tartrate from formulation F1, F2 and F3

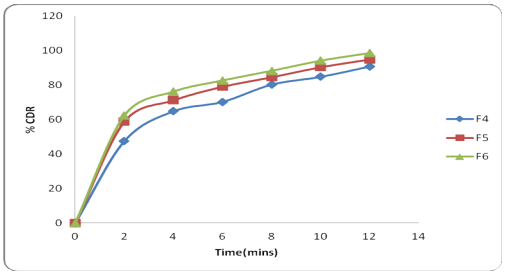

Fig.6: Comparative *In Vitro* Release Profile of Zolpidem Tartrate from Formulation F4, F5 and F6

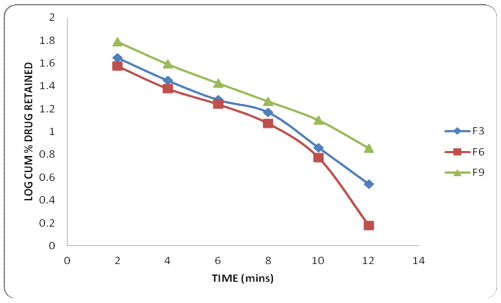

Fig.7: Comparative *In Vitro* Release Profile of Zolpidem Tartrate from formulation F7, F8 and F9

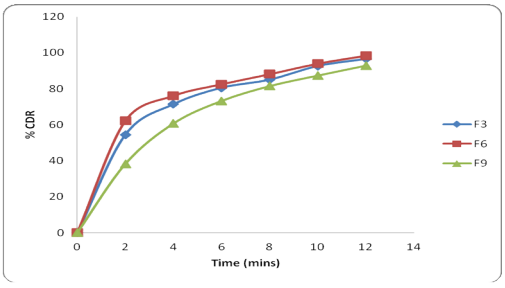

Fig.8 **:** Comparative In Vitro Release Profile of Zolpidem Tartrate from Formulation F3, F6 and F9

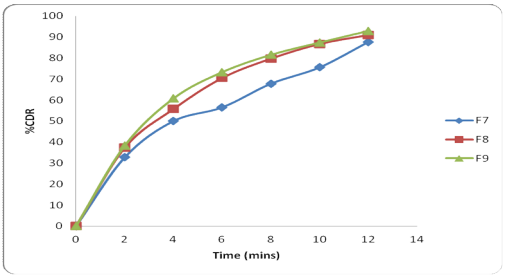

Fig.9: *In Vitro* Log Cumulative % Drug Retained V/s Time of Zolpidem Tartrate according to First Order Kinetics for Formulation F3, F6 & F9.

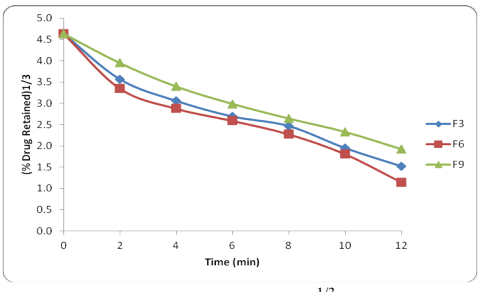

Fig 10: *In Vitro (*% Drug Retained) $^{1/3}$ V/s. Time (Hixson Crowell) from Formulation F3, F6 and F9

CONCLUSION

The fast dissolving tablets of Tolvaptan were prepared by wet Granulation 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 4% w/w to 8% 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 Dissolution 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. Formulation F3, F6 and F9 showed faster drug release in comparison to other formulation. *In Vitro* studies revealed that FDT of formulation (F9) 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 Tolvaptan.

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