RESEARCH ARTICLE

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Formulation and Characterization of Taste Masked Mouth Dissolving Tablets of Tramadol HCl Using Different Approaches

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Abstract: To overcome difficulty in swallowing tablets or capsules, scientists have considerably dedicated their effort to develop novel drug delivery systems which enhance safety and efficacy of drug molecule and to achieve healthier patient compliance. One such approach is mouth dissolving tablets (MDT). The purpose of this research was to mask the intensely unpleasant taste of tramadol HCl by inclusion complexation, complexing with resin and solid dispersion to formulate mouth dissolving tablets of the taste-masked drug. Tablets were formulated by wet granulation method using excipients. All formulations were evaluated for dispersion time, wetting time, % friability, content uniformity and *in-vitro* dissolution rate. Formulations with Kyron T314 showed the least disintegration time and wetting time. *In-vitro* drug release study of taste masked tablet showed complete drug release within 15 minutes and successful masking of taste and rapid disintegration of the formulated tablets in the oral cavity.

INTRODUCTION

More than 50% of pharmaceutical products are orally administered for several reasons and undesirable taste is one of the important formulation problems that are encountered with such oral products. Taste of a pharmaceutical product is an important parameter governing compliance. Hence taste masking of oral pharmaceuticals has become important tool to improve patient compliance and the quality of treatment especially in paediatrics. [1]

Different methods have been suggested for masking of taste of bitter drugs, which includes, coating of drug particles with inert agents, taste masking by formation of inclusion complexes, use of ion exchange resin, molecular complexes of drug with other chemicals, solid dispersion system, microencapsulation, multiple emulsions, using liposomes, prodrugs and mass extrusion method. [1]

Difficulties with and resistance to tablet-taking and swallowing hard gelatin capsules are common in all patient groups and can exacerbate compliance problems and undermine treatment efficacy. Physical problems with swallowing (dysphagia) can occur at any age but are particularly prevalent in the elderly and those with dementia, whereas refusal to swallow is often encountered in geriatric, pediatric and psychiatric patients. [2]

Mouth dissolving tablets (MDT) can be defined as an oral solid dosage form which when placed on tongue it disintegrates rapidly, releasing the drug, which dissolves or disperses in the saliva and then swallowed. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down in to the stomach.

The purpose of the current study was to develop a novel taste masked mouth dissolving tablets of Tramadol HCl. In the present investigation, the bitter taste of tramadol HCl was masked by three different approaches-solid dispersion, inclusion complex and ion exchange resin so as to prepare "patient friendly dosage form". [3]

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Tramadol HCl is a centrally acting opioid analgesic structurally related to codeine and morphine used in the treatment of moderate to severe pain in diverse conditions. Combined with low dependence/abuse potential, it has proven to be of significant advantage over other agents, especially in the elderly. [4] Patients suffering from arthritis or neuralgia have to take the therapy for longer duration of time. In such cases, oral route is the preferred route. Thus, the problems like unpleasant taste and ease of swallowing need to be solved for tramadol HCl therapy.

MATERIALS AND METHODS

The drug, Tramadol HCl was procured from Yarrow chemicals, Mumbai. Kyron T314 was obtained as a gift sample from Corel Pharma Chem, Ahmedabad. PEG 4000, PEG 6000, sucrose, Polyvinyl Pyrollidone, Talc, Camphor were purchased from Yarrow chemicals, Mumbai. β-cyclodextrin was obtained from Qualigens Fine Chemical, Mumbai. Sodium starch glycolate (SSG) was obtained from National Chemical, Vadodara and MCC, lactose, magnesium stearate were obtained from Chiti chem corporation, Baroda. All chemicals used were of analytical reagent grade.

Calibration Curve of Tramadol HCl

Solutions of tramadol HCl (2, 4, 6, 8, 10 µg/ml) was prepared using phosphate buffer pH 6.8 and absorbance was measured using UV-Visible spectrophotometer (Shimadzu 1700, Japan) at 273 nm (Figure 1).

Preparation of Solid Dispersion by Solvent Evaporation Method

Sufficient quantity (3 to 4 ml) of acetone was selected as a solvent. Tramadol HCl was added and dissolved in it. Now different polymer (PEG 4000, PEG 6000 and sucrose) was added with trituration until all the solvent was evaporated and solid dispersion complex become dry. The prepared solid dispersion was passed through sieves No. 22. All the formulation was prepared as 1:1 ratio of drug to polymer.

Preparation of Inclusion Complex by Kneading Method

The β-cyclodextrin and Tramadol HCl (1:1 and 1:2 molar ratio) were weighed, 0.5 ml of hydroalcoholic mixture

Table 1: Composition of Different Batches of Tramadol HCl MDT

Ingredients*	Formulation					
	F1	F2	F3	F4	F5	F6
Tramadol HCl	50	50	50	50	50	50
PEG 4000	50	-	-	-	-	-
PEG 6000	-	50	-	-	-	-
Sucrose	-	-	50	-	-	-
β-CD	-	-	-	50	100	-
Kyron T314	-	-	-	-	-	50
Camphor	15	15	15	15	15	15
SSG	15	15	15	15	15	15
Lactose	57	57	57	57	32	57
MCC	57	57	57	57	32	57
Talc	4	4	4	4	4	4
Magnesium Stearate	2	2	2	2	2	2

*All quantities are expressed in mg. All batches contain 10% PVP in ethanol. In batch F1, F2 and F3 blends of solid dispersion were utilized. In batch F4 and F5 blend of β-CD was employed. In batch F6, blend of resin-drug complex was used

Table 2: Bitterness Evaluation by a Panel of 10 Healthy Human Volunteers*

Formulation Code	Number of Volunteers Rating the Preparation as				
	0	1	2	3	4
Pure drug	-	-	-	2	8
F1	-	-	-	4	6
F2	-	-	-	5	5
F3	-	-	1	5	4
F4	-	1	3	3	3
F5					
F6	1	5	3	-	-

* 0-no bitterness, 1-threshold bitterness, 2-bitter, 3-moderate bitterness and 4-strong bitterness

Table 3: Evaluation of Physicochemical Parameters of Tramadol HCl MDT

Formulation Code	Weight Variation (mg)±SD (n=3)	Hardness (kg/cm²) ±SD (n=3)	Thickness (mm)±SD (n=3)	Friability (%)±SD (n=3)	Drug Content (%)±SD (n=3)	Wetting Time (s)±SD (n=3)	*In-vitro* Dispersion Time (s)±SD (n=3)
F1	250±1.61	3.2±0.23	3.5±0.02	0.54±0.04	98.41±0.62	48±0.57	54±1.02
F2	245±1.32	3.4±0.29	3.2±0.06	0.50±0.01	98.53±1.08	52±0.57	65±0.89
F3	245±1.46	3.2±0.53	3.2±0.05	0.52±0.05	97.93±1.21	50±0.57	62±0.63
F4	250±1.42	3.1±0.28	3.5±0.01	0.62±0.04	98.45±0.9	47±0.57	55±0.7
F5	245±1.68	3.3±0.76	3.2±0.06	0.48±0.07	98.62±0.85	50±0.57	65±1.0
F6	245±1.46	3.1±0.52	3.2±0.03	0.60±0.03	99.78±1.05	45±0.57	54±0.89

(50:50) were added and the paste obtained was cold triturated in a mortar for 30 minutes, after which it was dried in the oven at 50°C to a constant mass, while the obtained precipitate was dried, triturated in the mortar and complexation yields were determined.

Preparation of Drug-Resin Complex by Batch Method

The batch process was selected for complexation, weighed quantity of Kyron T314 (as per 1:1, 1:2, 1:3) was allowed to swell for 90 min in a beaker containing 200 ml of distilled water. Then, tramadol HCl was added to it and stirred for 30 min. The mixture was filtered through Whatman filter paper. The residue was washed with 100 ml of deionized water and dried. The filtrate analyzed at 273 nm spectrophotometrically. Ratio 1:1 was considered for tablet preparation because it showed optimum dissolution and taste masking.

Preparation of Tramadol HCl MDT

The melt in mouth tablets of tramadol HCl were prepared using subliming agent camphor, sodium starch glycolate as super disintegrates, Lactose and MCC as a diluent, aspartame as sweetening agent, alcoholic solution of PVP (10% w/v) as binder and magnesium stearate with talc as a flow promoter. The composition of the each batch is shown in Table 1.

The raw materials were passed through a 100-mesh screen prior to mixing. The drug (blend) and other ingredients were mixed together and a sufficient quantity of alcoholic solution of PVP (10% w/v) was added and mixed to form a coherent mass. The wet mass was granulated using sieve no. 12 and regranulated after drying through sieve no. 16. Granules were dried in a tray dryer at 60°C for 30 min. resulting in localized drying. Granules were then blended with 2% talc, 1% magnesium stearate

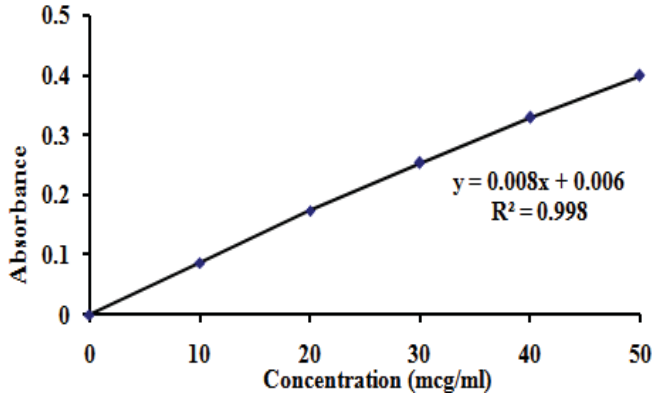

Figure 1: Standard curve of tramadol HCl in phosphate buffer pH 6.8

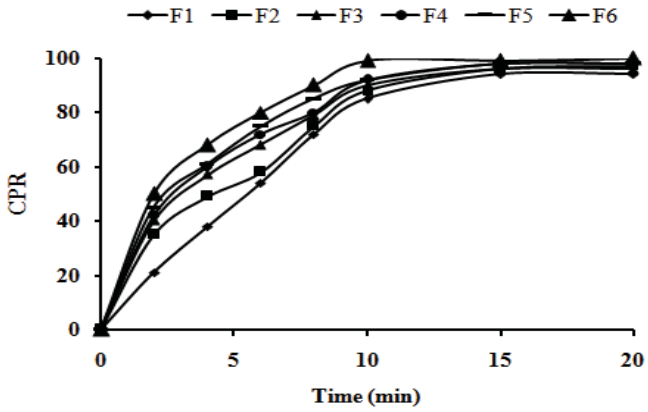

Figure 2: Dissolution profile of tramadol HCl MDT

and compressed into tablets using round tooling on a rotary tablet machine (Hardik Eng. Pvt. Ltd, Ahmedabad).

Evaluation of Prepared Tramadol HCl MDT Tablets

1. Weight variation

Randomly, twenty tablets were selected and weighed individually by using digital weighing balance. The average weight of the tablet was calculated. The percentage deviation of individual tablet from the value of average weight was calculated. Check that the tablet weight is within ±7.5% or not (according to USP tolerance limit for uncoated tablets). [5]

2. Hardness

The crushing strength of the tablets was measured using a Monsanto hardness tester (Rolex). Three tablets from each formulation batch were tested randomly and the average reading noted.

3. Thickness

Thickness of tablet was determined by using screw micrometer.

4. Friability

Twenty tablets were weighed and placed in a Roche friabilator (Electrolab). Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the following formula:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

5. Drug Content

An amount of the powder equivalent to 10 mg of tramadol HCl was dissolved in 100 ml of phosphate buffer pH 6.8, filtered, diluted suitably and analyzed for drug content at 273 nm using UV-Visible spectrophotometer (Shimadzu 1700, Japan).

6. Wetting Time

A piece of filter paper folded twice was placed in a Petri dish (Internal Diameter 9 cm) containing 9 ml of phosphate buffer pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted. [6]

7. *In-vitro* Dispersion Time

In-vitro dispersion time was measured by dropping a tablet in a 10 ml measuring cylinder containing 6 ml of phosphate buffer pH 6.8. [7]

8. Dissolution Study

In-vitro dissolution study was performed by using USP Type II Apparatus (Paddle type) (Electrolab model no. TDT 06P) at 50 rpm. Phosphate buffer pH 6.8, 900 ml was used as dissolution medium which maintained at 37±0.5°C. Aliquot of dissolution medium (5ml) was withdrawn at specific time intervals (2 min) and was filtered. The amount

of drug dissolved was determined by UV-Visible spectrophotometer by measuring the absorbance of the sample at 273 nm. [8]

Determination of Taste Masking Efficiency of Various Approaches

A panel of ten healthy human volunteers (age 20–25) was selected. The volunteers were asked to hold the tablet in oral cavity for 30 s and rate the taste on a scale from 0 to 4. Rinsing the mouth by distilled water and a gap of 30 min were applied between successive tests. Based on opinion of volunteers, the taste masking efficiency of various approaches was judged. [9]

RESULTS AND DISCUSSION

Complexation with ion exchange resin is a simple and efficient technique of masking the bitterness. The resin batch method was preferred because of its ease and convenience. Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. As the reaction is an equilibrium phenomenon, maximum efficacy is best achieved in batch process. Hence, the batch process is suitable for smaller particles. [10] Out of the three approaches selected, ion exchange resin Kyron T314 gave better taste masking. The drug: resin ratio of 1:1 was found to be optimum. Taste masking through inclusion complex was better than solid dispersion technique. However, satisfactory results were not obtained. The moderate bitterness value of the inclusion complex formulations was reported by the volunteers.

Kyron T314 is an ion exchange resin which is available for taste masking of bitter drug. Taste masking occurs by complex formation between drug and Kyron T314, which is insoluble in water but soluble in the stomach. Decomplexation occurs in the stomach and thus drug is released in the gastrointestinal tract. The *in-vitro* dispersion time and wetting time of F6 was also low in comparison to other formulation. F6 formulation also shows a good release profile as compared to other formulations (Figure 2). All the formulations exhibited low weight variation, thickness and hardness. Friability of tablet was found below 1% indicating good mechanical resistance. The drug content of all the formulations was found to be between 97.93-99.78% which was within the acceptable limits as per USP XXVII. [11]

CONCLUSION

Mouth dissolving tablets (MDT) of tramadol HCl are successfully prepared. Undoubtedly the availability of various technologies and the manifold advantages of MDT will surely enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect, good stability and its popularity in the near future. From the study, it was concluded that among the six trials formulation, F6 showed the maximum cumulative percentage drug release.

From the above study it was concluded that, taste masking by ion exchange resins was the best approach among the three approaches. Formulation F6 was concluded as an optimized formula due to its least dispersion time and good *in-vitro* release characteristics. Vacuum-drying technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulation of mouth dissolving tablets.

REFERENCES

1. Debunne V K Suhagiya, A N Goyani, R N Gupta. Taste masking by ion exchange resin and its new applications: a review. IJPSR, 1(4): 22-37, 2010.
2. Sajal Kumar Jha, P Vijayalakshmi, Roopa Karki, Divakar Goli. Formulation and evaluation of melt-in-mouth tablets of haloperidol. Asian J Pharm, 2(4):255-60, 2008.
3. Punit P Shah, Rajashree C Mashru. Development and evaluation of artemether taste masked rapid disintegratingtablets with improved dissolution using solid dispersion technique. AAPS, 9(2):494-500, 2008.
4. Raval S B. Formulation and evaluation of tramadol hydrochloride mouth dissolving tablet. Journal of Global Pharma Technology, 2(11):17-22, 2010.
5. Marshall K, Lachman N, Liberman H A. The theory and practice of industrial pharmacy. 3rd Ed, Varghese Publishing House, Mumbai, 66-69, 1987.
6. Yunxia B, Yorinobu Y, Kazumi D, Akinobu O. Preparation and evaluation of oral tablet rapidly dissolving in oral cavity. Chem Pharm Bull, 44:2121-2127, 1996.
7. Kimura S, Imai T, Otagiri M. Pharmaceutical evaluation of Ibuprofen syrup containing low molecular weight gelatin. J Pharm Sci, 81:141-144, 1992.
8. Kuchekar B S, Arumugam V. Fast dissolving tablets. Indian J Pharm Edu, 35:150, 2001.
9. Ashwini R Madgulkar, Mangesh R Bhalekar and Rahul R Padalkar. Formulation design and optimization of novel taste masked mouth-dissolving tablets of tramadol having adequate mechanical strength. AAPS Pharm Sci Tech, 10(2):574-82, 2009.
10. Padalkar. An approach towards taste abatement of roxithromycin. IJPRD, 7, 2009.
11. Garala K C, Patel J M, Dhingani A P, Dharamsi A T. Preparation and evaluation of agglomerated crystals bycrystallo-co-agglomeration: An integrated approach of principalcomponent analysis and Box–Behnken experimental design. International Journal of Pharmaceutics, 452:135–156, 2013.

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