

Formulation, Evaluation and Optimization of Fast dissolving tablet containing Tizanidine Hydrochloride

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Abstract:

Tizanidine HCl is a centrally acting α -2 adrenergic agonist muscle relaxant. It is slightly bitter in taste. In the present study an attempt has been made to prepare bitterless fast dissolving tablet of Tizanidine Hydrochloride using Eudragit E 100 as a taste masking agent. Mass extrusion was the technique used for preparing taste masked granules. The tablet was prepared with three super disintegrants e.g. sodium starch glycolate, croscarmellose sodium and crospovidone. The blend was examined for angle of repose, bulk density, tapped density and Hausner's ratio. The tablets were evaluated for hardness, drug content and friability and disintegration time. The disintegration in oral cavity was also tested and was found to be 22 sec. Other tablets were prepared by using camphor as sublimating agent. It was concluded that tablets prepared by addition of superdisintegrant has less disintegration time than those prepared by sublimation method.

Keywords: Fast dissolving tablet, Tizanidine HCl, Super disintegrating agents, Mass extrusion.

Introduction and Experimental

The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric population, as well as other patients who prefer the convenience of easily swallowable dosage forms. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva¹.

Tizanidine HCl is chemically 3-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-8-Thia-7,9-diazabicyclo [4.3.0] non a-2,4,6,9- tetraen-2-amine hydrochloride. It is a centrally acting α -2 adrenergic agonist. It is used to treat the spasms, cramping, and tightness of muscles caused by medical problems such as multiple sclerosis, spastic diplegia². 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 receptor³. Taste masked granules of bitter drugs can be prepared by using Eudragit E100 [cationic copolymer based on dimethyl amino ethyl methacrylate.] 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 product⁴.

In present study an attempt has been made to prepare taste masked granules of Tizanidine HCl. Taste masking of Tizanidine HCl was carried out by using Eudragit E 100 (Mass extrusion method). These taste masked granules or complex was further formulated into the mouth-dissolving tablet by direct compression method using sodium starch glycolate, crosscarmellose sodium and crospovidone as the superdisintegrants.

Materials and Methods

Tizanidine HCl was obtained as a gift sample from Blue Cross Pvt. Ltd. Nashik. Sodium starch glycolate, cross carmellose sodium, crospovidone and Eudragit E 100 were obtained as gift samples from Unichem Pvt. Ltd. Mumbai.

Preparation of drug-Eudragit e 100 taste masked granules by mass extrusion technique⁴:

Fixed amount of drug was mixed with different amount of powdered Eudragit E 100 i.e. they were mixed at 1:1, 1:2, 1:3 and 1:4 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 E 100 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.

Evaluation of formulated tablet

Tablet Hardness⁵

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into halves by compression. It was measured using a tablet hardness tester (Pfizer Hardness Tester).

Weight Variation Test⁵

Weight variation test is done by weighing 20 tablets individually; calculating the average weight and comparing the individual tablet weight to the average.

Friability⁵

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the Purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not loose more than 1% of their weigh.

Content Uniformity⁷

Five tablets were powdered and the blend equivalent to 4 mg of Tizanidine HCl was weight and dissolved in suitable quantity of pH 1.2 solution. Solution was filtered and diluted and drug content analyzed spectrophotometrically at 228 nm.

Disintegration Time⁵

The disintegration time of tablet was measured in water (37°C) according to USP disintegration test apparatus. Three trials for each were performed

Wetting Time⁶

The method reported by Yunixia et.al.was followed to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small petry dish (ID6.5cm) containing 6ml of pH6.8 (simulated saliva fluid). A tablet was put on the paper and the time for complete wetting was measured. Three trials for each were performed. Data revealed in table no. 2

***In-Vitro* Release Profile of Formulated Tablets**

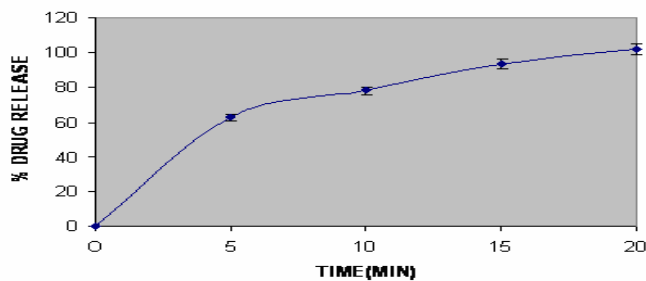
The dissolution of Tizanidine HCl tablets was carried out in basket type dissolution apparatus. The dissolution medium was 900 ml of gastric simulated fluid (without enzyme) pH 1.2 maintained at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$. The basket was rotated at 50 rpm for 20 min. The sample of 10 ml was withdrawn after every 5 min. and its absorbance was measured at 228 nm.

Table 2: Evaluation of batch B1-B9 and C1-C3

Formulation	Hardness (kg/cm ²) ±S.D	Friability (%)	Weight variation Test	Wetting time(sec) ±S.D	Thickness (mm) ±S.D	Drug Content (%)	Disintegration time(sec)
B1	3.13±0.005	0.44	Passes	46.66±0.03	2.24±0.01	99.95	30.33±0.01
B2	3.46±0.01	0.28	Passes	39.66±0.02	2.22±0.01	99.00	20.66±0.01
B3	4.00±0.01	0.2	Passes	22.66±0.05	2.20±0.02	101.21	10.66±0.02
B4	3.76±0.005	0.48	Passes	40.66±0.03	2.21±0.05	100.50	20.66±0.05
B5	3.96±0.01	0.36	Passes	36.33±0.05	2.21±0.02	100.07	16.00±0.02
B6	4.03±0.01	0.28	Passes	22.00±0.01	2.20±0.01	98.95	12.22±0.01
B7	3.96±0.01	0.52	Passes	43.33±0.06	2.22±0.03	99.90	23.66±0.01
B8	4.03±0.01	0.24	Passes	34.33±0.05	2.20±0.05	100.12	15.66±0.05
B9	4.06±0.005	0.16	Passes	19.66±0.06	2.19±0.01	101.10	10.33±0.01
C1	4.4±0.01	0.15	Passes	3.15±0.06 (min)	2.21±0.05	99.95	2.35±0.01
C2	3.1±0.005	1.96	Passes	2.20±0.05 (min)	2.24±0.01	100.25	1.68±0.02
C3	3.4±0.01	0.96	Passes	2.0±0.05 (min)	2.22±0.03	100.12	1.31±0.02

Optimization of Formula

From the above formulations the optimized formula from Drug: Eudragit E100 granules; tablets was selected, depending upon the several factors such as less disintegrant concentration, less disintegration time and fast dissolution rate. Dissolution profile given in figure no. 1

Figure No. 1: Dissolution profile of batch B9 (disintegrant addition method).

Stability Studies

The stability studies of formulated tablets were carried out at 40°C and 75% RH using a stability chamber for one month. The effects of temperature and time on the physical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The different parameters that were studied are disintegration time, hardness, friability, drug content and dissolution rate.

Formulation of [bitterless] mouth dissolving tablet of drug: Eudragit E 100 granules by sublimation method⁸.

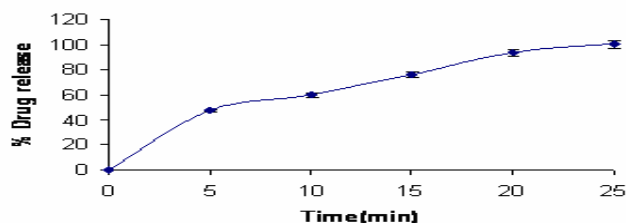
The second approach used in the preparation of fast dissolving tablet of Tizanidine Hcl-Eudragit E 100 granules was sublimation method. In this study mouth-dissolving tablet was prepared by using camphor in different ratios, as it sublimates readily. Camphor, which was used as a subliming agent, is nontoxic. Three formulations of drug Eudragit E100 granules containing camphor in different proportions were prepared by using mannitol as a diluent. It was compressed on single punch tablet machine using 8 mm punches to get tablet of 130 mg weight.

Evaluation of tablet^{5,9}.

Tablets prepared by sublimation method were evaluated for weight variation, hardness, content uniformity, wetting time, disintegration time, friability and in-vitro dissolution test. Dissolution profile of optimized batch given in figure no. 2

Comparison of tablets prepared by disintegrant addition and sublimation method.

The tablets prepared by both method i.e. disintegrant addition and sublimation method were compared using different parameters like *in-vitro* disintegration time, wetting time, friability and % drug release.

Figure No. 2: Dissolution of batch C3 (sublimation method).

Results and Discussion

Eudragit E100 was selected for the taste masking of Tizanidine Hcl. The taste-masked granules of drug and Eudragit E100 were prepared by simple mass extrusion technique using syringe. The drug content was found to be 88% in the granules.

The physical properties like bulk density, angle of repose and the shape of complex was found to be 0.7843 g/cm^3 , 27.54° and irregular respectively, Hausner's ratio was found to be 1.02. Above data indicate granules have good flowability. Nine formulations of drug Eudragit E100 granules (B1-B9) were prepared by varying the concentration of superdisintegrant.

Tablets were prepared using direct compression. Tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variation as per pharmacopoeial specification. The drug content found in the range of 98.95-101.21% (acceptable limit) and the hardness of the tablet was found between $3.13 - 4.06 \text{ kg/cm}^2$. The tablet thickness was found to be 2.19-2.24 mm, friability of tablet was found below 1% indicating good mechanical resistance. The wetting time of formulated tablets was found in the range of 19.66- 46.66 sec and disintegration time of all batches was found in the range of 10.33-30.33 sec.

Batch B-9 was selected as optimized batch containing crospovidone as super disintegrant in 5% concentration. It has less disintegration time of 10.33 sec. The dissolution study was carried out and 100.57% of drug release was occurring within 20 min.

The stability study of optimized batch was carried out at 40°C -75% RH. The tablets were found to be stable at such condition and other parameters were found to be unaffected.

On the other hand tablets formulation prepared with camphor (10%, 20%, 30%), the formulation C3 was chosen. This formulation disintegrated faster, 1.31 min., compared to C1 and C2 which showed disintegration time of 2.35 min. and 1.68 min. Hardness of all formulation was found in the range of $3.1 - 4.4 \text{ kg/cm}^2$. All

formulation passed the weight variation test. The wetting time of all formulation was found in the range of 2-3.15 min. The percent drug release was found to be 100.15% in 25 minutes. The friability problem occurs with the formulation prepared by sublimation method, tablets were more friable, the friability of batch C3 was found to be 0.96%.

Both formulation i.e. B9 & C3 showed good bioavailability. The formulation B9 was found to be best as this formulation showed less disintegration time, good hardness, short wetting time and good content of active ingredient.

Comparison of tablets prepared by superdisintegrants addition and sublimation method revealed that superdisintegrant addition method was superior to sublimation method.

It was concluded that fast dissolving tablet of Tizanidine Hcl can be successfully prepared by super disintegrant addition and sublimation method and super disintegration method was found to be superior to that of sublimation method. Taste masking with Eudragit E 100 was also found to be effective.

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