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DESIGN AND DEVELOPMENT OF FAST DISSOLVING TIZANIDINE TABLETS BY SUBLIMATION TECHNIQUE: FOR THE EFFECTIVE TREATMENT OF MUSCLE SPASM

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ABSTRACT

In the present invention Fast dissolving tablets of Tizanidine were prepared for the immediate and effective treatment of muscle spam by adopting sublimation method. Formulations were evaluated for precompressional parameters such as angle of ripose, % compressibility and hausner's ratio. Tablets were also subjected to post compress ional analysis for the parameters like hardness, friability, thickness, wetting time, water absorption ratio ,in-vitro disintegration time and in-vitro dissolution study. The results obtained showed that quantity of camphor is significantly affecting the response variables. Stability study carried out as per ICH guidelines for three months and results reveled that upon storage disintegration time of tablets decreased significantly($p<0.05$)

KEYWORDS: Tizanidine, fast dissolving tablets, camphor, crospovidone**.**

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INTRODUCTION

Fast dissolving tablets are a relative novel dosage technology that involves the disintegration or dissolution of the dosage form into a solution or suspension in the mouth without the need for the water[1-5.] The dosage form begins to disintegrate immediately after coming in contact with saliva, with complete disintegration normally occurring within 30-50 s after administraton[6].

Fast dissolving tablets are designed for the purpose of improving patient acceptance and compliance. A survey of 6158 GP patients conducted in Norway indicated that approximately 26% of all patients do not take their prescribed medication as they encounter problems when swallowing conventional tablets.

Tizanidine hydrochloride is centrally acting α-2-adrenergicagonist. Tizanidine HCL is a white to of white, fine crystalline powder, which is odourless, or with a faint characteristic odour. Tizanidine is slightly soluble in water and methanol, solubility in water decreases as the pH increases. Its chemical name is 5-chloro-4-(2imidazolin-2ylamino)-2,1,3-benzothiodiazole hydrochloride Its molecular weight is 290.2 and it is used as muscle relaxant with dose of 2 to 4 mg and its half life is 2.54 hrs. Hence in the present work we planned to prepare Tizanidine HCl fast dissolving tablets by sublimation method

MATERIALS AND METHODS

Tizanidine gift sample was obtained from AFD Lab Bangalore , cros povidone gift sample from Maple Biotech Pvt. Ltd Pune. Camphor, sprayed dried lactose, talc, magnesium stearate, aerosil were purchases from S.D Fine Chemicals Mumbai. All other ingredients used were of pharmaceutical grade.

Preparation of tablets

Tizanidine 4mg was taken and then it was mixed with sprayed dried lactose, superdisintegrant and different concentrations of camphor (1%, 2%, 3%, 5% and 10%) in a plastic container. Magnesium stearate, aerosil and talc were passed through sieve no. 60 mixed and blended with initial mixture in the plastic container followed by direct compression of the blend. After compression the tablets were collected and vacuum dried at 60°C in vacuum drier (Lab care Bangalore) until a constant weight of tablet was obtained to ensure the complete

removal of sublimable component to make the tablet porous (**Table 1and 2**).

Evaluation of tablets

Tablets were evaluated for hardness, friability, weight variation, thickness, disintegration time, wetting time, water absorption ratio and stability study[7]. The Pfizer hardness tester and Roche friabilator were used to test hardness and friability loss respectively. In weight variation test, 20 tablets were selected at random and average weight was determined using a electronic balance (Shimadzu,AX 200, Japan). Tablets were weighed individually and compared with average weight. Disintegration time was determined using USP Tablet disintegration test apparatus (ED 21, Electro lab, Mumbai) using 900 ml distilled water at room temperature. Thickness of the tablets was determined by using dial caliper (Mitutoya, model CD-6 CS Japan), wetting time study, a piece of tissue paper folded twice was kept in a culture dish containing 6 ml of distilled water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the tablet was recorded as the wetting time. In water absorption ratio study, the same procedure without amaranth was followed. The wetted tablets were weighed and the water absorption ratio, R, was calculated according to the following equation.

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

Where, Wb and Wa are the weights of the tablets before and after study.

For drug content analysis, a total 10 tablets were weighed and powdered. The powder equivalent to 4mg of Tizanidine was taken and dissolved in PH 6.6 buffer. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV 1700 Shimadzu Corpn Japan) at 320 nm. In-vitro dissolution of Tizanidine from tablets was monitored by using 900 ml of pH 6.6 buffer at 37 ± 0.5^{o}C at 100 rpm using programmable dissolution tester (Paddle type, model TDT- 08 L, Electrolab USP, India). Aliquots were withdrawn at 1 min time intervals and were replaced immediately with same volume of fresh buffer medium. Aliquots, following suitable dilutions were assayed spectrophotometrically at 320 nm. The stability study of the tablets was carried out according to ICH guidelines by storing the tablets in stability chamber (Lab- care, Mumbai) at 40 ± 2^{o} c / 75 ± 5 % RH for 3 months. The stability studies results are shown in **table 5**.

RESULTS AND DISCUSSIUON

Since, the flow properties of the powder mixture are important for the uniformity of mass of the tablets, the flow of the powder mixture was analyzed before compression into tablets. The values of precompressional parameters were within prescribed limits as per USP XXVII and indicated good free flowing properties. The results are shown in **Table 3**. The postcompressional parameters results are shown in **Table 4**. In all the formulation the hardness test indicates good mechanical strength. Hardness of the tablets decreased with increase in the amount of sublimable component[8]. Friability of all formulations was less then 1%, which indicates that the tablets had a good mechanical resistance. Drug content was found to be high (≥ 99.5%) and uniform in all the formulations. The tablet thickness was found to be 3.58 – 3.95 mm. The weight variation results reveled that average percentage deviation of 20 tablets of each formula was less than ± 7.5 %, which provides good uniformity in all formulations. The disintegration time of the tablets decreased significantly with increase in the concentration of subliming agent. The tablet prepared by sublimation technique rapidly exhibits high pores and disintegrates the tablets rapidly. It may be due to their lowest hardness and maximum porous structure was responsible for faster water uptake, hence it facilitates wicking action of crospovidone in bringing about faster disintegration[9]. Wetting time of tablets was decreased with the increase in the concentration of the subliming agent[10]. Water absorption ratio was found in the range 85.55 – 89.34. The dissolution of Tizanidine from the tablets is shown in the **fig1**. The results were compiled in **Table 5**. Dissolution of drug from tablet containing highest subliming agent were quicker then other formulations. It may be due to the highest porosity, lowest hardness and disintegrating property of MCC, which leads to faster water uptake hence it facilitates wicking action of crospovidone in bringing about the faster disintegration and dissolution. The stability studies results revealed that decrease in the disintegration and wetting time was observed in all the formulations. Since during sublimation method tablets were exposed to six hours at 60^{0} C only, where as 90 days and 45^{0}C were used during stability studies. The long storage of 90 days at 45^{0}C might have removed the trace amount of subliming agent.

CONCLUSION

The results of disintegration time, wetting time and dissolution rate revealed that the amount of subliming agent significantly effect the dependent variables like disintegration time, wetting time and dissolution rate. Thus it is concluded that fast dissolving tablet can be prepared with a view of obtaining faster action of the drug for the effective treatment of muscle spasm and advantageous in comparison to the currently available conventional formulations. With the adopted sublimation

technique, an optimum point can be reached in the shortest time with minimum efforts and this technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulation of fast dissolving tablets

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Table 1: Composition of fast dissolving tablets

Ingredients (mg/tab)	T1	T2	T3	T4	T5
Tizanidine	4	4	4	4	4
Spray dried Lactose	98	96.5	95	92	84.5
Aspartame	3	3	3	3	3
DC-MCC	30	30	30	30	30
Crospovidone	6	6	6	6	6
Camphor	1.5	3	4.5	7.5	15
Magnesium stearate	1.5	1.5	1.5	1.5	1.5
Talc	3	3	3	3	3
Aerosil	3	3	3	3	3

Table 2: Tablet weight before Sublimation (BS) and after Sublimation (AS)

Formulation	Tablet Weight	
	BS	AS
T1	150 (0.28)	148.5 (0.44)
T2	150 (0.48)	147.0 (0.90)
T3	150 (0.92)	145 .5(0.55)
T4	150 (1.32)	142.5 (1.20)
T5	150 (1.32)	135.0 (1.35)

Table 3: Pre-compressional parameters of powder blend

Formulation	Parameters		
	Angle of repose (θ) (± SD), n=3	Compressibility (%) (± SD), n=3	Hausner's ratio (± SD), n=3
T1	20.52 (0.32)	11.52 (1.29)	1.32 (0.08)
T2	24.20 (0.58)	10.21 (1.20)	1.24 (0.04)
T3	21.22 (0.82)	12.01 (0.90)	1.29 (0.08)
T4	23.32 (0.29)	10.38 (0.78)	1.05 (0.06)
T5	22.37 (0.52)	10.39 (1.34)	1.55 (0.09)

Table 4: Post-compressional parameters of tablets

Parameters	T1	T2	T3	T4	T5
Hardness (kg/cm^2) ± SD, n=6	4.60 ±0.46	4.46 ±0.44	4.24 ±0.44	4.00 ±0.45	3.90 ±0.49
Friability (% w/w) ± SD, n=10	0.44 ±0.03	0.37 ± 0.05	0.30 ±0.06	0.31 ±0.04	0.40 ±0.04
Thickness (mm) ± SD, n=4	3.95 ±0.090	3.87 ±0.082	3.58 ±0.070	3.82 ± 0.080	3.75 ±0.048
Weight variation ± SD, n=10	150 ± 1.55	151 ±1.12	152 ±1.30	151 ±1.59	150 ±0.55
Wetting time (Sec) ± SD, n=6	65 ±3.20	55 ±1.50	33 ±3.20	25 ±2.50	22 ±3.20
Water absorption ratio (%) ± SD, n=6	85.55 ±0.66	89.44 ±0.72	89.74 ±0.95	88.27 ±0.69	87.90 ±0.66
In-vitro disintegration time (Sec) ± SD, n=6	52 ±8.00	45 ±5.00	26 ±2.00	17 ±3.00	14 ±1.00
Drug content (%) ± SD, n=6	99.50± 1.20	101.0± 1.50	100.5± 2.00	102.10 ± 3.50	101.30± 2.0

Table 5: Dissolution data of Tizanidine tablets

Formulation	Percent drug release / Time in Min.						
	0	5	10	15	20	25	30
T1	0	27.55	39.18	49.5	60.65	75.18	81.92
T2	0	32.12	40.15	50.3	68.12	79.55	87.44
T3	0	34.15	43.61	53.33	71.56	82.34	89.56
T4	0	37.15	45.62	55.10	72.50	85.35	94.55
T5	0	40.00	50.15	58.90	82.20	89.50	99.56

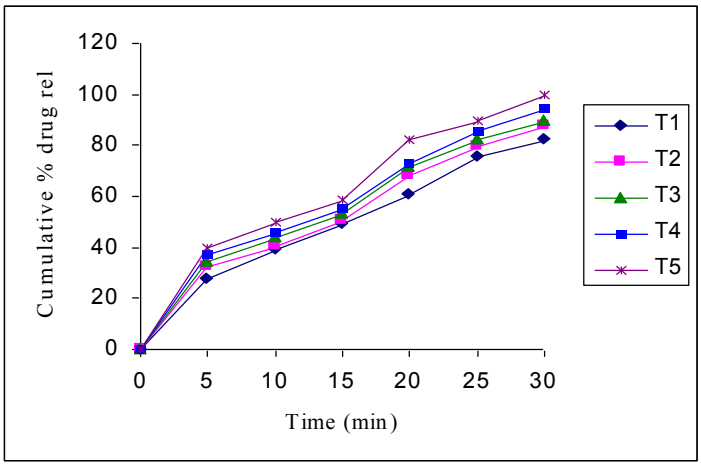

Figure1: Dissolution profile of Tizanidine tablet

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