Research Article

Formulation Optimization and Evaluation of Tramadol Oral Disintegrating Tablets

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ABSTRACT

The present study was to evaluate the effect of increasing crospovidone load on the characteristics of oral disintegrating tablets. Tramodol is a central acting synthetic analgesic used to treat moderate to moderately-severe pain. Tramadol undergoes first pass metabolism in liver and gut wall which has oral bioavailability of 43 -77%. An attempt has been made to prepare fast dissolving tablets of Tramadol using super disintegrant like crospovidone. Five different groups of formulations (F1, F2, F3, F4 and F5) with variation in tablet excipients were prepared by direct compression method. Tablet weight variation, hardness, friability, drug content, disintegration time was evaluated for each formulation. From pre-compression and post-compression studies the disintegration time of formulation F5 is very less this indicates that formulation F5 has fast disintegration when compared with F1, F2, F3 and F4. The aim of the research is mainly to develop Tramadol ODTs their by preventing it to undergoes first pass metabolism in liver and gut wall and can be used as central acting synthetic analgesic to treat moderate to moderately-severe pain.

Keywords: Oral disintegration tablets, Tramadol, direct compression method, crospovidone.

INTRODUCTION

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules. Drinking water plays an important role in the swallowing of oral dosage forms[1]. The main drawback of these dosage forms for some patients is however difficulty to swallow. Often people experience inconvenience in swallowing conventional tablets and capsules, when water is not available, during motion sickness (kinetosis), sudden episodes of coughing during the common cold, allergic conditions and bronchitis[2]. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way[3]. The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, porous tablets, rapimelts. However of all the above terms, United States Pharmacopoeia (USP) approved these dosage forms as ODTs. European Pharmacopoeia has used the term "orodispersible tablet" for tablets that disperse readily and within three minutes before swallowing.

MATERIALS AND METHODS

Materials

Tramadol was obtained as a gift sample from GlaxoSmithKline Pharmaceuticals Ltd., Nashik, Maharashtra, Eudragit and Crospovidone were obtained from Sd Fine Chem Limited, Mumbai. Aspartame was procured from Medrich Pharmaceuticals, Bangalore. MCC from Qualigens Fine Chemicals, Mumbai. Magnesium stearate obtained from Sd Fine Chem Limited, Mumbai. Aerosil from Medrich Pharmaceuticals, Bangalore.

Preparation of oral disintegrating tablets

The oral disintegrating tablets of Tramadol were prepared by direct compression method according to the formulae given in the Table 1. All the ingredients were powdered and passed through # 60 mesh sieve 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) aspartame (sweetening agent) eudragit EPO (taste masking agent) aerosil (adsorbant and as a glidant) magnesium stearate (lubricant) and crospovidone (super disintegrant).

Different concentrations of excipients were used to prepare different groups of oral disintegrated tablets. Compositions of various formulations are shown in Table 1. All the ingredients of the ODT tablets of Tramadol were weighed and mixed thoroughly, finally 0.6mg magnesium stearate as lubricant and 0.6 mg of aerosil was added as glidant and mixed well. Then the blended material was directly compressed on the 8 mm flat round punches to get tablets of 150 mg weight.

All batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution.

Table: 1 Composition of Tramadol oral disintegrating tablets prepared by direct compression

Ingredients (mg)	Unit formula (mg/tablet)				
	F1	F2	F3	F4	F5
Tramadol	50	50	50	50	50
Eudragit EPO	50	50	50	50	50
MCC	42.3	40.8	39.3	37.8	36.3
Crospovidone	1.5	3	4.5	6	7.5
Aspartame	5	5	5	5	5
Aerosil	0.6	0.6	0.6	0.6	0.6
Magnesium stearate	0.6	0.6	0.6	0.6	0.6
Total weight	150	150	150	150	150

Weight variation test

Weight variation test was conducted by selecting 20 tablets at random as per I.P.

Friability test

Six tablets from each batch were examined for friability[5] using Riche Rich Pharma, Mumbai and the equipment was run for 4 min at 25 revolutions per minute. The tablets were taken out, de dusted and reweighed.

Hardness test

The hardness[6] of the tablet was determined using a Monsanto hardness tester (Campbell Electronics, Mumbai, India).

Wetting time and water absorption test[7]

A piece of tissue paper folded twice was placed in a small petri dish (internal diameter 5cm) containing 6ml of water. A tablet was kept on the paper and the time required for complete wetting was measured. The wetted tablet was than weighed. The results were shown in table 3.

Drug content

Five tablets from each batch were finely powdered and the powder equivalent to 50 mg of Tramadol was weighed and dissolved in suitable quantity of methanol. The solution was filtered, suitably diluted and the drug content was analyzed spectrophotometrically (Shimadzu, UV-1700) at 270nm.

Disintegration time

The disintegration time of the tablets was determined as per Indian pharmacopoeia. The test was carried out using tablet disintegration apparatus (Scientific Engineering Corporation, Delhi, India). The pH 6.8 phosphate buffer was used as a disintegrating media at 37 ± 2°C. The time required to obtain complete disintegration of all the tablets were noted.

Dissolution study

In vitro dissolution of Tramadol mouth dissolving tablets was studied in USP XXIII type-II dissolution apparatus (Electrolab TDT-06N) employing a paddle stirrer at 100 rpm. 1000 ml of phosphate buffer of pH 6.8 was used as dissolution medium. The temperature of dissolution medium was maintained at 37 ± 0.5° C throughout the experiment. Six tablets were used in each test. Samples of dissolution medium (10ml) 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 270 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[8].

Preparation of Calibration Curve

Preparation of calibration curve in pH 6.8 phosphate buffer

150 mg of Tramadol was dissolved in 75 ml of pH 6.8 phosphate buffer by slight shaking (2000 mcg/ml). 2 ml of this solution was taken and made up to 50 ml with pH 6.8 phosphate buffer, which gives 80 mcg/ml concentrations (stock solution). From the stock solution, concentrations of 10, 20, 30, 40 and 50 µg/ml in phosphate buffer were prepared. The absorbance of these solutions was measured at 270 nm and standard plot was drawn using the data obtained. The correlation coefficient was calculated. The absorbance data of the above concentrations are shown in figure 1.

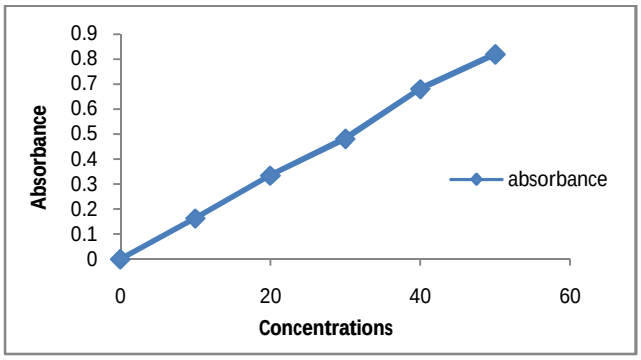

Figure 1: Standard graph of Tramadol in pH 6.8 phosphate buffer (λ_{max} 270)

RESULTS AND DISCUSSION

In the present study, an attempt has been made to formulate and evaluate oral dissolving tablets of Tramadol by direct compression method by employing directly compressible excipients. Total five formulations were prepared. The composition of five formulations is given in Table 1. The tablets were evaluated for pre-compression parameters and post compression parameters.

The oral disintegrated tablets of Tramadol were prepared by direct compression. All the tablets were subjected to weight variation, drug content uniformity, hardness, friability, water absorption ratio, wetting time, *in vitro* disintegration time. Based on the above study it was concluded that tablets prepared by direct compression was found to be good without any chipping, capping and sticking. The hardness of the prepared tablets was found to be in the range of 3.1 to 3.3 kg/cm^2.

Table 2: Pre-compression parameters of TRAMADOL formulations

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Compressibility index	Hausner's ratio
F1	0.462	0.539	27.4	14.46	1.16
F2	0.469	0.561	26.06	16.39	1.19
F3	0.478	0.586	24.28	18.43	1.22
F4	0.48	0.637	23.72	24.6	1.32
F5	**0.446**	**0.56**	**24.74**	**20.35**	**1.25**

Table 3: Post compression parameters of Tramadol tablets prepared by direct compression

Formulation Code	Hardness (kg/cm^2)	Friability (%)	*In vitro* disintegration time (s)	Wetting time/ water uptake mg/tab	Weight variation (mg)
F1	3.2	0.16	29	182.9	150 ± 0.0
F2	3.2	0.25	25	189.2	150±0.14
F3	3.3	0.67	21	198.2	150±0.09
F4	3.0	0.18	17	124.4	150±0.16
F5	3.1	0.11	12	153.01	150±0.03

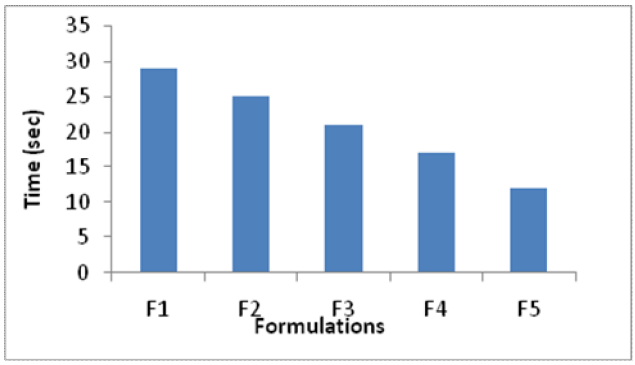

Figure 2: *In vitro* disintegration time of Tramadol tablet (ODT) from formulation F1-F5.

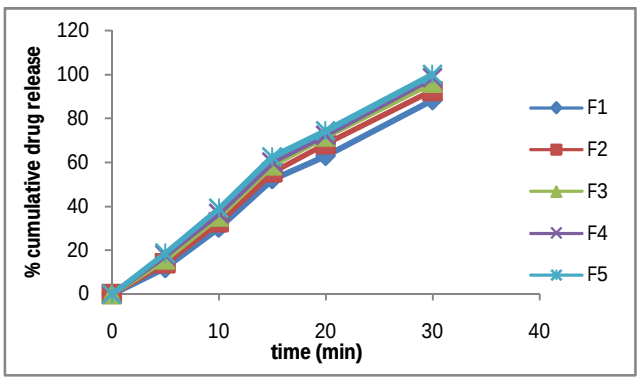

Figure 3: *In vitro* dissolution of Tramadol (ODT) formulations in pH 6.8 phosphate buffer.

The friability values were found to be in the range of 0.11 to 1.6%. The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared. The *in vitro* disintegration time of Tramadol tablets prepared by direct compression method was found to be in the range of 12 to 29s.

Drug release from the Tramodol tablets varying from 88.3% to 99.9%. Based on the *in vitro* disintegration time and dissolution studies formulation (F_5) was found to be promising and displayed *in vitro* disintegration time of 12s and drug release from the tablet 99.9%. Wetting time of formulations was found to be within 1 minute, which facilitates their faster dispersion in the mouth. The results of oral disintegrated tablets of Tramadol were shown in table 2 & 3 and graphically represented in figure 2 and 3 respectively.

CONCLUSION

From the pre-compression and post-compression studies, the mean % drug release and disintegration time of formulation (F_5) is comparatively good than with F1, F2, F3 and F4. This clearly indicates that fast disintegration and dissolution of formulation F5 is due to gradual increase in the concentration of crospovidone which acts as super disintegrating agent. Hence, the formulation F5 is selected as an optimized Tramadol oral disintegrating tablet. The aim of the present study is mainly to develop Tramodol ODTs, their by preventing it to undergo first pass metabolism in liver and gut wall. It is significance to exploit novel Tramodol ODTs which can used in the treatment of moderately-severe pain.

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