International Journal of Pharmaceutical Research and Development (IJPRD)
Platform for Pharmaceutical Researches & Ideas
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FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLETS OF TIZANIDINE HYDROCHLORIDE

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ABSTRACT

The main objective of this study was to formulate and evaluate the Fast disintegrating tablets of Tizanidine hydrochloride with superdisintegrants. Various formulations were prepared by direct compression using different concentrations of superdisintegrants i.e superdisintegrants namely crospovidone, croscarmellose sodium and sodium starch glycolate ranging from 2 % - 5%. The drug and excipients compatibility study was performed by FTIR and the study revealed that there was no interaction between drug and excipients. The blend of all formulations were evaluated for various precompression parameters like angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and were found to be satisfactory. The tablets were evaluated for various parameters like weight variation, thickness, hardness, friability, wetting time, water absorption ratio, disintegration time, content uniformity and In-vitro drug release. Formulation of crospovidone F3 shown less disintegration time of 15 seconds than other formulations of croscarmellose sodium and sodium starch glycolate. The in-vitro drug release of optimized formulation F3 was shown 99.29%. The optimized formulation was subjected to accelerated stability studies according to ICH guidelines for three months. The formulation was found to be stable, there was no change in the hardness, friability, disintegration time, drug content and in-vitro drug release pattern. It was concluded good percentage drug release, good mouth feel and improved better patient compliance.

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Key words: *Tizanidine HCl, Crospovidone, Direct compression.*

INTRODUCTION

I Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of administration, pain avoidance, versatility and patient compliance, less expensive to manufacture**.** The oral route

remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance [1, 2, 3,4 and 5]. Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of noncompliance and ineffective therapy [6, 7 & 8]. oral tablet administration to patients is a significant problem and has become the object of public attention. The problem can be resolved by the creation of rapidly dispersing or dissolving oral forms, which do not require water to aid swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way[9, 10].

The concept of Fast Disintegrating Drug Delivery System emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and hard gelatin capsules. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of Fast Dissolving Tablet. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva.

Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form[11,12].

Fast disintegrating tablet disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. FDDTs, as a novel dosage form, have several characteristics to distinguish them from the more traditional dosage forms[13,14]. Taste-masking is of critical importance in the formulation of an acceptable FDDT. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Many oral suspensions, syrups, and chewable tablets simply contain flavors, sugars and other sweeteners to overwhelm or complement the bitter taste of the drug. FDTs are the disintegrating tablets include sweeteners and flavors; however, these are not a sufficient means for taste-masking many bitter drugs. Most of the FDDT technologies incorporate unique forms of taste masking as well. The primary methods of taste-masking include adsorption onto or complexation with carriers and spray coating of solid dosage forms, which increase consumer choice, for the reason of rapid disintegrate/dissolve in oral cavity within seconds and swallowed without the need of water or chewing.As tablet disintegrates in mouth this could enhance the clinical effect of the drug through pre-gastric absorption from the mouth, pharynx and esophagus. This leads to an increase in bioavailability by avoiding first pass metabolism [15]

Tizanidine is an agonist at α2-agonist receptor sites and reduces spasticity by increasing presynaptic inhibition of motor neurons. In animal models, Tizanidine HCl has direct effect on skeletal muscle fibers or the neuromuscular junction, and no major effect on monosynaptic spinal reflexes.

The effects of Tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal

motor neurons. In the present study, an attempt had been made to prepare fast dissolving (in the oral cavity) tablets of Tizanidine HCl with enhanced dissolution rate and hence improved patient compliance.

Materials

Tizanidine HCl, crospovidone, crosscarmellose sodium, sodium starch glycolate, were obtained as gift samples from Alkem Ltd & yarrow chem Ltd and all other chemicals/ solvents used were of analytical grade.

Method of Preparation of Tizanidine HCl of fast disintegrating tablets

All ingredients were triturated individually in a mortar and passed through #60 sieve. Then required quantity of all ingredients were weighed for a batch size of 50 tablets and mixed uniformly in a mortar except talc and magnesium stearate. Finally magnesium stearate and talc were added as lubricant. This uniformly mixed blend was compressed in to tablets containing 4mg drug using 10 mm flat face surface punches on a cemach rotary tablet machine by direct compression method. The total weight of tablet was kept 250mg.

Drug-excipients compatibility study by FTIR

The spectrum analysis of pure drug and physical mixture of drug and different excipients which are used for preparation of tablets was studied by FTIR. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a Shimadzu Corporation (Japan) facilty (model - 8400S). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} in a scan time of 12 minutes. The resultant spectrum was compared for any spectral changes. They were observed for the presence of characteristic peaks for the respective functional group in the compound.

Table 1: Composition of Tizanidine hydrochloride containing different superdisintegrants

Ingredients (mg)	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tizanidine HCl	4	4	4	4	4	4	4	4	4
Mannitol	135	131	127	135	131	127	135	131	127
MCC	82	82	82	82	82	82	82	82	82
CP	4	8	12	-	-	-	-	-	-
CCNa	-	-	-	4	8	12	-	-	-
SSG	-	-	-	-	-	-	4	8	12
Pvp k30	12	12	12	12	12	12	12	12	12
Aspartame	3	3	3	3	3	3	3	3	3
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Flavour	qs	qs	qs	qs	qs	qs	qs	Qs	Qs
Total wt.	250	250	250	250	250	250	250	250	250

MCC: Microcrystallin cellulose, CP: Cros Povidone, CCNa: Cros Carmellose Sodium, SSG: Sodium Starch Glycolate.

Evaluation of Fast disintegrating tablets[3]

- Weight variation
- Thickness
- Hardness
- Friability
- Wetting time
- Water absorption ratio
- Content uniformity
- *In-vitro* disintegration time
- *In-vitro* release studies

- Fourier transform infrared spectroscopy
- Accelerated stability studies

Weight variation: Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated.

Thickness: Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by vernier calipers scale.

Hardness: 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 pieces by compression. It was measured using a tablet hardness tester. Three tablets from each formulation batch were tested randomly and the average reading noted.

Friability: Friability of the tablets was determined using Roche Friabilator (Electrolab, India). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution.

Preweighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula

$$F\ \% = (1 - W_0 / W) \times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test

Wetting time: Five circular tissue papers of 10-cm diameter were placed in a petri dish with a 10-cm diameter. 10 ml of water at $37^0C \pm 0.5^0C$ containing eosin, a water-soluble dye, was added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted.

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 paper and the time required for complete wetting was measured. The wetted tablet was then weighed.

Water absorption ratio R, was determined using following equation

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

Where, W_a = weight of tablet after absorption

W_b = weight of tablet before absorption

Content uniformity: 20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 4mg was weighed and dissolved in 100 ml of 6.8 pH buffer filtered and drug content analyzed spectrophotometrically at 228 nm.

***In-vitro* disintegration time:**

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at $37 \pm 2\ ^0C$, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

***In-vitro* release studies:**

In vitro drug release of tizanidine hydrochloride fast disintegrating tablet tablets was determined using USP Dissolution Apparatus II (Paddle type) (Electrolab TDT-08L).

The dissolution test was performed using 900 ml 6.8 pH buffer at $37^0C \pm 0.5^0C$. The speed of rotation of paddle was set at 50 rpm. 5 ml samples were withdrawn at time points of 1, 2, 3, 4, 5, 6,7 , 8, 9, and 10min and same volume was replaced with fresh media. Absorbance of solution was checked by UV spectrophotometer (ELICO- 164 double beam spectrophotometer, Hyderabad, India) at a wavelength of 228nm and drug release was determined from standard curve.

Dissolution study of Tizanidine hydrochloride fast disintegrating tablets:

Vessel temperature : 37 ± 0.5^oC

Bath temperature : 37 ± 0.5^oC

Dissolution media : 6.8 pH buffer

Volume of dissolution media : 900 ml
Aliquot withdrawn : 5 ml
Aliquot replaced : 5ml of the fresh solution
Dissolution apparatus : USP type II (paddle)
Revolutions per minute : 50 rpm

Accelerated stability studies: The optimized formulation was subjected to stability studies at 40^0C±75%RH for period of three months. Each tablet was individually wrapped in aluminum foil and packed in ambered colored bottle and put at above specified condition in a heating humidity chamber for three months. For every one month tablets were analyzed for the hardness, friability disintegration time, drug content and in vitro drug release. The results are obtained within the limits. It is given in Figures No: 4, 5, 6.

RESULTS AND DISCUSSION

Drug-excipients compatibility study by FTIR:

FTIR study was done to verify if there was any interaction between the pure drug and various excipients were employed. The various FTIR graphs both of pure drug and optimization formula formulated into IR pellet and scanned.

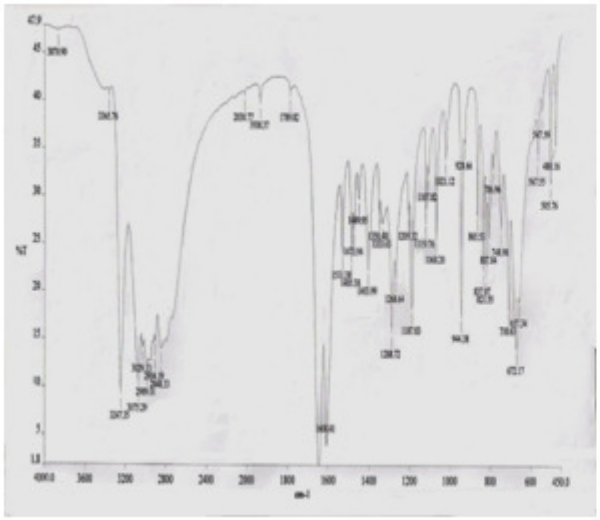

Fig.1 IR spectra of Tizanidine HCl

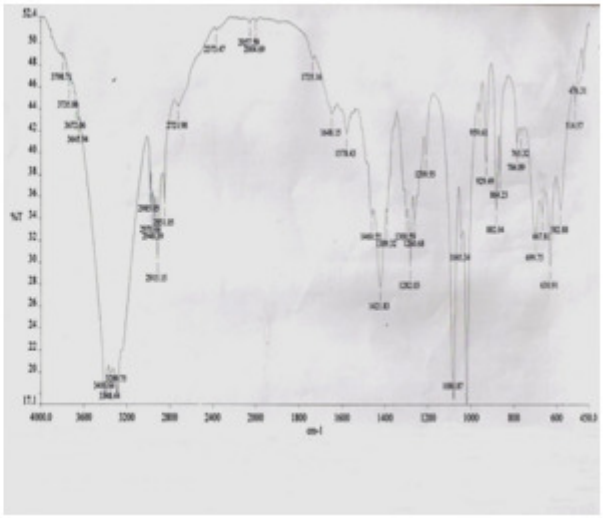

Fig.2 IR spectra of Optimized formulation

Table 2: Interpretation of IR graph

Tizanidine HCl	Region in cm^{-1}	Type of vibration and Functional groups
1	3247	NH - stretching
2	3365	NH - stretching
3	1205	N - stretching
4	1187	N - stretching
5	1199	N - stretching
6	1403	S - stretching
7	1789	Cl - stretching

Precompression parameters:

Precompression parameters of all formulations blend were conducted for angle of repose, bulk density, tapped density, compressibility index, *Hausner's* ratio. The two most important attributes for the direct compression formula are good flow and good compressibility. Interparticulate interactions that influence the bulking properties of a powder with powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder, such a comparison is

often used as an index of the ability of the powder to flow. The angle of repose gives important information about the flow characteristics of the powder mixture.

The powder flow depends on three general areas: the physical properties of the particle (e.g., shape, size, compressibility), the bulk powder properties (e.g., size distribution, compaction), and the processing environment (e.g., storage, humidity).

Table No 3: Preformulation studies of blend of all formulation

Formulation	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Angle of repose(θ)	Carr's Index(%)	*Hausner's* ratio
F1	0.40	0.47	21.5	14.8	1.17
F2	0.41	0.46	20.1	10.86	1.12
F3	0.41	0.47	19.6	12.7	1.14
F4	0.43	0.48	17.8	10.4	1.11
F5	0.41	0.45	19.2	8.88	1.09
F6	0.40	0.44	18.4	9.09	1.10
F7	0.44	0.50	18.5	12.0	1.13
F8	0.41	0.46	17.4	10.86	1.12
F9	0.42	0.48	17.8	12.5	1.14

Evaluation studies of tablets

Table No 4: Evaluation of tablets

Formulations	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Wetting time (sec)	Water absorption ratio	Disintegration time (Sec)	Content uniformity (%)
F1	250±0.707	2.5±0.028	1.2±0.063	0.65±0.035	34±1.414	51±0.707	25±0.0707	98.02±0.615
F2	248±0.98	2.4±0.15	1.1±0.1	0.66±0.05	26±1.06	42±1.52	20±0.57	98.47±0.4
F3	249±0.848	2.6±0.057	1.2±0.05	0.63±0.040	21±1.527	34±1.00	15±0.577	99.89±0.085
F4	248±0.282	2.4±0.10	1.2±0.135	0.66±0.026	54±0.793	61±0.802	46±1.00	98.64±0.145
F5	248±0.424	2.4±0.152	1.1±0.057	0.69±0.067	48±1.101	56±1.159	41±1.527	99.1±0.2
F6	251±0.777	2.4±0.656	1.2±0.1	0.65±0.020	44±1.014	47±1.418	37±1.137	98.73±0.218
F7	250±0848	2.4±0.200	1.1±0.045	0.65±0.026	61±1.258	64±0.702	56±1.527	97.51±0.438
F8	249±0.777	2.5±02.30	1.1±0.115	0.64±0.035	53±0.721	62±1.193	46±1.63	98.37±0.132
F9	252±0.707	2.5±0.1	1.10.0577	0.66±0.015	44±1.527	52±1.310	39±1.41	98.56±0.065

Values are expressed as Mean ±SD, n=3

The hardness of the tablets was found to be 2.4 ± 0.10 to 2.6 ± 0.057 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance. The thickness of the tablets was found to be 1.1± 0.057 to 1.2± 0.04. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. ±7.5%. The drug content was found to be 98.02 to 99.89%, indicating uniform distribution of drug in the tablets.

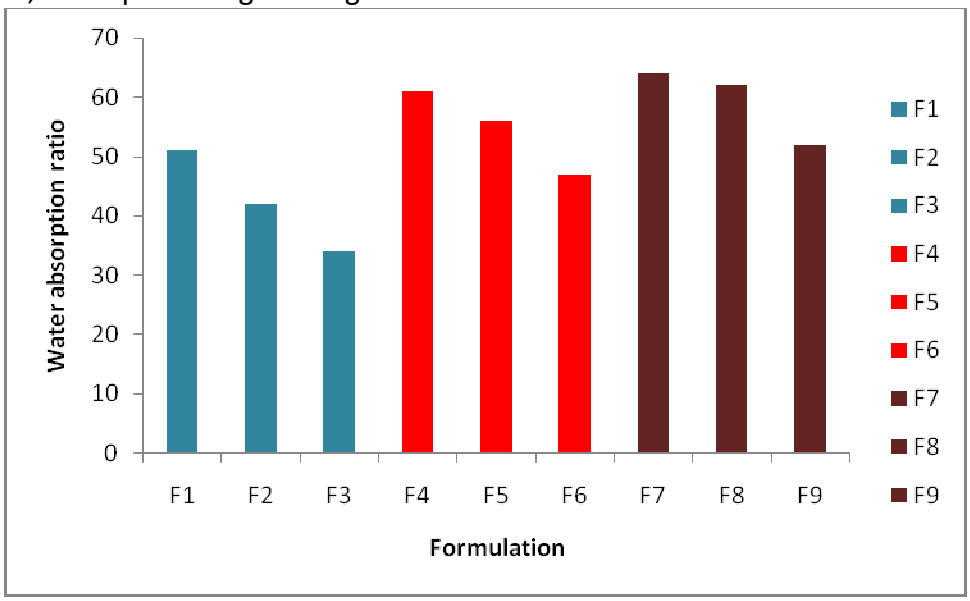

Fig 3: Disintegration time of all formulations

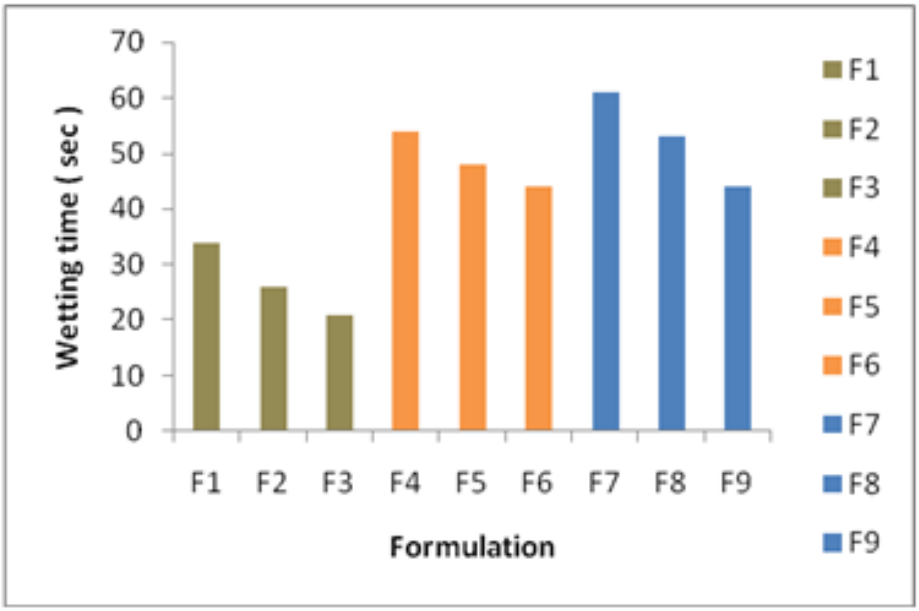

Fig 4: Wetting time of all formulations

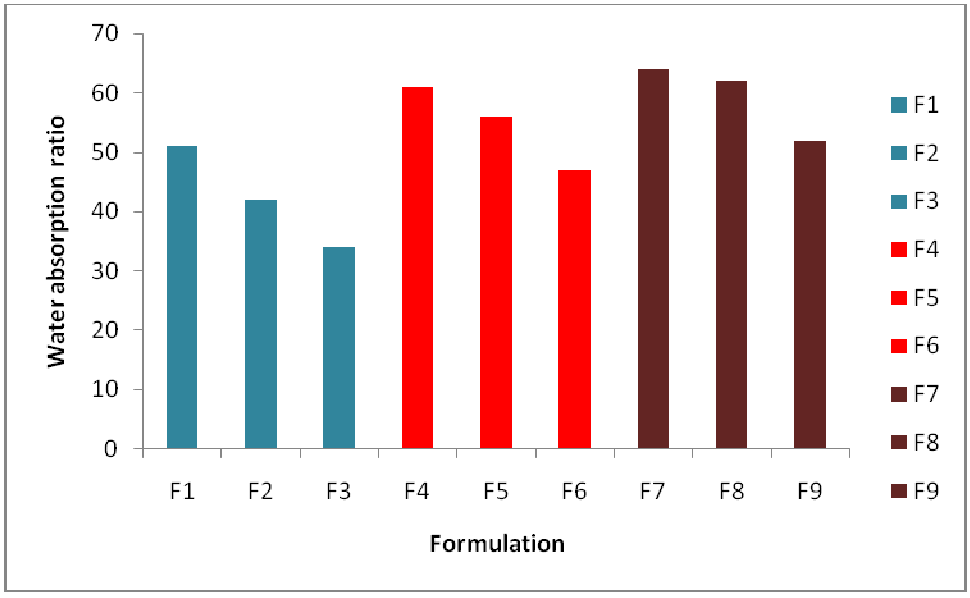

Fig 5: Water absorption ratio of all formulations

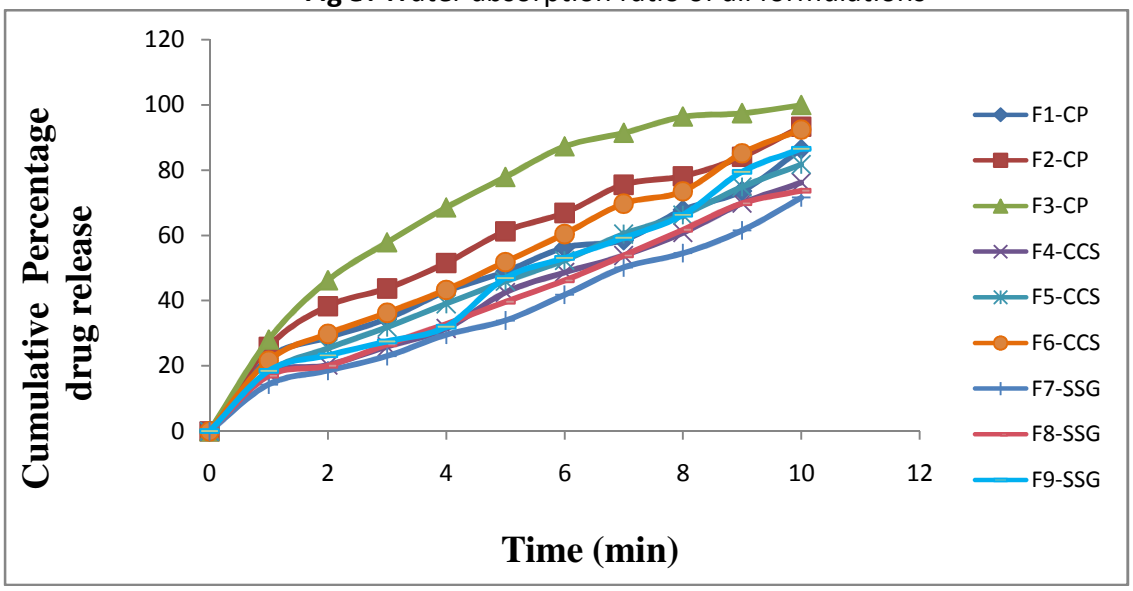

Fig 6: Cumulative % Drug Release

DISCUSSION

Nine formulations of Tizanidine HCl were prepared with varying concentrations of three superdisintegrants: crospovidone, crosscarmellose sodium, sodium starch glycolate, were used. (Table 1). For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as specified earlier. The powder blend was compressed using direct compression technique. Bulk density was found in the range of 0.40-0.44 g/cm^3 and the tapped density between 0.44-0.50 g/cm^3 and Angle of repose between 21.5-17.4 Using these two density data Hausner's ratio and compressibility index were calculated. The powder blends of all formulations had Hausner's ratio less than 1.25 indicating better flow property. The compressibility index was found between 8.88-14.8, which indicates good flowbility of the powder blend values are given in table 3. The good flowability of the powder blend was also evidenced with angle of repose (range of 26-30) which is below 40^o indicating good flowability. Tablets were prepared using direct compression technique. Since the powder material was free flowing, tablets were obtained of uniform weight due of uniform die fill, with acceptable weight variations as per I.P.

The drug content was found in the range of 98.02% - 99.89% (acceptable limit) and the hardness of the tablets were found below 2.6 kg/cm^2 and friability were found 0.63-0.66 indicating a good mechanical resistance of the tablets, and the parameters were found well within the specified limit for FDT tablets. The *in-vitro* disintegration time (DT) of the tablets was found to be less than 60 sec , wetting time 21-61 sec ,water absorption ratio 34-64sec ,the percentage drug release was found to be 99.29% in a 10 mints table4 &fig 3,4,5&6. Tablets containing 5% Crospovidone (F3) showed disintegration time of 15 sec. The order of enhancement of the dissolution rate with various superdisintegrants was found to be: crospovidone > crosscarmellose > sodium starch glycolate. The preparation process in direct compression tablets includes co- grinding of all the excipients before compression, results an increase in solubility due to the reduction in the effective particle size of the drug following increase in the wetting of drug particle by the excipients and improved dissolution of drugs. It was concluded that fast disintegrating tablets of Tizanidine HCl can be successfully prepared with selected superdisintegrants in order to improve disintegration/dissolution of the drug in oral cavity and hence better patient's compliance leading to effective therapy.

COCLUSION

Fast disintegrating tablets of Tizanidine hydrochloride were prepared by using different superdisintegrants like crospovidone, croscarmellose sodium and Sodium starch glycolate by direct compression. FTIR studies revealed that there was no interaction between Tizanidine hydrochloride and excipients used in tablet formulations. Precompression parameters were conducted for all formulations blend and were found to be satisfactory. The prepared tablets were evaluated for various parameters like hardness, friability, wetting time, water absorption ratio, disintegration time, drug content and *in-vitro* dissolution. The results indicated that the tablets complied with the official specifications. The disintegration studies shown that the all formulations disintegrated in less than 1 minute. The formulation F3 shown less disintegration time of 15 seconds. The croscarmellose sodium and sodium starch glycolate shown more disintegration time than crospovidone.An accelerated stability study on optimized formulation was performed. The formulation was found to be stable, with insignificant change in the hardness, friability, disintegration time, and *in vitro* drug release . In the present study, three Superdisintegrants representing each of the three main classes of superdisintegrants differed in their ability to disintegrate model tablet into their primary particles when used at the same w/w percentage concentration. In conclusion, it can be stated that the objective of the study has been achieved. From the above study the formula used for F3 formulation was concluded as an optimized formulation due to its less disintegration time when compared with other formulations.

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