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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET OF TRAMADOL HYDROCHLORIDE

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Abstract

Mouth dissolving tablet is a novel dosage form, have several characteristics to distinguish them from the more traditional dosage form. The purpose of this research was to prepare mouth dissolving tablet of tramadol hydrochloride by sublimation method with a view to enhance patient compliance. Tramadol hydrochloride is a centrally acting analgesic, which is orally and intravenously administered drug. The sublimating agent used in this study was camphor & ammonium bicarbonate, The prepared batches of tablets were evaluated for uniformity of weight, thickness, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study. Amongst all formulations, formulation F3 prepared by 5% crosscaramellose sodium & 15% camphor showed least disintegrating time and faster dissolution.

Keywords: Tramadol HCL, Mouth dissolving tablets, *In vitro* evaluation, Sublimating agents.

Introduction

The tablet is the most widely used dosage form existing today because of its convenience in terms of self-administration, compactness and ease in manufacturing. However, some patients, particularly pediatric and geriatric patients, have difficulty during swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to a fear of choking. In order to assist these patients, several fast-dissolving drug delivery systems have been developed. A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintrigrats in the oral cavity without the need of water, Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach.[3,4] The formulation is more useful for the bed-ridden and patients who have the swallowing problem. The benefits of MDTs is to improve patients compliance, rapid onset of action, increased bioavailability and good stability which make these tablets popular as a dosage form of choice in the current market. The background behind MDT is, approximately one-third of the population, primarily the geriatric and pediatric populations, has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. Hence fast dissolving drug delivery system was developed. Tramadol hydrochloride is centrally acting analgesic, which is administered an orally & intraveinously. Tramadol HCL provides pain relief for acute, chronic & moderate to severe

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pain. The sublimating agent used in this study was camphor & ammonium bicarbonate, this is the one approach to developed mouth dissolving tablets by using the camphor & ammonium bicarbonate the pore structure of the tablets was maximizes by Vacuum drying and freeze-drying techniques, vacuum-drying technique was adopted in the present investigation after addition of a subliming agent to increase porosity of the tablets, Camphor is a good subliming agent and in many formulations it is used as subliming agent. .In the present study, an attempt was made to develop mouth dissolving tablets of tramadol HCL and to investigate the effect of various concentration of subliming agent on the disintegration time, wetting time and release profile of the drug in the tablets.

Materials and methods

Tramadol HCL, camphore, ammonium bicarbonate, Crosscarmilose sodium, aspartame, mannitol, talc, aerosil and magnesium stearate was supplied as a gift sample from JCPL Pharma Pvt. Ltd. Jalgaon. All other chemicals, solvents and reagents were used of analytical grade.

Preparation of mouth dissolving tablets

In this study fast-dissolving tablet were prepared by using camphor and ammonium bicarbonate as sublimating agent. The sublimating agent used in varying concentration to develop the tablets. Four formulations of Tramadol HCL containing camphor & ammonium bicarbonate in different proportions were prepared by using Mannitol as a diluent. All the ingredients were accurately weighed and passed through # 60 mesh separately. The drug and the diluents was mixed in small portion of both each time and blending it to get uniform mixture and set aside. The other ingredients were weighed and mixed in geometrical order, mixed thoroughly with lubricant. The tablets of weight 200 mg were prepared by direct compression technique using 8 mm punch in 16-station rotary tablet machine cadmach Ahmadabad. After that the compressed tablets are dried for 5 hours for the sublimation of sublimating agent.

Evaluation of Mouth Dissolving Tablets of tramadol HCL

Pre-compression parameters

Bulk density

Bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume and Mass of the powder was determined. The bulk density was calculated by using below mentioned formula,

$$D_b = M / V_b$$

Where,

D_b = Bulk density

M = mass of the powder blend

V_b = bulk volume of the powder blend

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder and the Mass of the blend was measured. The tapped density was calculated using the following formula,

$$D_t = M / V_t$$

Where,

D_t = Tapped density

M = mass of powder blend

V_t = Tapped volume of powder blend

Carr's Index

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by

carrs' index The value below 16% indicates a powder with usually give rise to good flow characteristics, whereas above 23 % indicate poor flowability. which is calculated as follows,

$$I = D_t - D_b / D_t \times 100$$

Where,

I = Carr's Index (compressibility)

D_t = Tapped density

D_b = bulk density

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. Hausner's ratio value is Less than 1.5 indicate good flow & greater than 1.5 indicate poor flow. It is calculated by the following formula,

$$H = D_t / D_b$$

Angle of repose

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (φ) was calculated using the formula,

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

Post-compression parameters

Weight variation test

Twenty tablets were selected randomly and average weight was determined. Then individual tablets were weighed and was compared with average weight.The comparison variation within the I.P limits, it passes the weight variation test.

Tablet hardness

Tablet crushing strength or hardness, the force required to break a tablet in a diametric compression, was measured using Monsanto tablet hardness tester.

Thickness

The thickness of individual tablets was measured using Vernier caliper, which permits accurate measurements and provides information of the variation between tablets.

Tablet friability

The friability of the tablets was measured in a Roche friabilator. Tablets sample of a known weight (W_0) were dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.

$$\% \text{ friability} = \frac{W_0 - W}{W_0} \times 100$$

Drug content uniformity

Four tablets from each formulation were weighed and taken in mortar and crushed to make powder. A quantity of powder weighing from this equivalent to 50 mg of tramadol HCL was taken in 100 ml volumetric flask and dissolved in 5 ml of pH 6.8 phosphate buffer & diluted upto 100ml . It was then shaken vigorously on a Magnetic stirrer for 2 hr & filtered by using whatman filter paper. Further appropriate dilution was made & absorbance was measured at 271 nm.

In-vitro disintegration test

The in-vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

Wetting Time

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 mL of water-containing Eosin a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

$$R = 100 \times W_a - W_b/W_a$$

Where,

W_a = Weight of tablet after water absorption

W_b = Weight of tablet before water absorption.

In Vitro Dissolution studies

In vitro drug release of all formulations was carried out using USP- type II dissolution apparatus (paddle type). The dissolution medium 900 ml 6.8pH phosphate Buffer was placed into the dissolution flask maintaining the temperature of 37^0 C $\pm 0.5^0$ C & rpm of 50. Tablets were placed in the dissolution apparatus. . Dissolution studies were carried out for 30min. 5ml of the Aliquot was taken at intervals of 1, 2, 3, 5, 10, 15min. After collecting the sample, the dissolution medium was replenished with the same volume of fresh medium, and the sample was filtered 1ml of the filtrate was diluted to 10ml with 6.8pH phosphate Buffer and analyzed spectrophotometrically at 271 nm.

Result & discussion

The powder blend for all formulation containing superdisintegrating agent CCS (5%) & various concentration of Sublimating agent Camphor (5, 10, 15 %) & ammonium bicarbonate (15%) was prepared. Water insoluble diluents such as microcrystalline cellulose and dicalcium phosphate were omitted from the study as they are cause an unacceptable feeling in the mouth. Among the soluble diluents, mannitol was selected as diluents considering its advantages. Table 2 shows that all the formulated tablets exhibited low weight variation. Hardness of the tablets are (2-3kg/cm^2)

and friability of the tablets are within the limit(>1%), Tablets with lower friability may not break during handling on machines. . The drug content of all the formulations was found to be between 98.02-99.02% which was within the acceptable limits. the disintegration time was found to be less than 42 seconds. The results shown in Table 2 reveal that sublimation of camphor from tablets resulted in faster disintegration. The low value of wetting time and disintegration time indicate that the porosity of tablets of batch F3 would be greater than batches F1,F2 & F4. The thickness of tablets varies from 3.1 to 3.2 mm. *In vitro* release studies were carried out using USP-type II tablet dissolution test apparatus paddle method at 37^0c±0.5 °C, taking 900 ml of pH-6.8 phosphate buffer dissolution medium. Speed of rotation of the paddle was set at 50 rpm. Aliquots of 5 ml were withdrawn after 1, 2, 3, 5, 10, 15 min and analyzed by U.V spectrophotometrically at 271 nm. The *in vitro* dissolution profile (Fig.1) indicated faster and maximum drug release from formulation F3. Formulation F3 prepared by sublimation of camphor from tablets showed release 97.23% drug at the end of 15 min.

Table No. 01: Formulation of Tramadol HCL mouth dissolving tablets

Ingredients	Formulation Code			
	F1	F2	F3	F4
Tramadol HCL	50	50	50	50
Camphore	10	20	30	---
ammonium bicarbonate	---	---	---	30
Croscarmellose sodium	10	10	10	10
Aspartame	05	05	05	05
Aerosil	02	02	02	02
Magnesium stearate	04	04	04	04
Talk	05	05	05	05
Mint flavor	02	02	02	02
Mannitol	112	102	92	92

*All quantities are in mg.

Table No. 02: Pre-compression Parameters of Formulation

Batch No.	Pre-compression Parameters				
	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's Index (%)	Hausner's ratio	Angle of repose(^{o})
F1	0.523	0.587	10.90	1.12	23^0
F2	0.535	0.599	10.68	1.11	24^0
F3	0.564	0.613	7.99	1.08	25^0
F4	0.544	0.595	8.57	1.09	22^0

Table No. 3.1: Post-compression parameters of Formulations

Batch No.	Post-compression parameters				
	*Weight variation	*Hardness (Kg/cm^2)	*Thickness (mm)	Friability (%)	Drug Content (%)
F1	199 ±1.56	2.3 ±0.2	3.2±0.02	0.81	98.04
F2	198 ±2.19	2.4 ±0.3	3.0±0.03	0.75	99.02
F3	197 ±2.08	2.1 ± 0.1	3.2±0.05	0.78	98.05
F4	199 ±1.90	2.3 ±0.4	3.1±0.04	0.80	98.02

*Value expressed as mean ±SD , n=3

Table No. 3.2: Post-compression parameters of Formulations

Batch No.	Post-compression parameters		
	*Wetting time (sec)	*Water absorption ratio (%)	*Disintegration time (sec)
F1	39 ±1.7	58.11 ±1.2	42 ±2.1
F2	35 ±1.2	69.89 ±1.4	39 ±1.5
F3	27 ±0.9	64.47 ±2.2	31 ±2.0
F4	35 ±1.6	59.00 ±1.7	38 ±1.2

*Value expressed as mean ±SD , n=3

Table No. 04: In vitro Drug release studies

Time (min)	% Cumulative drug release			
	F1	F2	F3	F4
0	0000	0000	0000	0000
1	29.82	31.53	35.22	32.45
2	35.73	38.44	45.12	39.27
3	59.43	61.33	66.87	62.78
5	65.48	67.35	69.54	68.85
10	70.21	72.88	78.99	72.90
15	87.25	91.37	97.23	89.33

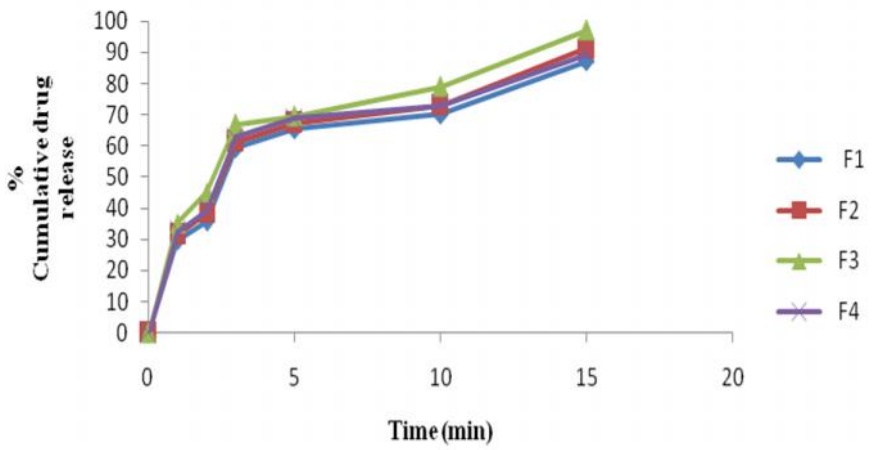

Fig. No. 01: In-vitro dissolution of Tramadol HCL mouth dissolving tablets of different batches

Conclusion

It can be concluded that the present investigation successfully formulated mouth-dissolving tablets of tramadol HCL with improved drug release profile. overall results suggests that the MDTs containing Camphore (F3) shows best results in terms of percent drug release, compressibility index, hardness and disintegration time. Thus MDTs may be developed for Tramadol HCl, for quick onset of action however further studies are required for the development of MDT of Tramadol HCl.

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