Formulation and Evaluation of Fast Disintegrating Tablets of Muscles Relaxants Using Different Super Disintergents

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ABSTRACT

Tizanidine hydrochloride is a short-acting drug for the management of spasticity. Tizanidine hydrochloride is an agonist of 2-adrenergic receptor sites and presumably reduces spasticity by increasing presynaptic inhibition of motor neurons.The aim of the research was to formulate the fast dissolving tablets of Tizanidine hydrochloride, Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing, attempt was been made to prepare fast dissolving tablets of Tizanidine hydrochlorideusing super disintegrants like sodium starch glycolate and croscarmellose sodium and the prepared granules were subjected D.C method. The granules thus prepared were evaluated for hardness, friability, weight variation, in vitro disintegration time and in vitro dissolution study. Compatibility of the drug and the excipients were studied by FTIR spectroscopy ,from the results obtained no interaction between the drug and excipients were observed .From this study it was concluded that fast dissolving tablets of Tizanidine hydrochloride prepared from three different super-disintergrants enhanced dissolution will lead to improved bioavailability, improved the effectiveness of Tizanidine hydrochloride.

Keywords: Tizanidine hydrochloride, super disintegrates and fast disintegrating tablets.

INTRODUCTION:

Fast-dissolving tablets are becoming popular as novel delivery systems for drug administration. They are more convenient for children, elderly patients, patients with swallowing difficulties, and in the absence of potable liquids.It is one of the most desirable formulation for the elderly as it is easy to swallow easy to handle. Taking these requirements into consideration, attempts have been made to develop a fast-disintegrating tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity.

Disintegrating agents are the substances routinely included in the tablet formulations to aid in the break-up of the compacted mass into the primary particles to facilitate the dissolution or release of the active ingredients when it is put into a fluid environment. They enhance moisture penetration and dispersion of the tablet matrix. The major function of disintegrants

is to oppose the efficiency of the tablet binder and physical forces to act under compression to form the tablet. Recently new materials termed as “superdisintegrants” have been developed to improve the disintegration processes. Superdisintegrants are another version of super-absorbing materials with swelling properties as required. These materials swell quickly and are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Superdisintegrants are generally used at a low quantity in the solid dosage form, typically 1 - 10 % by weight relative to the total weight of the dosage unit. Generally, one gram of superdisintegrant absorbs 10-40 g of water or aqueous medium. After absorption, swelling pressure and isotropic swelling of the superdisintegrant particles create stress concentrated areas where a gradient of mechanical properties will exist due to which whole

structure will break apart.

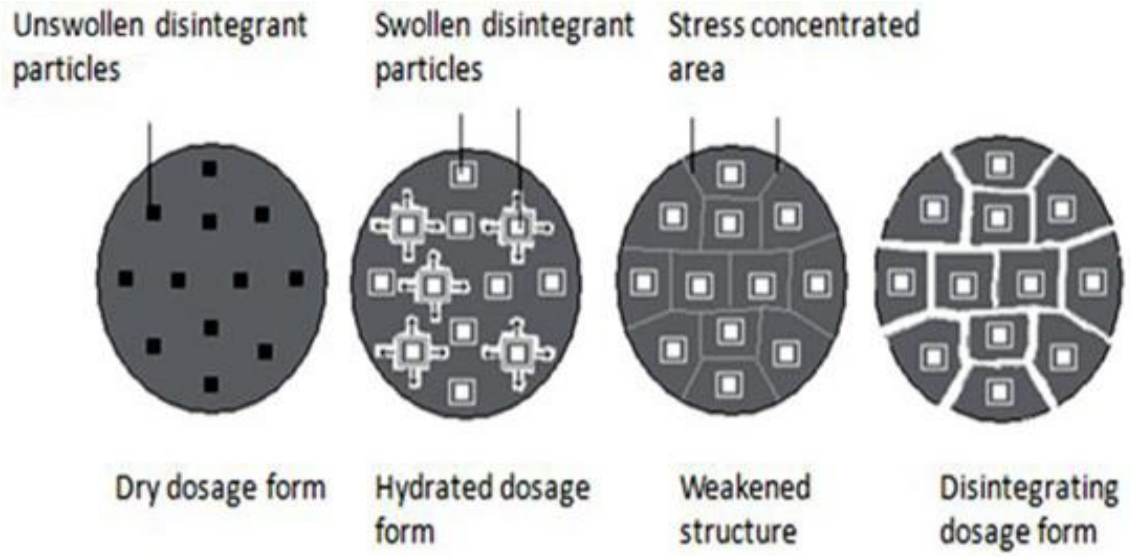

Figure 1: Superdisintegrants breaking the tablet structure

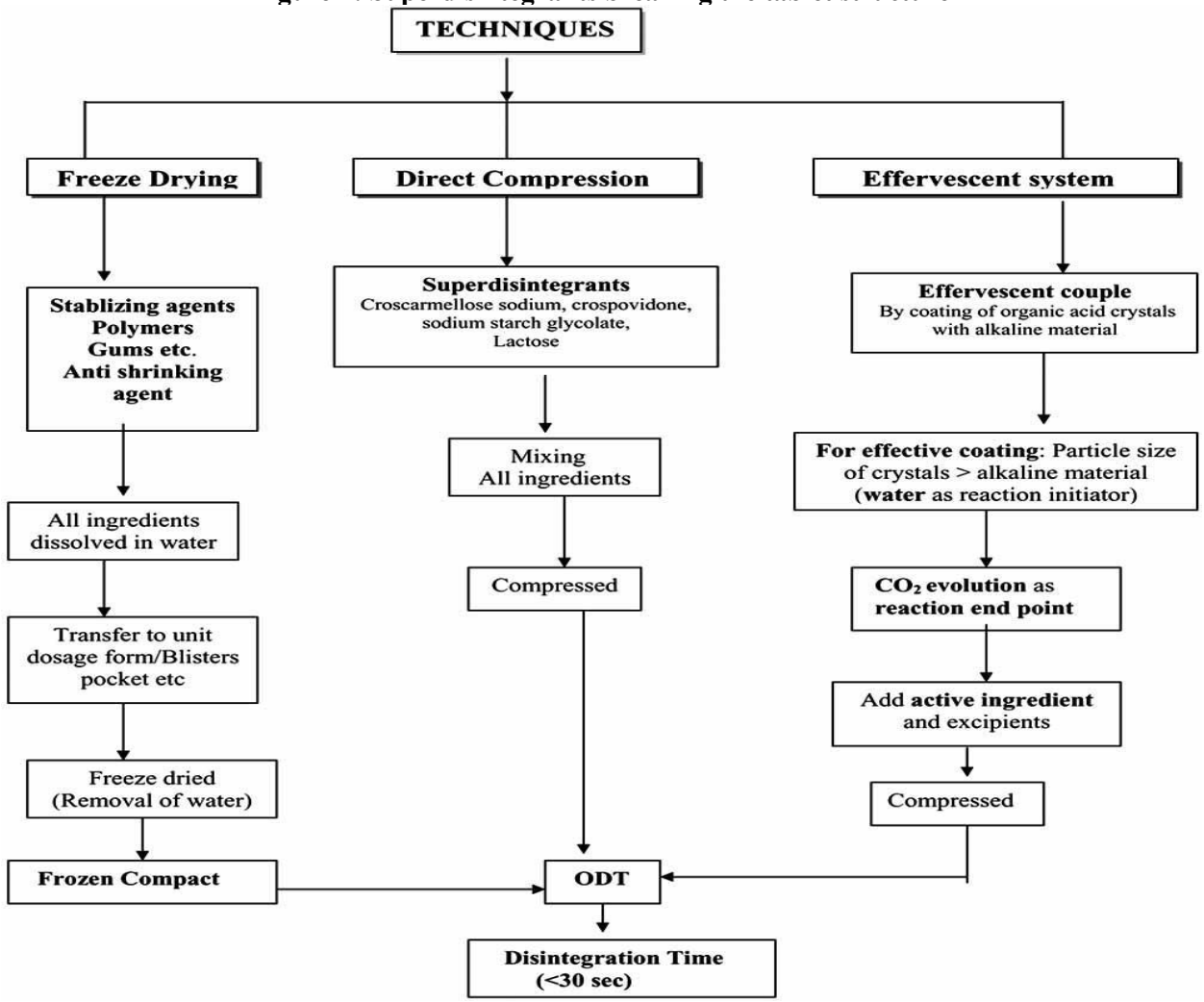

Figure 2: Manufacturing techniques for FDTs

MATERIALS AND METHODOLOGY:

Tizanidine Hydrochloride wasobtained from Sun pharma Mumbai croscarmellose sodium.sodium starch glycolate was gift sample from Astra Zeneca Bangalore and other chemical obtained from laboratory.

Formulation of Tizanidine HCL Fast Dissolving Tablets:

Method for preparationof FDTs:

Tablets containing 4 mg of Tizanidine Hydrochloride were prepared by direct compression technique. The drug and all other excipients, except sodium stearyl fumarate were previously sieved through a 60 mesh were accurately mixed for 15 min by using a poly bag. The resulting mixture was mixed with sodium stearyl fumarate and combined for mixing, up to 5 min. The mixer was compressed by using 10mm concave punches on sixteen station rotary tablet compression machine.

Table1: General composition of formulation prepared by direct compression method

Formula	Drug	SSG	CMS	Microcrystalline cellose	Mannitol	Aspartame	Sodium stearyl fumarate	Talc
F1	4mg	4mg	-	30mg	56mg	4mg	1mg	1 mg
F2	4mg	6mg	-	30mg	54mg	4mg	1mg	1 mg
F3	4mg	8mg	-	30mg	52mg	4mg	1mg	1mg
F4	4mg	10mg	-	30mg	50mg	4mg	1mg	1 mg
F5	4mg	12mg	-	30mg	48mg	4mg	1mg	1 mg
F6	4mg	-	4mg	30mg	56mg	4mg	1mg	1 mg
F7	4mg	-	6mg	30mg	54mg	4mg	1mg	1 mg
F8	4mg	-	8mg	30mg	52mg	4mg	1mg	1 mg
F9	4mg	-	10mg	30mg	50mg	4mg	1mg	1 mg
F10	4mg	-	12mg	30mg	48mg	4mg	1mg	1 mg

Estimation of Tizanidine Hydrochloride:

Development of calibration curve for Tizanidine hydrochloride:

Preparation of Standard Stock Solution:

10 mg of Tizanidine hydrochloride was accurately weighed and transferred in to 10 ml volumetric flask. The drug was then dissolved and diluted up to the mark with 6.8 pH buffer to get a concentration of 1000 µg/ml of stock solution I.

Preparation of working standard solutions:

From the stock solution I pipette out 2 ml and transfer it into 100 ml volumetric flasks and diluted up to the mark with6.8 pH buffer to get a concentration of 20 µg/ml of stock solution II. Now from the stock solution II aliquots were pipette out 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 ml and transferred into 10 ml volumetric flasks and diluted up tothe mark with6.8 pH buffer to get concentration of 2, 4, 6, 8, 10 and 12 µg/ml respectively.The absorbance of the solutions was measured at λ_{max}228nm.

Drug to Polymer Compatibility Study's:

IR spectrum of pure drug and other excipients were recorded using FTIR spectrophotometry.

Pre-Compression Parameters:

Angle of Repose: The angle of repose is the constant, three-dimension angle (relative to horizontal base) assumed by a cone like pile of material formed by any of several different methods. When the angle of repose exceeds 50degrees, the flow is rarely accepted for manufacturing purpose.

Bulk Density: The bulk density was determined by transferring the accurately weighed sample of powder to the graduate cylinder. The initial volume and weight were noted. Ratio of weight of the sample was calculated by using the following formula.
Bulk Density =Mass /Bulk volume.

Tapped Density: Weighed powder sample was transferring to a graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (100). The tapped density was determined by the following formula.
Tapped Density =Mass/Tapped volume.

Percentagecompressibility: Based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by the following formula
% Compressibility=Tapped Density-Bulk density×100/ Tapped density.

Hauser's Ratio: It is measured by the tapped density to bulk density.
Hauser's Ratio= Tapped density/Bulk density

Post Compression Parameters:
Tablet thickness:
Randomly 5 tablets were taken from each formulation trial batch and their thickness was determined by using screw gauge.

Weight Variation Test:
20 tablets were randomly selected from each formulation trial batch and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight.

Measurement of Tablet Hardness:
Hardness of 10 tablets was found using Monsanto hardness tester, mean and standard deviation were computed and reported. It is expressed in kg/cm ^{2}

Friability:
10 tablets were weighed and placed in Roche friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. The Friabilator was operated at 25 rpm for 4 mins. After 100 revolutions, tablets were removed, deducted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

Disintegration Time:
The test was carried out on the 3 tablets using the apparatus specified in USP distilled water at 37 ^{0} C ± 2 ^{0} C was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Wetting Time:
A sample of the final tablet was placed in a petri dish (10 cm in diameter) containing 10 ml water at room temperature. The wetting time is the time necessary for the complete wetting of the tablet is noted.

In Vitro Dissolution:
Freshly prepared 0.1N HCl of 900 ml was placed in each dissolution vessels of dissolution test apparatus (USP, II paddle method). The tablets were placed in the dissolution medium. The temperature of the dissolution medium was maintained at 37± 0.5^{0}C and the paddle was rotated at 50 rpm. 5 ml samples were withdrawn. The sample volume was immediately replaced with the same volume of fresh media as when a sample was taken. The samples withdrawn were filtered, diluted and estimated spectrophotometrically at 228 nm.

Water absorption ratio:

Apiece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper and time required for complete wetting was measured. The wetted tablet was then weighed.Water absorption ratio,R was determine dusing following equation.

$R=100\ (W_a - W_b)/W_b$

Where, W_b – weightoftabletbeforeabsorption

W_a – weightoftabletafterabsorption

Three tablets from each formulation were tested. Average and standard deviation were determined.

Uniformity of drug content:

Ten tablets from each batch were weighed accurately and powdered. An amount of powder equivalent to 4mg of the drug was transferred into a 25ml volumetric flask. The volume was made with 6.8 pH phosphate buffer and sonicated for 10 min. The resulting solution was filtered and assayed at 228 nm using spectrophotometer and drug content per tablet was determined.

RESULT AND DISSCUSSION:

Fig No 3 :FTIR spectra of pure drug

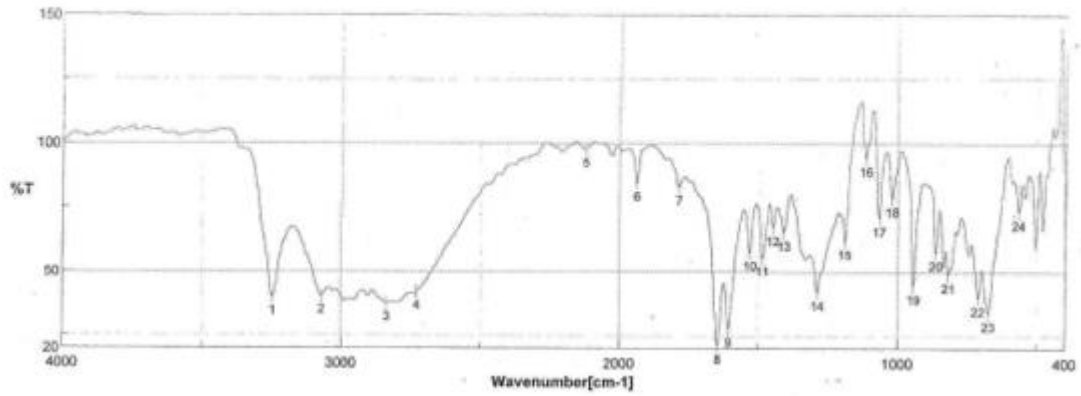

Fig No 4:FTIR spectra of pure drug and excipients.

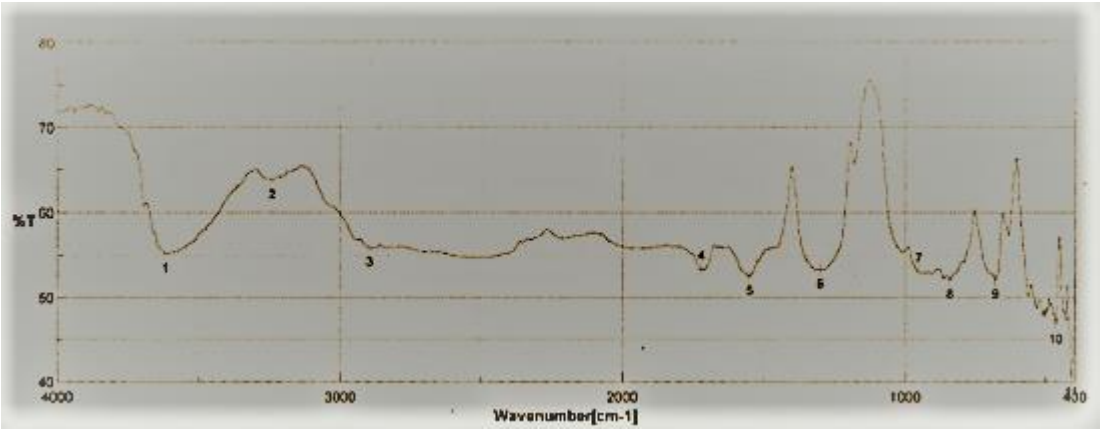

Table No.2 Data for pre-compression parameters.

Formulations	Angle of repose Ɵ	Bulk Density (g/cc)	Tapped Density (g/cc)	% Carr's index	Hausner's Ratio %
F1	21.5± 0.270	0.481±1.295	0.509±0.915	4.98±1.759	1.05±0.656
F2	22.61±0.813	0.484±0.48	0.512±0.974	5.46±1.245	1.057±0.128
F3	20.91±0.270	0.490±1.295	0.509±0.915	3.16±1.759	1.03±0.956
F4	21.51±0.270	0.479±1.295	0.506±0.915	5.4±1.759	1.057±0.056
F5	23.22±0.257	0.568±0.421	0.625±0.730	9.12±1.350	1.10±0.164
F6	23.21±0.270	0.501±1.295	0.60±0.915	16.6±1.759	1.2±0.556
F7	22.22±0.270	0.512±1.275	0.610±0.912	16.68±1.759	1.17±0.520
F8	23.14±0.270	0.449±1.230	0.540±0.315	7.58±1.650	1.19±0.530
F9	21.23±0.270	0.512±1.394	0.622±0.615	17.68±1.732	1.08±0.556
F10	23.23±0.270	0.533±1.394	0.628±0.615	17.75±1.732	1.77±0.556

Table No.3:Data for post -compression parameters

Formulation	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Uniformity of Content (%)	Water absorption ratio(%)	Disintegration Time (seconds)
F1	100±1.35	2.8±0.98	0.24±0.89	2.95±0.23	90.78±0.14	89.91±0.96	44.50±0.13
F2	101±0.97	2.7±0.29	0.36±0.04	2.28±0.12	91.48±0.13	93.48±0.59	41.2±0.11
F3	100±0.43	2.8±0.16	0.32±1.2	2.32±0.54	93.62±0.23	94.58±0.45	39.23±0.23
F4	100±1.56	2.9±1.16	0.25±0.69	2.41±0.43	92.23±0.06	91.98±0.49	32.31±0.03
F5	100±1.25	2.8±0.26	0.36±0.48	2.34±0.13	93.57±0.01	97.32±0.48	31.23±0.12
F6	101±1.09	2.9±0.64	0.34±0.18	2.31±0.25	95.83±0.02	98.25±0.75	35.24±0.14
F7	102±1.22	2.9±0.9	0.22±0.8	2.28±0.23	97.52±0.05	97.62±0.98	20.21±0.23
F8	101±1.82	2.7±0.8	0.34±0.4	2.29±0.18	98.15±0.18	98.48±0.87	19.02±0.43
F9	102±2.4	2.8±0.9	0.37±0.6	2.76±0.16	99.42±0.24	99.58±0.84	18.22±0.19
F10	103±2.4	2.76±0.9	0.38±0.6	2.88±0.16	97.42±0.24	97.58±0.84	20.22±0.19

Table no 4:Data for dissolution profile

Time (min)	Cumulative %Drug released									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
5	9.2	9.42	9	9.55	9.23	9.42	9.81	9.8	9.4	9.33
10	27.8	25.81	28.45	27.28	20.26	26.51	20.25	24.6	22.4	20.4
15	55.6	49.57	50.25	46.58	38.49	44.72	35.33	44.6	44.8	38.8
20	60.75	65.95	67.77	65.44	56.45	63.88	50.32	61.75	64.2	63.2
25	82.68	74.83	78.34	76.73	65.37	76.83	65.66	74.28	76.4	77.4
30	92.56	82.74	88.92	86.36	77.69	87.98	70.52	82.92	85.2	86.2
45	93.93	91.41	92.35	92.97	85.69	90.36	95.32	94.92	88.6	87.6
60	94.67	92.98	93.02	93.26	91.96	91.42	96.38	97.92	99.2	93.2

CONCULSIONS:

In the present study, Tizanidine hydrochloride was used as a model drug. Fast dissolving tablets containing Tizanidine hydrochloride were prepared by direct compression technique. Superdisintegrants used were added each in different concentrations to formulate 10 formulations. The prepared tablets of Tizanidine hydrochloride were evaluated for pre-compression parameters like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio and post-compression parameters like hardness, thickness, friability, weight variation, wetting time, water absorption ratio, drug content, *in-vitro* disintegration time and *in-vitro* dissolution studies.

The observations have shown that all the FDT formulations were acceptable with reasonable limits of standards required for fast dissolving tablets. The study reveals that the formulations prepared by Croscarmellose was best than Sodium starch glycolate .Formulation prepared by Croscarmellose F9 was the best formulation. The study revealed that superdisintegrants used were effective in low concentration level.

Thus, it was concluded that the fast dissolving tablets containing Tizanidine hydrochloride was successfully prepared by direct compression technique and characterized.

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