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DESIGN OF FAST DISINTEGRATING TABLETS OF TRAMADOL HCL BY USING SUBLIMATION METHOD

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ABSTRACT
An *ODT* is a solid dosage form that disintegrates and dissolves in the mouth (either on or beneath the tongue or in the buccal cavity) without water within 60 seconds or less. ODTs also are called orally disintegrating, orodisperse, mouth-dissolving, quick-dissolve, fast-melt, and rapid-disintegrating tablets and freeze-dried wafers. In the present work, fast disintegrating tablets of tramadol HCl were designed with a view to enhance patient compliance by sublimation method. Tablets containing tramadol Hcl, menthol, Carscarmellose, Microcrystalline cellulose, Magnesium Stearate, Talc and mannitol were prepared by direct compression technique. Menthol was sublimed from the tablets by exposing to vacuum. The tablets were first prepared and later exposed to vacuum. A total 6 formulations were developed by varying the amount of carscarmellose and menthol. The tablets were evaluated for precompression and post compression parameters such as percentage friability and disintegration time etc. The result analysis indicated that for obtaining fast dissolving tablets; optimum amount of menthol and higher percentage of carscarmellose should be used. Sublimation of menthol from tablets resulted in rapid disintegration as compared with the tablets prepared from granules that were exposed to vacuum. The optimized tablet formulation containing 20% menthol and 20% carscarmellose shows drug release of 98.95% within 15min. *In vitro* drug dissolution data of formulations were subjected to goodness of fit test by linear regression analysis which indicates the drug dissolution follows first order kinetics. From the results, it was concluded that fast dissolving tablets with improved dissolution could be prepared by sublimation of tablets containing suitable subliming agent.

KEYWORDS: Oral disintegrating tablets, tramadol HCl, subliming agent, menthol.

INTRODUCTION
Formulation of drugs into a presentable form is the basic requirement and need of today. The dosage form is a mean of drug delivery system, used for the application of the drug to a living body. Various type of dosage forms are available such as tablets, syrups, suspensions, suppositories, injections, transdermal and patches having a different type of drug delivery mechanisms. United States Food and Drug Administration (USFDA) defined fast dissolving tablet (FDT) as "a solid dosage form containing a medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds when placed upon the tongue". The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets. The process of an ODT disintegration shown in figure1.

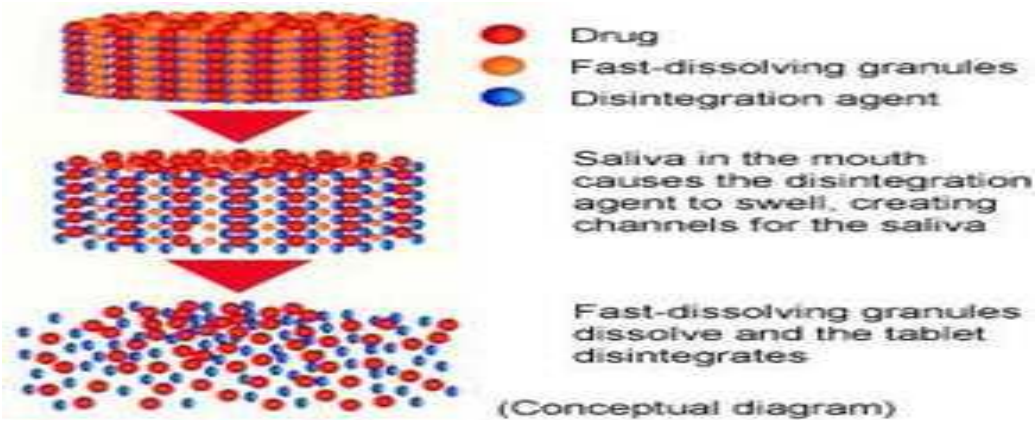

Fig. 1: Fast dissolving tablets.

Advantages of fast dissolving tablets

- No need of water to swallow the tablet.
- FDTs can be easily administered to pediatric, elderly and mentallydisabled patients.
- Accurate dosing as compared to liquids.
- Dissolution and absorption of the drug is fast, offering rapid onsetof action.
- Bioavailability of drugs is increased10as some drugs are absorbed from mouth, pharynx and oesophagus through saliva passing downinto the stomach.
- Advantageous over liquid medication in terms of administration aswell as transportation.
- First pass metabolism is reduced, thus offering improvedbioavailability and thus reduced dose and side effects offering improved safety.
- Suitable for sustained/controlled release actives.
- Allows high drug loading shown in figure 2

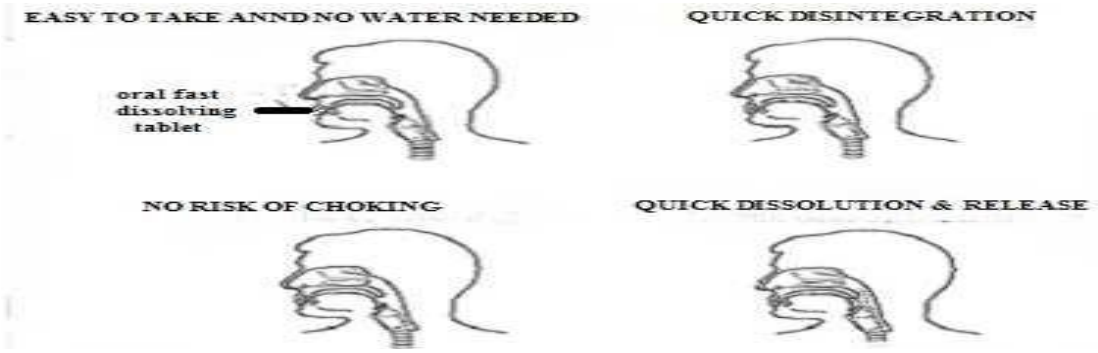

Fig. 2: Advantage of ODT.

Techniques for preparing fast dissolving tablets: Various conventional manufacturing techniques for FDDDS.

Freeze-drying or lyophilization is a pharmaceutical process that allows the drying of heat sensitive drugs and biological under low temperature by the application of vacuum to remove water by sublimation. Drugs are dissolved or dispersed in aqueous solution of a carrier, transferred to preformed blister packs and subjected to nitrogen flush to freeze out, then placed in the refrigerator to complete the process. Characteristics of lyophilization techniques are, they possess high porosity and specific surface area and gets dissolve rapidly in mouth presenting high drug bioavailability. The major drawback of this system is high cost, time-consuming procedure and fragility, making conventional packing inappropriate for packing this dosage form and stability issues under stress condition.

The major advantage of using this technique is that the tablets produced by this technology have very low disintegration time and have great mouthfeel due to fast melting effect.

Moulding method: In this method tablets are designed using hydrophilic ingredients, with the aim to get maximum drug dissolution. Powder mass is wetted with hydroalcoholic solvent and compressed into a dosage form. The solvent system is then allowed to evaporate. Taste of drug particles is developed by spray congealing the molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethene glycol with an active ingredient into lactose based tablet triturate. Characteristics of moulding method are, very porous as solvents are removed by drying leaving porous mass which promotes rapid dissolution.

Melt granulation: It is a process by which the pharmaceutical powders are capably agglomerated by a

meltable binder. The benefit of this technique compared to a conventional granulation is that no water or organic solvents is required. Since there is no drying step, the process is less time consuming and requires less energy than wet granulation. It is a technique useful to enhance the dissolution rate of poorly water-soluble drugs, such as griseofulvin.

Mass-extrusion: In this the mixed ingredients are softened by water soluble ingredient i.e. polyethene glycol, using methanol as solvent, passing through an extruder to form thin cylinders. Which further get sliced with a heated blade to form small tablets. Characteristics of this method is these products can be used to mask bitter tasting drugs making small granules thus enhancing oral bioavailability.

Sublimation: Rapid disintegration and dissolution is acquired by formulating into porous mass by incorporating inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate and hexamethylene-tetramine. They were mixed with other ingredients and compressed. The volatile material is evolved by reduced pressure and applying slight temperature leaving the mass in porous form. Characteristics of sublimation method are, they are porous in nature, solvents like cyclohexane and benzene can be used. Sublimation techniques for preparing fast dissolving tablets is shown in figure 3.

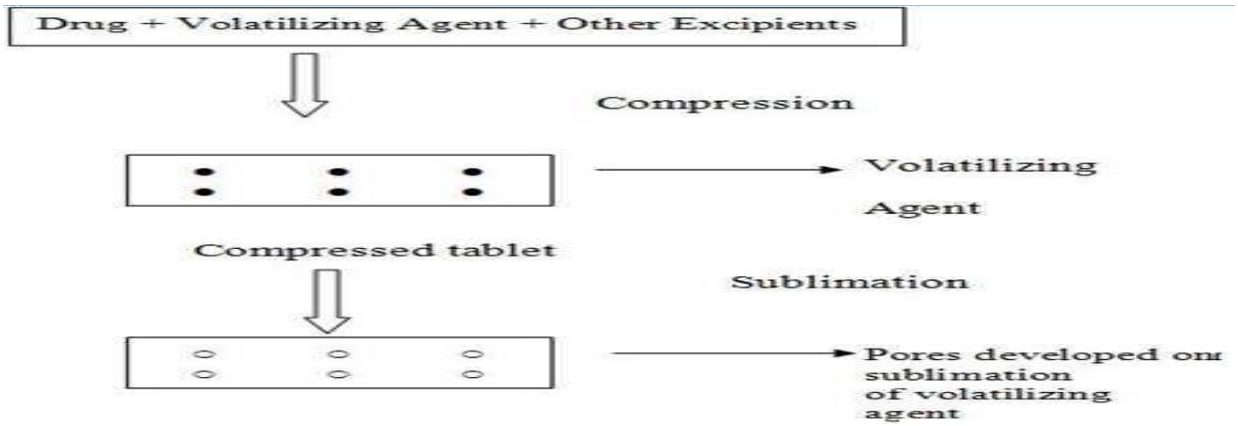

Fig. 3: Schematic diagram of sublimation techniques for preparing fast dissolving tablets.

MATERIALS AND METHODS

The materials used for the preparation of orally disintegrating tablets of Tramadol HCl were listed in Table1.

Table 1: Materials employed in the study.

S.NO	Materials	Source
1	Tramadol HCl	NatcoPharma; Hyderabad
2	Carscarmellose	NatcoPharma; Hyderabad
3	Menthol	NatcoPharma; Hyderabad
5	Mannitol	Merck Finar Ltd, India
6	Microcrystalline cellulose	Merck Finar Ltd, India
7	Magnesium Stearate	Merck Finar Ltd, India
8	Talc	Merck Finar Ltd, India

Equipments Used in the Study: The equipments used for the preparation of orally disintegrating tablets of Tramadol HCl were listed in Table 2.

Table 2: Equipment's employed in the study.

S.NO	Materials	Source
1	Electronic Balance AX200	Dolphin, India
2	Digital Balance ELB 300	K-ray
3	Digital pH meter L1120	Dolphin, India
6	Single beam UV-Visible Spectrophotometer	Elico, Hyderabad SL159

Analytical Method for Estimation of Tramadol Hcl

A) Detection of absorption maxima (λ max): The prepared Tramadol HCl solution was scanned between 200-400nm regions on UV-Visible spectrophotometer. The absorption maximum was found to be 271.4 nm shown in Figure 4.

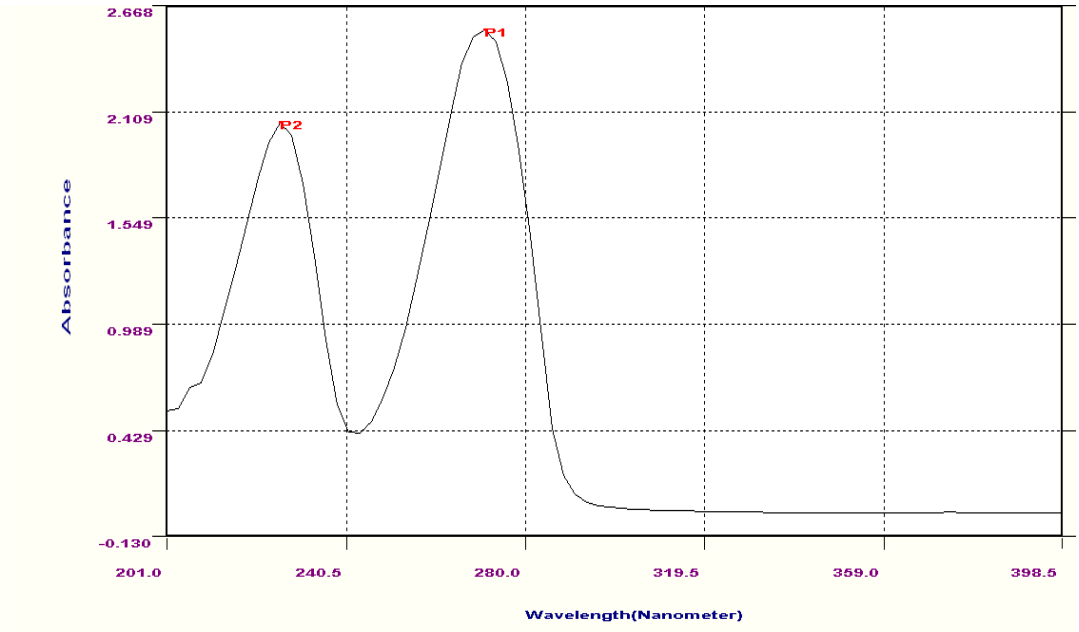

Figure 4: UV spectrum of Tramadol HCl.

B) Construction of standard calibration curve

Standard solution: Accurately weighed 10mg of Tramadol HCl was dissolved in 10ml of buffer pH 6.8 to get a stock solution containing 1000 µg/ml.

Stock solution: From standard solution, a stock was prepared to give a concentration of 100mcg/ml in pH 6.8 buffer. Aliquots of 1, 2, 3, 4 and 5ml of stock solution were pipetted out into 10ml volumetric flasks. These dilutions were gives 10, 20, 30, 40, 50µg/ml concentration of Tramadol HCl respectively. The absorbance of above solutions was measured at 271.4nm in UV-Visible spectrophotometer against a blank (6.8 pH buffer). The concentration and absorbance data was given in Table 3 and shown in Figure 5.

Table 3: Standard Calibration data of Tramadol HCl in pH 6.8 buffer.

Concentration (µg/ml)	Absorbance at 271.8nm				
	Trail-I	Trail-II	Trail-III	AVG	S.D
0	0	0	0	0	0
10	0.122	0.102	0.09	0.105	0.016
20	0.236	0.212	0.171	0.206	0.033
30	0.322	0.301	0.271	0.298	0.026
40	0.428	0.412	0.349	0.396	0.042
50	0.542	0.512	0.472	0.509	0.035

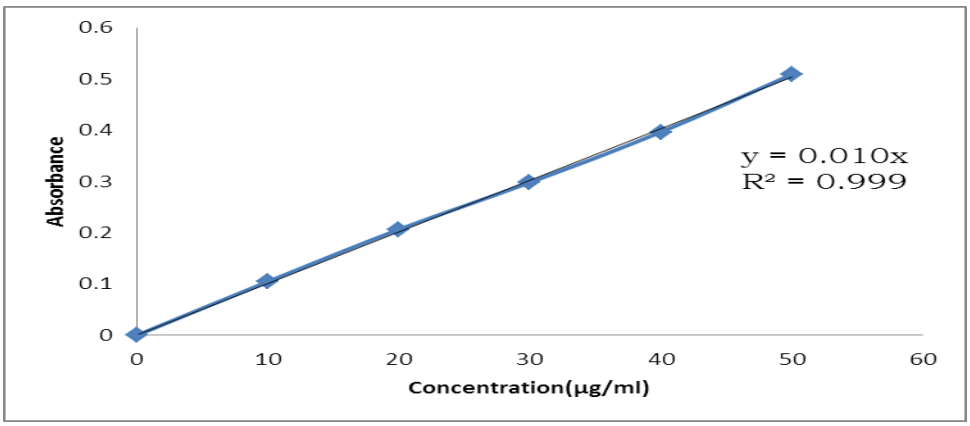

Figure 5: Standard Calibration Curve of Tramadol HCl in pH 6.8 buffer.

Preparation of Odts of Tramadol Hcl

The oral disintegrating tablets of Tramadol were prepared by direct compression method. All the ingredients were powdered and passed through # 60 mesh sieves separately. The drug and directly compressible excipients were mixed by adding small portion of each at a time and blended to get a uniform mixture and kept aside. The excipients used were MCC (diluents), Mannitol (sweetening agent), Talc (glidant), magnesium stearate (lubricant) and croscarmellose (super disintegrant). Different concentrations of sublimation agent and superdisintegrant were used to prepare different groups of oral disintegrated tablets. Compositions of various formulations are shown in Table 4. All the ingredients of the ODT tablets of Tramadol were weighed and mixed thoroughly; finally 2% magnesium stearate as lubricant and 2% of talc was added as glidant and mixed well. Then blended material was directly compressed on the 8 mm flat round punches to get tablets of 200 mg weight. The compressed tablets were than subjected to sublimation at 50^0C for 60 min. The tablets were evaluated for disintegration time and mean tablet weight.

Table 4: Composition of Odts Formulations.

Ingredients per tablet	F1	F2	F3	F4	F5	F6
Tramadol HCL	50	50	50	50	50	50
Menthol	-	-	10%	20%	10%	20%
Carscarmellose	10%	20%	10%	10%	20%	20%
Mannitol	10%	10%	10%	10%	10%	10%
Microcrystalline cellulose	Q.S.	Q.S.	Q.S.	Q.S.	Q.S	Q.S.
Magnesium Stearate	2%	2%	2%	2%	2%	2%
Talc	2%	2%	2%	2%	2%	2%
Total weight(mg)	200	200	200	200	200	200

Evaluation of blend

Pre-Compression Parameters

Angle of repose: The frictional forces in a powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile ofpowder and the horizontal plane.

$\text{Tan } \theta = \frac{h}{r}$ $\theta = \tan^{-1}(h/r)$

Where θ= angle of repose, h =height, r = radius.

Bulk density: Accurately weighed amount of powder taken in a 10 ml capacity measuring cylinder was tappedfor 3 times on a plane hard wooden surface and estimated the BD by using following formula:

$\text{Bulk density } (\rho_b) = \frac{powderweight(mg)}{bulkvolume(ml)}$

Tapped Density: Accurately weighed amount of powder taken in a 10 ml capacity measuring cylinder was tappedfor 100 times on a plane hard wooden surface and estimated the TD by using following formula

$\text{Tapped density } (\rho_t) = \frac{powderweight(mg)}{tappedvolume(ml)}$

Hauser's ratio: Percent compressibility of powder mix was determined byHauser's ratio, calculated by using following formula.

$\text{Hauser ratio} = \frac{TD}{BD}$

Carr's index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula.

$\%CI = \frac{TD - BD}{TD} \times 100$

Post-Compression Characterization of Tablet

After compression of powder blends, the prepared tablets were evaluated for organoleptic characteristics like color, odor, taste, diameter, thickness and physical characteristics like hardness, friability, disintegration time, wetting time, dispersion time.

Weight variation: Ten tablets were selected at random and weighed individually. The average weight of the tablets was calculated. Individual weight of tablet was compared with average weight. The values were within the limits given in Table 8.

Thickness variation: Ten tablets from each formulation weretaken randomly and their thickness was measured with avernier calipers.

Hardness: Six tablets were randomly selected from each batch and hardness of tablets was determined by using Monsanto hardness tester (Dolphin.TM). The mean values and standard deviation for each batch were calculated.

Friability: Friability indicates the ability of a tablet to withstand mechanical shocks while handling. Six tablets from each batch were examined for friability by using CAT.NO-1015-C friabilator (Dolphin.TM) and the equipment was run for 4 min at 25 revolutions per minute. The tablets were taken out and reweighed. Percent friability (f) was calculated by using the following formula

$\text{Friability } (\%) = \frac{WO - W}{WO} * 100$

Where W_0= weight of tablet before testing, W=weight of tablet after testing.

Uniformity of drug content: Orally disintegrating tablets of Tramadol HCl was powdered in glass motor and transferred the powder into 100ml volumetric flask 50ml of pH6.8 buffer. The drug was extracted from the powder by occasional shaking for 20min.The remaining volume was made up to 100ml and filtered through whattmann filter paper. The filtered solution was analyzed in UV-Visible spectrophotometer at 271.4nm against blank. The values of uniformity of content were given in Table 6.

Disintegration test: Disintegration of orally disintegrating tablets is achievedin the mouth owing to the action of saliva, however amount ofsaliva in the mouth is limited and no tablet disintegration test wasfound in USP and IP to simulate *in vivo* conditions. A modified method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10 mesh a screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve. To determined disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml 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.

***In vitro* dissolution studies:** In vitro dissolution studies for all the prepared tablets was carried out using USP-type II dissolution test apparatus at 50rpm in 900ml of phosphate buffer pH 6.8 as dissolution media, maintained at 37±5ºC. Five ml aliquots were withdrawn at the specified time intervals, filtered through whatmann filter paper and assayed spectrophotometrically at 271.4nm. An equal volume of fresh medium, which was pre-warmed at 37±5ºC, was replaced into the dissolution media after each sampling to maintain the constant volume thought the test. Dissolution studies were performed in triplicate.

Drug release kinetics[20]

Zero-order equation: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming area does not change and no equilibrium conditions are obtained) can be represented by the following equation

$Q_t=Q_0+K_0t$

Where Q_0 is the initial amount of drug in solution (it is usually zero), Q_t is the amount of drug released or dissolved at time t and K0is the zero-order release constant.

First order equation: This model is used to describe absorption and/or elimination of some drugs.

$Qt=Q_0e^{-k1t}$ or $\ln Q_t=\ln Q_0+K_1t$

Where Q_0 is the initial amount of drug in solution (it is usually zero), Qt is the amount of drug released or dissolved at time t and Ktis the first-order release constant.

RESULTS AND DISCUSSION

Evaluation Pre-Compression Parameters

The pre-compression properties of powder blend may influence compressibility, tablet porosity, dissolution of dosage form. Hence measurement of pre-compression properties of powder blend *viz.* angle of repose, bulk density, and tapped density, Carr's index, Hausner's ratio is necessary. The angle of repose, bulk density and tapped density were found between the ranges 27-32, 0.451±0.16 and 0.584±0.13 which indicates that good packing capacity of powder blend. The Carr's index values indicating of inter-particulate cohesiveness of powder blend, I_c value below 15% gives good flow characteristic and above 25% gives the poor flow rate. Carr's index found between 10-20%. Hausner's ratio is simple method to evaluate the stability and flow property of powder blend. Low range of Hausner's ratio was observed that indicate good flow ability. The results of pre-compression properties were reported in Table 5.

Table 5: Pre-compression properties of orally disintegrating tablets of Tramadol HCl.

Formulation code	Angle of repose(θ)	Bulk density(g/cm^3)	Tapped density(g/cm^3)	Hausner ratio	Carr's index (%)
F1	27.9±0.9	0.456±0.02	0.529±0.01	1.16009	13.80
F2	28.5±0.5	0.451±0.01	0.546±0.05	1.21064	17.40
F3	27.3±0.5	0.464±0.07	0.541±0.04	1.16595	14.23
F4	29.5±0.5	0.449±0.04	0.542±0.07	1.20713	17.16
F5	31.7±0.8	0.465±0.02	0.551±0.01	1.18495	15.61
F6	30.3±0.9	0.434±0.03	0.545±0.03	1.25576	20.37

Evaluation of Post Compression Parameters

The orally dispersible tablets were evaluated for hardness, thickness, diameter and drug content.

Hardness, thickness and diameter of the tablets: Hardness of the tablet was determined by Monsantohardness tester. Hardness of the tablet is very important parameter because it alters the drug release characteristic, when tablet having more hardness decrease the rate of penetration of dissolution fluid around the surface of the tablet. The hardness of the ODTs tablets was found between 4 to 6 kg /cm^2. The

thickness and diameter of the all formulation measured by vernier calipers. Thickness and diameter of the tablet were found between range of 2±0.06 and 8±0.01 respectively. The values were within the limits given in Table 6.

Friability and drug content: The values of friability and drug content were given in table in Table 7 and. The friability of the all tablets less than 1% *i.e.* within the range of %. The drug content was in the range of 96.5±0.2 and 103±0.12 indicating good content uniformity in all formulations. It indicates that the drug is uniformly distributed in all formulations. The values were within the limits given in Table 6.

Table 6: Post-compression properties of orally disintegrating tablets of Tramadol HCl.

Formulation code	Average weight(mg)	Tablet thickness (mm)	Hardness kg/cm^2
F1	201± 0.8	2.1±0.01	5.6±0.3
F2	200± 1.6	2.0±0.13	4.2±0.29
F3	199± 1.5	2.1±0.14	5.1±0.27
F4	199± 1.2	2.0±0.51	4.8±0.49
F5	201± 1.3	2.0±0.62	5.2±0.24
F6	202±1.4	2.0±0.41	5.4±0.45

***In-vitro* disintegration study:** The disintegration time decreases as the concentration of superdisintegrating agent increases. The sublimation agent can influence the disintegration time, as concentration increases the disintegration time decreases. The disintegration time of F6 formulation was 51sec. The values were within the limits given in Table 7.

Table 7: Post-compression properties of orally disintegrating tablets of Tramadol HCl.

Formulation code	Friability (%)	Drug content (%)	Disintegration time(sec)
F1	0.64±0.08	99.83±0.6	305±0.4
F2	0.50±0.12	97.18±0.5	204±0.2
F3	0.43±0.04	98.82±0.4	95±0.5
F4	0.30±0.05	99.05±0.3	76±0.6
F5	0.56±0.19	98.87±0.4	65±0.7
F6	0.45±0.15	97.74±0.5	51±0.4

***In-vitro* drug dissolution studies:** The *in vitro* dissolution data of orally dispersible tablet Tramadol HCl showed as the concentration of superdisintegrating agent increases the dissolution time decreases and as the concentration of sublimating agent increases the dissolution time decreases. The *in vitro* drug dissolution data of formulations were subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations. The results of linear regression value indicates the drug dissolution follows first order kinetics shown in table 8.

Table 8: *In vitro* drug dissolution of Orally disintegrating tablet of *Tramadol HCl.*

Time (min)	Cumulative percentage of drug dissolved±S.D					
	F1	F2	F3	F4	F5	F6
5	15.2±0.42	19.96±0.52	26.042±1.2	39.24±0.34	59.72±0.25	60.76±0.56
10	18.30±1.02	29.37±0.85	35.41±0.85	54.86±0.51	75.35±0.12	85.06±0.45
15	26.18±0.42	35.06±0.54	43.40±0.74	64.93±0.64	84.13±0.24	98.95±0.75
20	30.59±0.47	42.36±0.85	60.76±0.98	87.15±0.25	99.96±0.14	
25	38.19±0.36	50.34±0.96	71.18±1.25	97.96±0.34		
30	44.44±0.45	60.76±0.56	85.06±0.47			
35	54.86±0.26	71.18±0.84	95.48±0.23			
40	61.46±0.78	85.06±0.45				
45	70.14±0.91	98.95±0.75				
50	81.60±0.95					
55	89.58±0.48					
60	98.96±0.75					

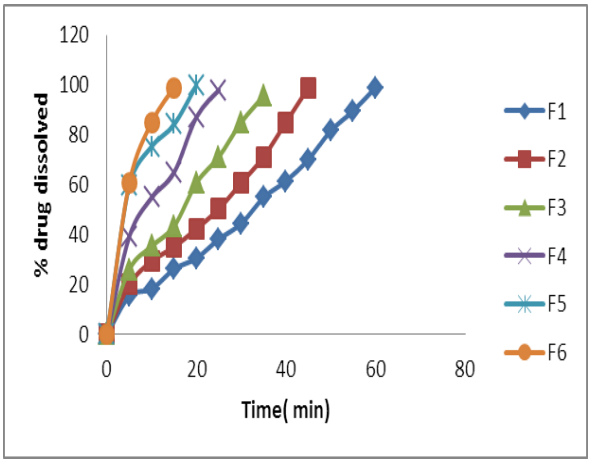

Figure 6: Dissolution profile of Orally dispersible tablet of Tramadol HCl.

CONCLUSIONS

The orally dispersible tablets of Tramdol HCl were prepared by sublimation method by using menthol as sublimating agent. As the concentration of superdisintegrating agent increases the disintegration time decreases. Many ingredients used in the formulation are highly stable and safe for the oral delivery. Sublimation method is one of the suitable procedures to formulate ODT in laboratory conditions and improve the disintegration rate of formulations. Finally "Patients may benefit from the convenience of Tramadol in an orally disintegrating dosage form particularly those who have difficulty swallowing tablets, or those who may not, or do not, always have access to water. Orodispersible tablet gives onset of action and quick relief to patient compliance. Oral delivery appears better and effective drug delivery system as compared to other drug delivery system.

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