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Design and Evaluation of Orally Disintegrating Tramadol Hydrochloride Tablets by Direct Compression Method

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SW, ARM, MNA and SDB designed the study, wrote the protocol, of the manuscript and supervised the entire work performed analysis of the study. Authors Suhair S. Al Saleh and Suha S. Al Saleh managed the literature searches, and involved in manuscript writing. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To design and evaluate an orally disintegrating tramadol hydrochloride tablets (ODT).
Methods: Tramadol hydrochloride orally disintegrating tablets were designed and manufactured by direct compression method, using Cross povidone, Precirol, EPO, Sorbitol, PEG 6000, Aerosol, HCL, magnesium stearate, xylitol, acesulfame potassium, as key excipients, and peppermint flavor and sweetener, respectively. These formulations were then evaluated using pharmacopoeial and non-pharmacopoeial physical and chemical tests. Dissolution and assay tests were performed using USP apparatus II and ultraviolet (UV) spectrophotometry, respectively.
Results: The tablet formulation prepared with crospovidone (F1) showed good flow properties, low disintegration time (13 s) and improved drug release (100% at 30 min) compared with those of the

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other formulations (84% at 30 min). All the formulations exhibited satisfactory physicochemical characteristics. The results indicated that suitable ODT of tramadol could be prepared.
Conclusion: A suitable preparation of tramadol Hcl ODT which contains Crospovidone (superdisintegrant) and sorbitol (bulking agent) was found to be the best among Tramadol hydrochloride ODT formulations prepared by direct compression method, because it has exhibited good disintegration time and good dissolution profile when compared to other formulations.

Keywords: Tramadol hydrochloride; superdisintegrants; orally disintegrating tablets.

1. INTRODUCTION

According to United States Food and Drug Administration (USFDA) 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 [1].

ODTs are a tablet form of medication that dissolves on the tongue, aided only by saliva without the need of water, ODTs can dissolve in as little as few seconds to minutes, depending on the different fast dissolve/disintegration technologies used to manufacture the tablets [2]. ODTs are convenient for administration and patient compliant for disabled, bedridden patients, and for travelers and busy people who do not always have access to water [3]. Paediatric, geriatric patients are especially well suited for this alternative to traditional tablets. Medications used for treating nausea, allergies, migraines, arthritis, depression, and schizophrenia are already available in ODT form. Orally disintegrating tablets have many advantages compared with the other oral dosage forms, such as better bioavailability, better patient compliance, and improved efficacy. Difficulty in swallowing is experienced by patient such as mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of non-compliance and ineffective therapy. To improve the quality of life and treatment compliances of such patients fast disintegrating or orally disintegrating tablets dosage form is a better alternative for oral medication [4]. One negative aspect of solid oral dosage forms is dysphagia (difficulty in swallowing) and chewing in some patients particularly in geriatric and paediatric patients [5].

However, United States Pharmacopoeia (USP) approved these dosage forms as ODTs (orally disintegrating tablets). Recently, European Pharmacopoeia has used the term oro-dispersible tablet for tablets that disperses readily and within three minutes in mouth before swallowing [6].

Tramadol Hydrochloride is a centrally acting analgesic, which is administered an orally and intravenously. The drug has been clinically proven to provide pain relief for both acute chronic, and moderate to severe pain. Tramadol hydrochloride gets rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of tramadol hydrochloride is approximately 75%. The peak plasma concentration occurs after two hours of administration. Only 20% of the given dose is bound to the plasma proteins. Tramadol hydrochloride is extensively metabolized after oral administration by CYP2D6 and CYP3A4 in the liver. The mean terminal plasma elimination half-life of tramadol is 6.3±1.4 hours [7].

In present study an attempt has been made to prepare and evaluate orodispersible tablets of tramadol hydrochloride using direct compression techniques.

2. MATERIALS AND METHODS

2.1 Materials

Tramadol hydrochloride was obtained as a gift sample from Aurobindo labs, Hyderabad. Cross povidone was a drug purchased from local market Hyderabad. Precirol, EPO, Sorbitol, PEG 6000, magnesium stearate, xylitol, acesulfame potassium, peppermint flavor were obtained from SD fine chem., Mumbai, India. Aerosol was obtained from Meenakshi Pharma, Hyderabad India & HCL. All chemical reagents used in the study were of analytical grade.

2.2 Methods

2.2.1 Formulation of orally disintegrating tablets of tramadol

2.2.1.1 Direct compression

The ODT's were prepared by direct compression technique. Required quantities of all the

ingedients were individually passed through mesh # 40 and were mixed with the taste masked drug, Except magnesium stearate and aerosil, which were individually passed through mesh#60 and mixed with other ingredients in a poly bag by sumbling technique.In this technique all 9 formulations were Formulated. Final blend was compressed into tablets using 7mm punch at corresponding dies on single stage tablet punching machine. Ingredients are depicted in Table 1.

2.3 Preformulation Studies

2.3.1 Evaluation of blends

The powder blend was evaluated for Precompression parameters like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose all the values were given in (Table 2).

2.3.2 Bulk density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by:

$$D_b = \frac{M}{V_0}$$

Where, M is the mass of powder, V_0 is the bulk volume of the powder.

2.3.3 Tapped density (D_t)

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$$D_t = \frac{M}{V_1}$$

Where, M is the mass of powder, V_1 is the tapped volume of the powder.

2.3.4 Carr's index (%)

The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density (Table 2).

$$\text{Carr's index} = 100 \times \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}}$$

2.3.5 Hausner's ratio

Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18, 1.12-1.18, 1.26-1.34 and greater than 1.6 indicates excellent, good, passable and very very poor flow properties, respectively.

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

2.3.6 Angle of repose (θ)

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

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

Where θ the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. A value for angle of repose $\geq 40^o$ suggests a poorly flowing material.

2.4 Evaluation of Tablets

2.4.1 Weight variation

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Mettler Toledo), and the test was performed according to the official method.

2.4.2 Hardness

Hardness of 20 tablets was determined individually, using Hardness tester (Monsanto Hardness Tester) and data were statistically analyzed using control chart [8].

2.4.3 Friability

Friability of 20 tablets was determined using Friabilator (Electrolab India and Mettler Toledo). Percent friability was calculated by using equation 1.

$$F\ (\%) = [(W1 - W2)/W1] \times 100 \quad (1)$$

Where, F = friability, W1 = Weight of the tablet before testing and W2 = Weight of the tablet after testing. The results were tabulated in Table 3.

2.4.4 Content uniformity test

Ten tablets from each batch were powdered. The powdered sample equivalent to 100 mg of drug was transferred to a volumetric flask. 100 mL of 0.1 N Hcl was added, mixed and filtered. 1 mL of filtrate was diluted to 10 mL with 0.1N Hcl and analyzed against blank by UV spectrophotometer at 271 nm [9].

2.4.5 Wetting time and water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish (internal diameter 5 cm) containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured, the wetted tablet was then weighed. The results were tabulated in Table 4 Water absorption ratio 'R' was determined using following equation

$$R = 100 \times \left(\frac{W_b - W_a}{W_a} \right)$$

Where, W_a is weight of tablet before water absorption and W_b is weight of tablet after water absorption.

Table 1. Formulation of orally disintegrating tablets of tramadol Hcl

Formulation/ Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Tramadol	50	50	50	50	50	50	50	50	50
Sorbitol	50	25	-	-	-	-	-	-	-
Epo	-	-	25	12.5	-	-	-	-	-
Precirol	-	-	-	-	12.5	12.5	12.5	12.5	12.5
Aerosil	1	1	1	1	1	1	1	1	1
Mg.stearate	1	1	1	1	1	1	1	1	1
Peg-6000	5	2.5	-	-	-	-	-	-	-
Sorbitol	31.25	58.75	-	-	-	-	-	-	-
Xylitol	-	-	61.25	73.75	73.75	76.25	78.75	74.75	68.75
Acesulfame.K	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Pipperment flavour	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Cross povidone	10	10	10	10	10	7.5	5	9	15
Total	150	150	150	150	150	150	150	150	150

Table 2. Evaluation of pre compression parameters of powder blend

Formulation code/Parameters	Bulk density *(g/cm-3)*	Tapped density (g/cm-3)	Angle of repose *(θ)*	Compressibility index (%)	Hausner's ratio
F1	0.52	0.55	25.98	15.45	1.057
F2	0.43	0.49	26.75	12.24	1.14
F3	0.45	0.55	26.36	18.18	1.22
F4	0.46	0.53	29.64	13.20	1.15
F5	0.53	0.62	28.34	16.120	1.19
F6	0.48	0.56	27.56	14.28	1.19
F7	0.469	0.561	31.24	16.39	1.19
F8	0.45	0.55	30.98	1.18	1.22
F9	0.48	0.637	26.64	24.6	1.19

Table 3. Physicochemical characteristics of ODT tablets

Formulation code/ Parameters	Hardness (Kg/cm2)	Friability (%)	Content uniformity (%)	Weight variation	Disintegration time (sec)	Wetting time (Sec)	Water absorption ratio (%)
F1	3.5	0.21	99.45	Pass	13	10	103.2
F2	3.6	0.38	99.35	Pass	15	13	98.6
F3	3.4	0.115	98.69	Pass	16	14	97.2
F4	3.6	0.41	101.21	Pass	19	16	92.7
F5	3.5	0.28	99.26	Pass	22	19	86.5
F6	3.5	0.61	99.62	Pass	27	25	76.3
F7	3.5	0.44	99.79	Pass	29	27	69.4
F8	3.4	0.26	98.95	Pass	24	21	92.6
F9	3.5	0.46	99.48	Pass	11	11	100.8

2.4.6 *In vitro* dispersion time

The disintegration time was calculated using a disintegration apparatus where 0.1N Hydrochloride was used as a disintegration medium. The ODT was placed on the sieve of the apparatus which was maintained at 37±0.5ºC and the time by which the tablet completely disintegrates and falls from the sieve was calculated.

2.4.7 Assay of tramadol

Tramadol Hcl (10 mg) was dissolved in methanol in a 10 ml volumetric flask and diluted quantitatively with methanol to obtain a solution having a known concentration of 1000 µgm/ml. Diluting the standard stock solution with 0.1N Hcl buffer to obtain a series of dilutions containing different concentrations were measured in UV-Visible spectrophotometer (Lab India) at 271 nm using 0.1 N Hcl buffer as blank. From the absorbance of the sample solution and standard solution, the amount of drug in the percentage assay of ODTs was calculated.

2.4.8 *In vitro* dissolution study

In vitro dissolution of Tramadol mouth dissolving tablets was studied in USP type-II dissolution apparatus (Electro lab) employing a paddle stirrer at 50 rpm. 900 ml of pH 1.2 Hcl buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37±0.5ºC throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5 ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 271 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent Tramadol released was calculated and plotted against time.

2.4.9 Stability studies

The product formulation was subjected to short term stability testing for the stability indicating parameters such as appearance, weight variation, hardness, disintegration, dissolution and assay. The stability conditions used were temperature maintained at 40±2ºC and 75±5% RH for 3 months as per ICH guidelines [10].

3. RESULTS

Flow properties of Tramadol hydrochloride i.e., angle of repose, bulk density; tapped density, compressibility index and Hausner's ratio were estimated as mentioned in Table 2. Angle of repose value (31.24) indicated that the powder had good flow property, but the compressibility index and Hausner's ratios were indicating that powder had passable flow property. So, finally from these results it was concluded that the drug has good to passable flow property.

The bulk density of pre-compression blends was found to be in the range of 0.43 to 0.53g/cc, tapped density in the range of 0.49 to 0.63 gm/cc, the Carr's index values were in the range of 1.18 to 24.6%, Hausner's ratio in the range of 1.057 to 1.22 and angle of repose between 25.98 to 31.24. All the values were found to be within the prescribed limits according to the I.P, thus ensuring good flow properties to the formulation blends.

The hardness of the tablet formulations was found to be in the range of 3.4 to 3.6 kg/cm^2. The friability values were found to be in the range of 0.21 to 0.46%, which was found to be

according to the I.P limits and thus ensuring good mechanical strength to all the formulations Post compression parameters of the prepared formulation were depicted in Table 3. The weight of all the tablets was found to be uniform with low values of standard deviation.

The percent drug content of all the tablets was e in the range of 98.69 to 101.21%. Wetting time was determined for all the formulations of Tramadol Hcl. The varied wetting time for different formulations may be due to the changes in the compressional pressures, which could not be controlled during the production of tablets. Water absorption ratio value is decreased with increasing in the bulking agent(xylitol).The water absorption ratio of all formulations was 69.4 to 103.2 F1 has low concentration of bulking agent so it shows good results. Among the tablets prepared F1 formulation has shown an *in vitro* dispersion time of 13sec, whereas the in-vitro dispersion time of all the formulations ranged from 11 to 29 sec respectively, which was found to be within the I.P limits.

The time for disintegration of orodispersible tablets (orally disintegrating tablets) is generally < 1 minute and the actual time that patient can experience ranges from 5 to 30s.

In vitro dissolution studies were performed in pH 1.2 Hcl buffer. The dissolution results showed in Table 4. In all formulations 50% of drug was released in 5 mins. Among all formulations F7 releases the drug slowly. 84% of drug was released in 30 mins because of low concentration of superdisintegrant and more conc of xylitol (bulking agent), F9 shows 100% results within 15 mins because of more addition of crosspovidone. Among all the formulations F1 is economic and it shows 100% release in 30 mins. From the above results F1 was selected as a best ODT formulation among all the Tramadol hydrochloride formulations prepared by direct compression method.

From the stability studies of the compressed tablets all parameters found satisfactory which concluded that active ingredient is stable in the formulation.

Table 4. *In-vitro* dissolution profile of tramadol hydrochloride

Formulation code/Time	5 min	10 min	15 min	30 min
F1	69±1.8	82±1.6	93±1.5	100±1.3
F2	66±2.1	78±1.9	91±1.4	98±1.2
F3	68±1.9	81±1.7	93±1.5	98±1.2
F4	62±2.4	74±1.6	85±1.6	92±1.5
F5	60±2.6	72±1.9	83±1.7	91±1.3
F6	52±2.8	66±2.2	79±1.6	86±1.1
F7	46±2.9	59±2.4	72±1.8	84±1.4
F8	57±2.1	69±1.9	81±1.5	89±1.2
F9	72±1.6	93±1.4	100±1.3	--

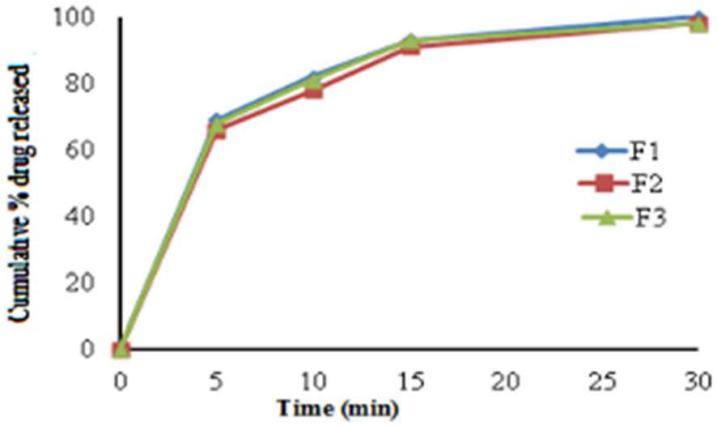

Fig. 1. *In vitro* drug release profile of formulation F1, F2, F3

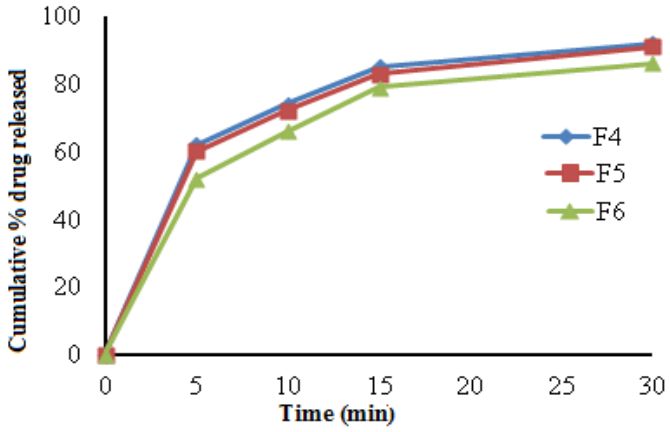

Fig. 2. *In vitro* drug release profile of formulation F4, F5, F6

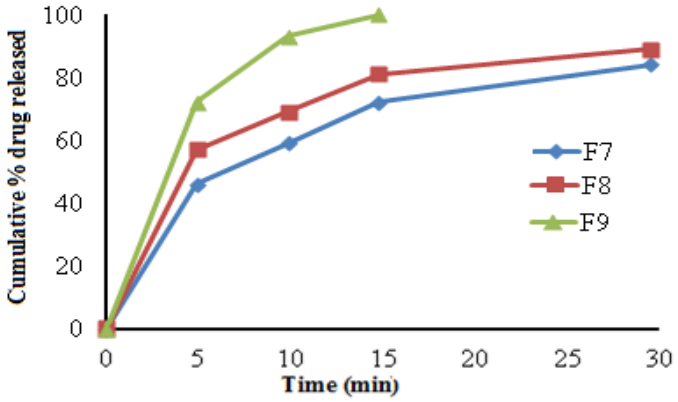

Fig. 2. *In vitro* drug release profile of formulation F7, F8 and F9

4. DISCUSSION

Orally dispersible tablets are being named as orodispersible, rapid-dissolving, mouth-dissolving, rapid-disintegrating tablets [3]. Oral drug delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, the most convenient and most economical method of drug delivery with the highest patient compliance [11]. ODT tablets which disintegrate in the mouth within seconds without the need for additional liquid. ODT was originally developed to improve the compliance of patients who had difficulty in swallowing tablets, such as children, the elderly and bedridden patients. ODTs combine the advantages of solid dosage forms with those of liquid forms and appeal to broader groups of patients than originally expected. ODTs may prove to have higher bioavailability and an earlier pharmacological effect than conventional tablets.

One of the simplest method to manufacture tablets is direct compression, because of Low manufacturing cost, limited number of processing steps. However disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, water soluble excipients and effervescing agents. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure quick disintegration and dissolution [12].

A total of nine formulations were proposed for product development. Based upon the physical and chemical characteristics of the product, it was concluded that F1 is more appropriate as it takes less time 13 SEC to disintegrate (100%) then other formulations because quick disintegration is the core objective of ODTs.

In the developed formulations of ODTs, the active ingredient amount was minute thus the performance of tablet was widely dependent

upon the excipients used. Crospovidone used as superdisintegrant which showed greater disintegrating efficiency and mechanical strength [12], direct effect on the disintegration of compression tablets in the mouth cavity also the active drug will be absorbed more rapidly due to presence of crospovidone. Remaining excipients included were acesulfame potassium, as key excipients, and peppermint flavor and sweetener Precirol, PEG 6000, magnesium stearate, Results obtained from the physicochemical characteristics data clearly illustrate the significant role of crospovidone and bulking agents in the integrity of the formulation.

Short term accelerated stability study was conducted for compressed formulation formulations and observed that all parameters (appearance, weight variation, hardness, disintegration, dissolution and assay) were found to be within the limit and the drug was stable for a period of 3 months at accelerated condition without any noticeable change and confirmed that which concluded that active ingredient is stable in the formulation.

5. CONCLUSION

In the present study it can be concluded from the characterization of orally disintegrating tablets of Tramadol hydrochloride that formulation containing crospovidone and sorbitol (bulking agent) is most acceptable. The developed formulation of Tramadol hydrochloride ODT should lead to improved efficacy, rapid onset of action, better patient compliance.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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