Research Article **CODEX: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

FORMULATION AND *IN VITRO* EVALUATION OF TREMADOL HYDROCHLORIDE FAST DISSOLVING TABLETS

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ABSTRACT

The aim of the work is an attempt to made formulation and evaluation of fast dissolving tablets of Tramadol by direct compression and wet granulation method with the aid of superdisintegrant addition. Fast dissolving tablets of Tramadol were prepared by direct compression and wet granulation method. Six formulations were developed by using three different superdisintegrants in varying concentrations in such a way that total weight of the tablet remains the same. The drug and polymer incompatibility was ruled out by FTIR studies. All the formulated tablets were subjected for pre and post-compression. Evaluation parameters from the FTIR studies, the drug-polymers computability were confirmed. All the formulated tablets were shown satisfactory results which complies with official limits. Among the six formulations, the formulation containing 3% crospovidone (F6) showed highest drug release of 98.46% in 10 mins than other formulations. From this study we can made the conclusion that formulated tablets of Tramadol containing Crospovidone, Crosscarmilose sodium are better and effective than conventional tablets to meet patient compliance and give fast relief from allergic.

KEYWORDS

Tramadol, Crospovidone, Crosscarmilose sodium, Fast dissolving tablets and *In vitro* drug release.

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INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desire therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at a particular frequency[1].

Thus drug may be administered by variety of routes in a variety of dosage forms.

Drugs are more frequently taken by oral route. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of administration is the most popular and has been successfully used for conventional delivery of drug. It is considered most natural, uncomplicated, convenient and safe route for administering drugs[2].

The concept of Mouth Disintegrating Drug Delivery System emerged with an objective to improve patient's compliance. These dosage forms rapidly disintegrate and/or dissolve to release the drug as soon as they come in contact with saliva, thus obviating the need for water during administration, an attribute that makes them highly attractive for pediatric and geriatric patients. Difficulty in swallowing conventional tablets and capsules is common among all age groups, especially in elderly and dysphasic patients[3]. This disorder of dysphagia is associated with many medical conditions including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy[4].

According to Federation International Pharmaceutics (FIP) / American Association of Pharmaceutical Scientists AAPS guidelines, specifically for coated particles or granules in Mouth disintegrating tablets (MDTs), the relative assessment of taste is performed using release studies in a neutral pH medium to establish an approximate baseline for early time-point (e.g. less than or equal to 5 minutes) dissolution values. Such a dissolution criterion (typical example: less than or equal to 10% dissolved in five minutes) would largely depend on the taste intensity of the drug and might enable the in vitro evaluation of the taste masking properties while avoiding organoleptic measurements. Taste-masked MDTs should be formulated in a manner such that the delay in drug release needs only to be long enough to pass through the oral cavity, followed by fast and complete release as for any immediate release dosage form.

MATERIAL AND METHODS

Material

Tramadol was obtained as a gift sample from Spectrum Pharma, Hyderabad, India. Magnesium stearate, Talc, were obtained from CDH, New Delhi, Crosspovidone, Crosscarmellose sodium, Sodium starch glycolate were obtained from Sanofi Aventis Pvt. Ltd., Goa. Aspartame was obtained from Dr. Reddy Pvt. Ltd., Hyderabad. All the ingredients used were of analytical grade.

Methods

Formulation of fast dissolving tablet of Tramadol[5, 6]

Fast dissolving tablets were prepared by Wet granulation and direct compression using Tramadol, The formula included variable amounts of superdisintegrants and other excipients. The amount of complex equivalent to 25 mg of drug per tablet were taken and then mixed with directly compressible diluents and superdisintegrant in a mortar with the help of pestle, then finally Aspartame as sweeter and aerosil as lubricant was added. The blend was then compressed using 6 mm flat-faced punch using a 16station Rotary tablet press machine. The total weight of the tablet was maintained 100mg.

EVALUATION PARAMETERS[5-7]

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

Infrared spectra of Tramadol, PVP and its inclusion complexes were recorded by KBr method using Fourier Transform Infrared Spectrophotometer.

In the present study, the potassium bromide disc method was employed. The powdered sample was intimately mixed with dry powdered potassium bromide. This mixture was then compressed into transparent disc under high pressure using special dies. This disc was placed in IR spectrometer and

spectrums were recorded. The scanning range was 450-4000 cm^{-1} and the resolution was 1 cm^{-1}.

Pre-compression studies of fast dissolving tablets

Angle of repose

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

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

Where,

θ = is the angle of repose

H = is the height

R = is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

Bulk density and Tapped Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. The accurately weighed amount of sample taken in a 25ml measuring cylinder of Borosil measured/recorded the volume of packing and tapped 100 times on a plane hard wooden surface

And tapped volume of packing recorded and LBD and TBD calculated by following formula

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Bulk Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

Hausner's ratio: Tapped Density / Bulk Density

Compressibility index

Percent compressibility of powder mix was determined by Carr's Index Compressibility index calculated by following formula.

$$\text{Carr's Index \%} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Pre-compression studies of fast dissolving tablets

Shape and color of tablets

Uncoated tablets were examined under a lens for the shape of the tablet, and colour was observed by keeping the tablets in light.

Uniformity of thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while packaging, handling and transportation. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and analyzed for hardness. The mean and standard deviation values were calculated.

Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by,

% Friability = (loss in weight / Initial weight) X 100

Weight variation test

Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed in the weight of a tablet by U.S. Pharmacopoeia. The following percentage deviation in weight variation is allowed.

Drug content uniformity

Tablet containing 25 mg of drug is dissolved in 100ml of Phosphate buffer pH 6.8. The drug is allowed to dissolve in the solvent, the solution was filtered and 1ml of filtrate was taken in 10 ml of volumetric flask and diluted up to the mark with

phosphate buffer pH 6.8 and analyzed spectrophotometrically at 221 nm. The amount of Tramadol was estimated by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each batch of formulation.

Wetting time

The method was applied to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small Petri dish (i.d. = 6.5 cm) containing 6 ml of water, a tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of distilled water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using equation:-

$$R = 100 \times Wa - Wb/Wb$$

Where,

Wb = weight of the tablet before water absorption

Wa = weight of the tablet after water absorption

Three tablets from each formulation were performed and standard deviation was also determined.

***In vitro* disintegration time**

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in vitro* disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37 ± 2^0C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 maintained at 37 ± 2^0C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

***In vitro* dispersion time**

In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of pH 6.8 (simulated saliva fluid). Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed. Standard deviation was also determined and *in vitro* dispersion time is expressed in seconds.

***In vitro* dissolution**

In vitro release studies were carried out using tablet dissolution test apparatus USP XXIII. Two objectives in the development of *in vitro* dissolution tests are to show (1) that the release of the drug from the tablet is as close as possible to 100% and (2) that the rate of drug release is uniform from batch to batch and is the same as the release rate from those batches proven to be bioavailable and clinically effective.

RESULTS AND DISCUSSION

Pre-formulation Studies

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference in the functional groups as the principle peaks of the Tramadol were found to be unaltered in the spectra of the drug-polymer physical mixture (Figure No.1 and 2).

Pre-compression Studies

All the formulations prepared by both the methods showed the angle of repose less than 30^{o}C, which reveals good flow property (Table No.2). The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.55 gm/cm^3 to 0.60gm/cm^3 and 0.67 gm/cm^3 to 0.73gm/cm^3 respectively (Table No.2). The results of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 13.23 to 15.49%. The results of Hauser's ratio range of 1.152 - 1.218.

Post-compression Studies

Shape and color of tablets showed flat, circulars in shape and white in color. The thickness was almost uniform in all the formulations and values ranged from 2.43 mm to 2.62 mm respectively. The hardness values ranged from3.87 kg/cm^2 to 4.70 kg/cm^2 for formulations were almost uniform. Tablet hardness is not as absolute strength. Friability values were found to be within the limit. Thus tablets possess good mechanical strength. The percentage weight variation for all the formulation is determined. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±10 %. It was found to be from 298.9 to 301.0 mg. The weight of all the tablets was found to be uniform. The drug content of the tablets was found between 59.742 % to 60.00 % of Tramadol. The results indicated that in all the formulations the drug content was uniform. Wetting time is closely related to the inner structure of the tablet. This experiment mimics the action of saliva in contact with the tablet to illustrate the water uptake and subsequent wetting of tablet. This showed that wetting process was very rapid in almost all formulations. This may be due to ability of swelling and also capacity of water absorption and cause swelling (Table No.4). Water absorption ratio, which is important criteria for understanding the capacity of disintegrates to swell in presence of little amount of water, was calculated. It was found to be in the range of 56.64 ± 1.163 to 65.04 ± 1.236 seconds. 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 shown in (Table No.4). This was determined as per I.P. procedure for all the formulations. All formulations showed disintegration time less than 30 seconds. Among the three superdisintegrants used, crospovidone showed less disintegrating time followed by crosscarmellose sodium and sodium starch glycolate. *In vitro* dispersion time is measured by observing the time taken by the tablets to undergo uniform dispersion in pH 6.8 buffer. Rapid dispersion of the tablets was observed in all the formulations. This indicate that the efficiency of superdisintegrants was in the order crospovidone > crosscarmellose > sodium starch glycolate. The values obtained are recorded in (Table No.4).

***In vitro* dissolution studies**

All the six formulations were subjected for the *in vitro* dissolution studies using tablet dissolution tester USP XXIII. The samples were withdrawn at different time intervals and analyzed at 271 nm. Cumulative drug release was calculated on the basis of mean amount of Tramadol present in the respective tablet. The results obtained in the *in vitro* drug release for the formulations are tabulated. The plots of cumulative % drug release V/s. time are shown in (Figure No.3 and 4).

Table No.1: Composition of fast dissolving tablets of Tramadol

S.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Tramadol	25	25	25	25	25	25
2	Sodium starch glycolate	3	_	_	3	_	_
3	Cross carmellose sodium	_	3	_	_	3	_
4	Crosspovidone	_	_	3	_	_	3
5	Mannitol	60	60	60	65	65	65
6	Starch	7	7	7	_	_	_
7	Aspartame	2	2	2	2	2	2
8	Magnesium Stearate	2	2	2	2	2	2
9	Peppermint oil	1	1	1	_	_	_
10	Talc	_	_	_	3	3	3

Table No.2: Results of flow properties of fast dissolving tablet (F1 to F6)

Formulation Code	Angle of repose (θ)	Loose bulk density(gm/cm^3)	Tapped bulk density(gm/cm^3)	Hausner's ratio	Compressibility %
F1	29.17	0.59	0.69	1.169	14.49
F2	28.91	0.56	0.67	1.196	16.41
F3	30.01	0.55	0.67	1.218	17.99
F4	28.18	0.59	0.68	1.152	13.23
F5	28.69	0.60	0.73	1.216	17.80
F6	28.41	0.60	0.71	1.183	15.49

Table No.3: Uniformity of thickness, Hardness, Friability, Uniformity of weight and Drug content

Formulation code	Uniformity of thickness (n=3) (mm)	Hardness (n=3) (kg/cm^2)	Friability percentage (n=10)	Uniformity of weight (n=10) (mg)	Drug content (n=3) (mg)
F1	2.57±0.01	3.90±0.19	0.2792	101.0±1.032	59.871±0.023
F2	2.62±0.03	4.40±0.13	0.2866	100.5±2.151	58.903±0.067
F3	2.51±0.05	4.70±0.21	0.3493	100.3±2.163	59.968±0.021
F4	2.43±0.02	3.87±0.29	0.2834	99.7±2.88	59.742±0.031
F5	2.47±0.01	4.30±0.23	0.3261	100.0±1.021	59.935±0.113
F6	2.53±0.04	4.41±0.21	0.2451	01.0±1.021	60.00±0.046

Table No.4: Wetting time, Water absorption ratio, *In Vitro* Disintegration time and *In Vitro* Dispersion time

Formulation code	Wetting time (n=3)	Water absorption ratio(n=3)	*In vitro* disintegration time (sec)*	*In vitro* dispersion time(sec)*
	Mean ± sd	Mean ± sd	Mean ± sd	Mean ± sd
F1	35.01 ± 0.37	56.64 ± 1.163	25.30 ± 1.69	26.34 ± 0.86
F2	33.74 ± 1.55	57.26 ± 1.712	20.43 ± 0.65	20.63 ± 1.48
F3	28.53 ± 1.57	59.41 ± 2.531	17.21 ± 1.43	21.63 ± 1.51
F4	35.60 ± 0.76	59.45 ± 2.144	23.68 ± 1.53	24.54 ± 1.15
F5	27.28 ± 1.25	62.74 ± 0.671	17.64 ± 1.15	20.23 ± 1.78
F6	20.21 ± 1.43	63.31 ± 1.121	14.38 ± 2.19	17.33 ± 1.24

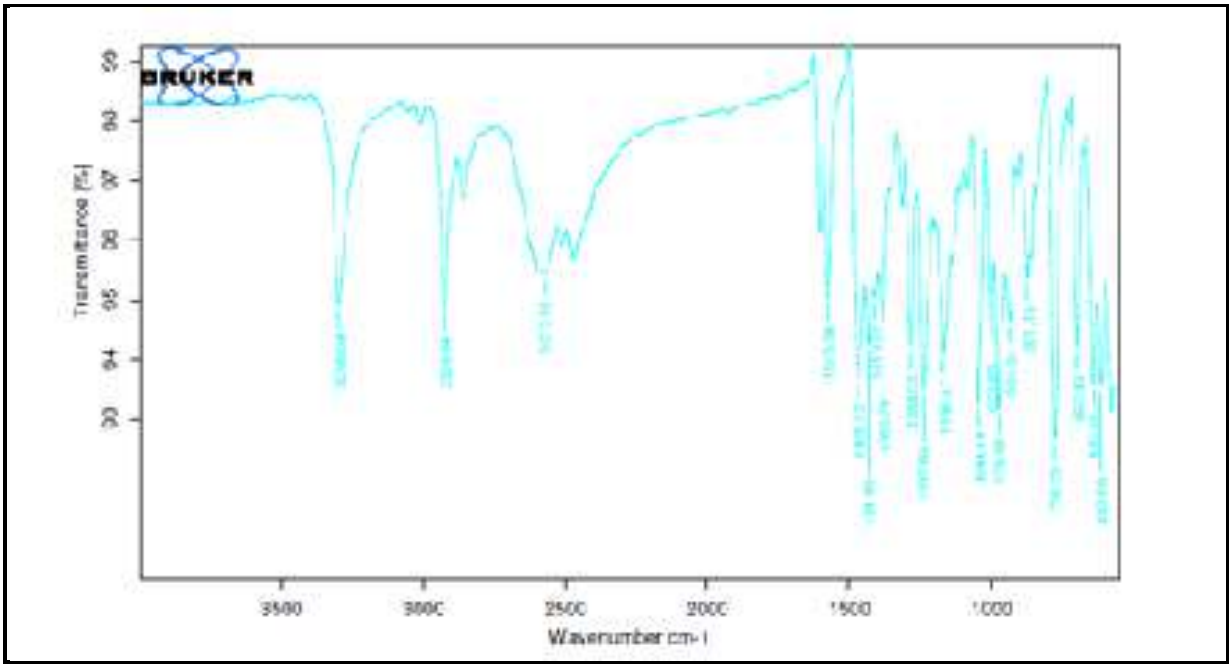

Figure No.1: FT-IR spectra of pure Tramadol

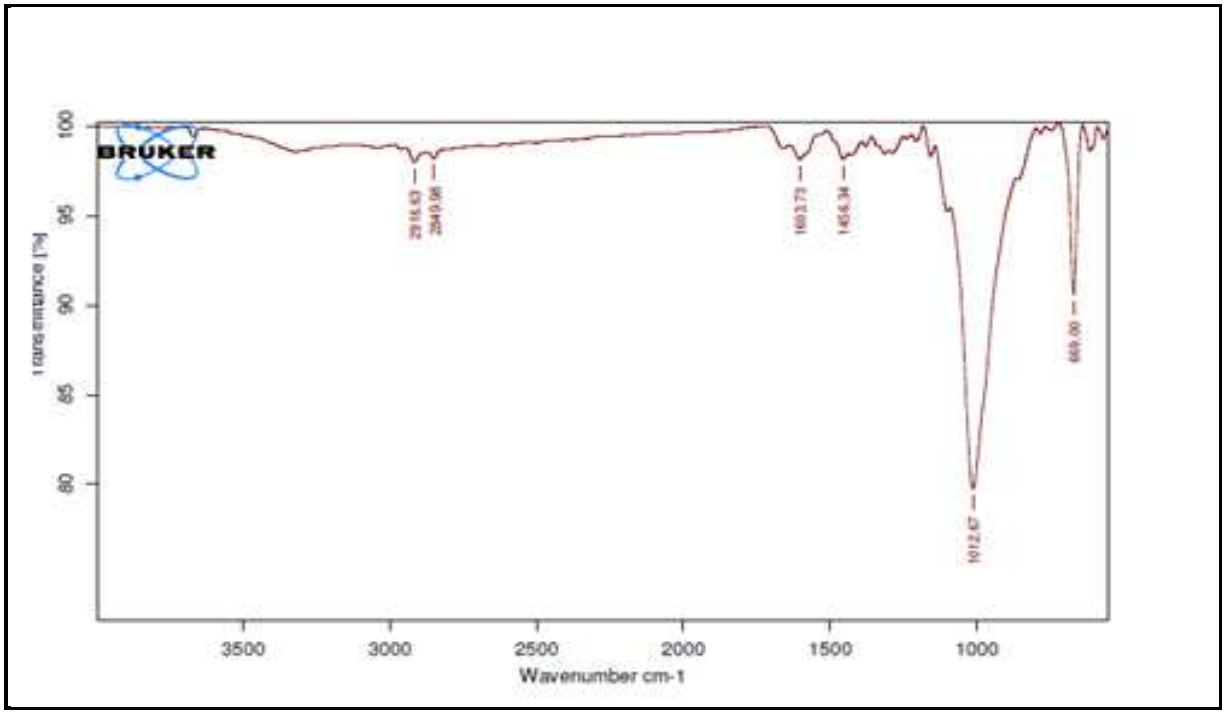

Figure No.2: FT-IR spectra of optimized formula (F6)

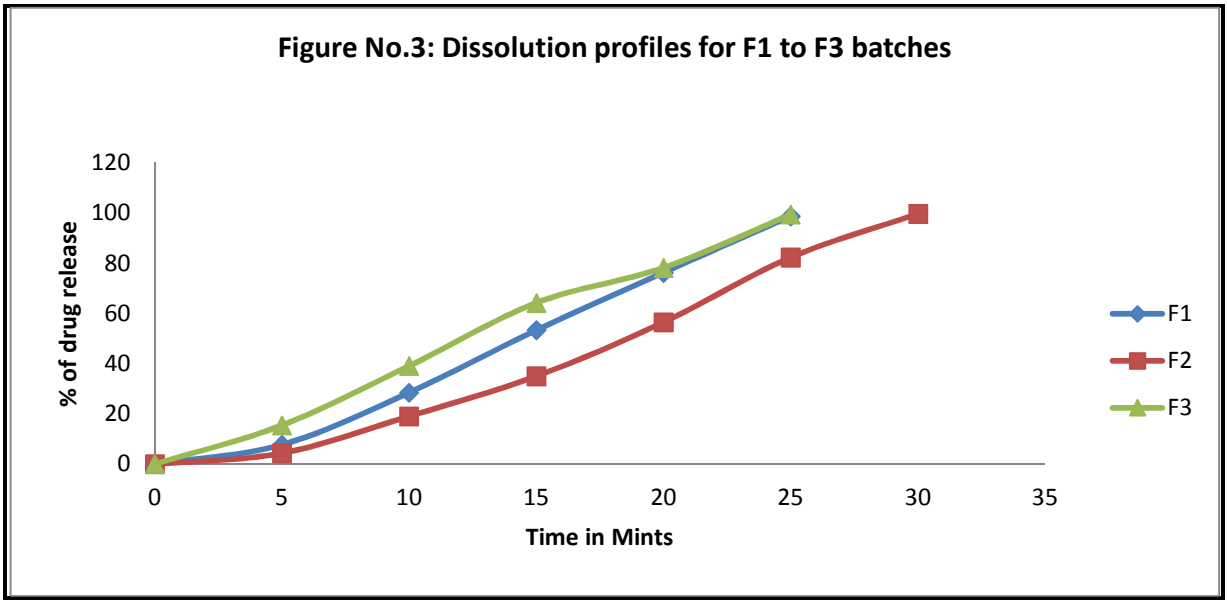

Figure No.3: Dissolution profiles for F1 to F3 batches

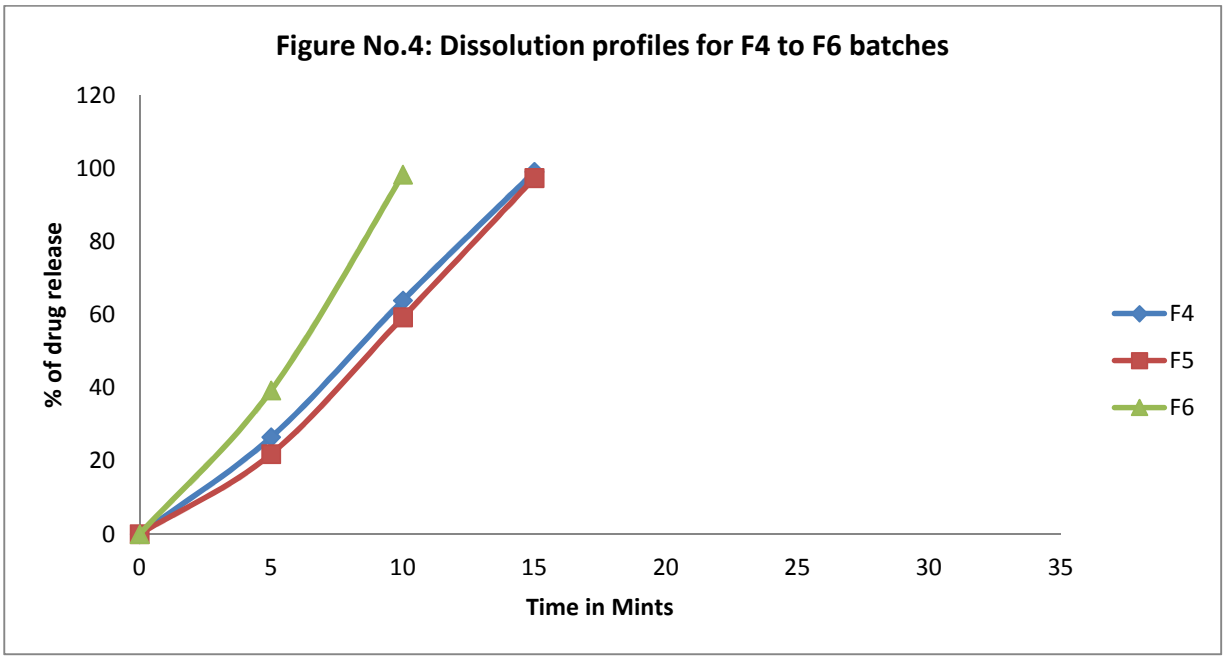

Figure No.4: Dissolution profiles for F4 to F6 batches

CONCLUSION

The fast dissolving tablets of Tramadol were prepared by direct compression and wet granulation method using different superdisintegrants such as polyplasdone XL-10 (CP), Ac-di-sol (CCS), Sodium starch glycolate in different concentration. Disintegration time decreased with the increase in the concentration of superdisintergrants. Among all formulation, formulation containing Polyplasdone XL-10 (CP) as superdisintegrants is fulfilling all the parameters satisfactorily. It has shown excellent *in vitro* disintegration, *in vitro* dispersion time, compared to other superdisintegrants. The relative efficiency of these superdisintegrants to improve the disintegration and dissolution rates of tablets was in order Polyplasdone XL-10 (CP)> Ac-di-sol (CCS)> Sodium starch glycol ate. *In vitro* release studies revealed that almost 90% drug was released from all the formulation were within 30 mints. Formulation F3 and F6 showed faster drug release in comparison to other formulation. Formulation F6 prepared by direct compression showed faster drug release in comparison to the formulations prepared with wet granulation method.

ACKNOWLEDGEMENT

The authors are sincerely thanks to A.M Reddy Memorial College of Pharmacy, Narasaraopet, Guntur, and Andhra Pradesh, India for providing the facilities to complete this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Supriya S. *et al*. Formulation and *in vitro* evaluation of tremadol hydrochloride fast dissolving tablets, *International Journal of Research in Pharmaceutical and Nano Sciences,* 1(2), 2012, 239-248.