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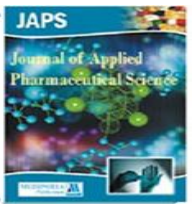

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Formulation and evaluation of orally disintegrating tablet containing tramadol hydrochloride by mass extrusion technique

Mansing G. Patil, Suhas M. Kakade and Sandhya G. Pathade

Mansing G. Patil
Department of Quality Assurance, School of Pharmacy, Technology and Management, NMIMS University, Shirpur, Dhule - 425 405, India.

Suhas M. Kakade
Department of Pharmaceutics, J. N. Medical College, KLE University, Belgaum – 590010, India.

Sandhya G. Pathade
Department of Pharmaceutics, School of Pharmacy, Technology and Management, NMIMS University, Shirpur, Dhule - 425 405, India.

For Correspondence:
Mr. Mansing G. Patil
Department of Quality Assurance School of Pharmacy, Technology and Management, NMIMS University, Shirpur, Dhule - 425 405, Maharashtra, India. Mob. No. 09860947478

ABSTRACT

Orally disintegrating tablets are gaining popularity over conventional tablets due to their convience in administration and suitability for patients. The purpose of this research was to mask the intensely bitter taste of tramadol hydrochloride and to prepare orally disintegrating tablets for achievement of quick onset of action of the drug. Trammadol hydrochloride is an analgesic which has been proved to be efficient in managing relief from pain and including pain after surgery. In the present study an attempt has been made to prepare bitterless orally disintegrating tablet of Tramadol Hydrochloride using Eudragit E 100 as a taste masking agent. Mass extrusion was the technique used for preparing taste masked granules and tablet was prepared with using superdisintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate, were prepared blend and evaluated for the pre-compression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. Among the formulations containing Crospovidone was least and tablets showed fastest disintegration. The drug release from orally disintegrating tablets increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing Crospovidone. Thus results conclusively demonstrated successful masking of taste and fastest disintegration of the formulated tablets in oral cavity.

Key words: Tramadol hydrochloride, Superdisintegrants, Mass extrusion, Orally disinintegrating tablets.

INTRODUCTION

Recent advance in novel drug delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being for the administration. (Kuchekar et al., 2003). Difficulty in swallowing is experienced by patient such as pediatric, geriatric, bedridden, disabled and mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of non-compliance and ineffective therapy. (Seager et al., 1998). 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. (Yutaka et al., 2002). Orally disintegrating tablets are solid dosage form containing medical substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilate swallowing. (Shu et al., 2002). It is suited for tablets undergoing high first pass metabolism and is improving bioavailability with reducing dosing frequency to minimize side effect. Tramadol hydrochloride is a synthetic opioid analgesic used for moderate to severe pain

like labor pain, postoperative surgeical pain, traumatic pain and cancer pain. Tramadol hydrochloride can be administered orally, intravenously or rectally. Tramadol hydrochloride is rapaidly absorbed orally is subjected to first pass metabolism and absolute bioavailability is only approximately 68%. (Lehman et al., 1997). It is bitter in taste. Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques. Two approaches are commonly utilized to overcome bad taste of the drug. The first includes reduction of drug solubility in saliva, where a balance between reduced solubility and bioavailability must be achieved. Another approach is to alter the ability of the drug to interact with taste receptor. (Brahmankar et al., 1995). Taste masked granules of bitter drugs can be prepared by using Eudragit E100 and ethanol. The extrusion technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. The process involves embedding a drug in a polymeric carrier while shaping the composite material to form a pharmaceutical product. (Watanabe et al., 1999).

In present study an attempt has been made to prepare taste masked granules of Tramadol hydrochloride. Taste masking of Tramadol hydrochloride was carried out by using Eudragit E100 (Mass extrusion method). These taste masked granules or complex was further formulated into the orally disintegrating tablets by direct compression method using sodium starch glycolate, crosscarmellose sodium and crospovidone as the superdisintegrants for rapid dissolution of drug and absorption, which may produce the rapid onset of action in the treatment of analgesic for postoperative pain.

MATERIALS AND METHODS

Materials

Tramadol hydrochloride was obtained as a gift sample from Virupaksha Organics Pvt. Ltd. Medak, India. Crospovidone was gift sample from Signet Chemical Corporation, Mumbai. Eudragit E-100 was gift sampl from Evonik Degussa India Pvt. Ltd. Mumbai. Croscarmellose sodium, Sodium starch glycolate and Avicel PH 102 were gift samples from Sunrise Remedies, Ahmedabad, India. All chemicals and reagents used were of analytical grade.

Methods

Preparation of drug-Eudragit E100 taste masked granules by mass extrusion Technique

Fixed amount of drug was mixed with fixed amount of powdered Eudragit E100 i.e. they were mixed at 1:1 ratios with the help of mortar and pestle. Then 10% ethanol was added to each mixture. Then gel was prepared using the mixture of the drug and Eudragit E100 which was converted into the taste-masked granules by the extrusion method. The prepared gel was manually extruded (pressed out) using a syringe. After extrusion of the gel, ethanol was removed by evaporation overnight and subsequently the solidified gel in the shape of string was crushed into granules using a mortar. (Watanabe et al., 1999).

Formulation of [bitterless] fast dissolving tablet of drug: Eudragit E 100 granules by disintegrant addition method

Fast dissolving tablets of Tramadol hydrochloride: Eudragit E100 granules were prepared using direct compression method after incorporating different superdisintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. Mannitol, Avicel PH 101 was used as directly compressible diluents. Nine formulations of Tramadol hydrochloride: Eudragit E100 granules were prepared and each formulation contained one of the three disintegrant in different concentration. Tablet weight was 200 mg; 8 mm punch was used for compression. Ingredient are depicted in Table 1.

Table 1: Formulation of Tramadol hydrochloride Orally Disintegrating Tablets.

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tramadol Hydrochloride	50	50	50	50	50	50	50	50	50
Eudragit E100	50	50	50	50	50	50	50	50	50
Mannitol	66	64	62	66	64	62	66	64	62
Avicel PH102	25	25	25	25	25	25	25	25	25
Crospovidone	6	8	10						
Crosscarmellose sodium				6	8	10			
Sodium starch glycolate							6	8	10
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aspartame	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation of fast dissolving tablets of Tramadol hydrochloride

Precompression parameters

Angle of repose (θ): 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.

$$\tan \theta = h/r$$

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

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. (Subramanyam, 2001).

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas. (Subramanyam, 2001).

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

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

Carr's Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula. (Subramanyam, 2001).

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

Post compression parameters

All the batches of tablets were evaluated for various parameters like weight variation, friability, hardness, drug content, disintegration and dissolution and results reported in Table 2.

Table 2: Evaluation data of the prepared Tramadol hydrochloride orally disintegrating tablets.

Formulation code	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time (sec.)	Water absorption ratio (%)	Wetting time (sec.)	% Drug release
F1	3.6 ±0.02	0.41±0.03	98.60	33±2.00	26.89±1.11	22.00±1.12	90.73
F2	3.93±0.12	0.34±0.06	98.15	24±2.00	19.24±2.13	18.00±0.61	93.23
E3	4.1 ±0.26	0.24±0.05	99.45	19±1.00	18.45±2.10	17.33±1.55	99.29
F4	3.5 ±0.03	0.52±0.05	98.29	29±0.00	31.45±1.63	24.87±0.36	86.11
F5	3.36±0.13	0.45±0.01	99.20	32±1.00	29.69±1.55	23.67±0.5	87.91
F6	3.59±0.23	0.53±0.04	99.18	20±2.00	29.09±1.52	22.34±1.58	91.76
F7	3.8 ±0.06	0.36±0.02	97.34	36±2.00	36.89±1.32	32.39±0.58	78.96
F8	3.6 ±0.01	0.39±0.01	98.45	25±2.00	34.37±1.96	26.01±1.01	83.26
F9	4.0 ±0.01	0.43±0.03	98.36	22±1.00	35.09±1.92	25.33±0.59	87.15

*Weight variation test:*Twenty tablets were taken and their weight was determined individually and collectively on a digital weighting balance. The average weight of one tablet was determined from the collective weight. (Lachman et al., 2003).

Hardness test: The hardness of the tablet was determined using Monsanto Hardness Tester. (Lachman et al., 2003).

Friability test: Six tablets from each batch were examined for friability using Roche Fribilator (Tropical Equipment Pvt. Ltd. Mumbai, India) and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. (Lachman et al., 2003).

$$\%\text{Friability} = (\text{Loss in weight/Initial weight}) \times 100$$

Water absorption ratio: A piece of tissue paper folded twice was kept in a Petri dish (internal diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighted. Water absorption ratio, R was determined according to the following equation.

$$R = 100\ (Wa - Wb)/Wb$$

Where Wb and Wb are the weight before and after water absorption, respectively. (Rajitha et al., 2009).

*Wetting time:*A piece of tissue paper folded twice was kept in a Petri dish (inter diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded. (Rajitha et al., 2009).

*Content uniformity test:*Five tablets were weighed and powdered, 10 mg of equivalent of tramadol hydrochloride was weighed and dissolved in suitable quantity of methanol, the solution was filtered suitably diluted and the drug content was analyzed using UV spectrometer at 270 nm. (Sreenivas et al., 2006).

In vitro disintegration time: The disintegration test was performed using an USP disintegration apparatus, with distilled water at 24 ± 0.5^0C. The time reported to obtain complete disintegration of six tablets were recorded and average was reported. (Rajitha et al., 2009).

In vitro dissolution testing: Dissolution study was conducted for all the formulation using USP type-II apparatus (Electolab, Mumbai, India.). The dissolution test was performed using 500 ml of phosphate buffer (PH 6.8) was taken as the dissolution medium at 50 rpm and $37^0C\pm0.5^0$C. Five millilitres of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 270 nm. (Rajitha et al., 2009).

RESULTS AND DISSCUSSION

Eudragit E100 was selected for the taste masking of Tramadol hydrochloride. The taste-masked granules of drug and Eudragit E100 were prepared by simple mass extrusion\ technique using syringe. Flow properties of the powder, resistance to particle movement can be judged from the angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading as might be applied in mixing and tabelting. Bulk density was found in the range of 0.431-0.529g/cm^3 and the tapped density between 0.536-0.675g/cm^3. The powder blends of all the formulations had Hausner's factor values which were in the range of 1.031-1.112 indicating good flowability. The compressibility index was found between 09.71-12.95. Hence the prepared blends possessed good flow properties and these can be used for tablet manufacture.

All batches of the tablets were preliminarily evaluated for various physical parameters such as hardness, friability, drug content, wetting time, water absorption ratio, disintegration and dissolution which were reported in Table 2. All above properties and value were near to boundary of standard limit. All the tablets maintained hardness in the range 3.5–4.1kg/cm^2. The loss in total weight of the tablets due to friability was in the range of 0.24-0.53%. The drug content in different formulation was highly uniform and in the range of 97.34-99.45%. Wetting time is used as an indicator of the ease of tablet disintegration and found to be 17-32sec. Water absorption ratio ranged from 18.45-36.89. The result

in vitro disintegration were within the prescribe limit and comply with the criteria for orally disintegrating tablets, the value were with 18-43sec. In vitro dissolution studies are shown in Table 2 and Figure 1. The cumulative % of drug release increased in 15 min with increased in the concentration of superdisintegrant. At 5% superdisintegrant level the drug release at the end of 15 min. were found to be 99.29%, 91.76% and 87.15% with crospovidone, croscarmellose sodium and sodium starch glycolate respectively.

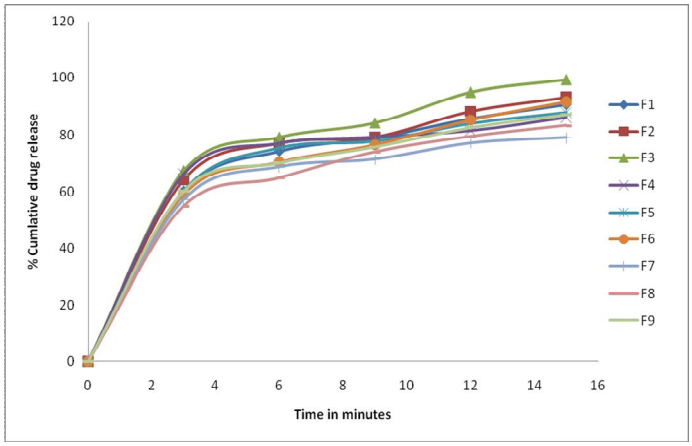

Fig 2: Drug release profile of Prepared Tramadol fast dissolving tablets.

CONCLUSION

In the present study it can be concluded from the characterization of orally disintegrating tablets of Tramadol hydrochloride that formulation containing crospovidone is most acceptable. It was observed that to further increase the drug release from orally disintegrating tablets, solubility enhancement of tramadol hydrochloride required and is under investigation.

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