IJPSR (2013), Vol. 4, Issue 4 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 21 December, 2012; received in revised form, 27 January, 2013; accepted, 19 March, 2013

DESIGN AND EVALUATION OF SUSTAINED RELEASE MULTIPARTICULATE SYSTEM OF TIZANIDINE HYDROCHLORIDE

M. Thriveni [1], A. Brahma Reddy [2], D. Srinivas Reddy [1], D. Vasavi Reddy*[1]

Department of Pharmaceutics, Vaageswari College of Pharmacy [1], Beside L.M.D Police Station, Thimmapur, Karimnagar Dist., 505481, Andhra Pradesh, India
Glukem Pharmaceuticals Pvt. Ltd [2], Phase II, Cherlapally, Hyderabad, 500051, Andhra Pradesh, India

Keywords:

Tizanidine hydrochloride, Pellets, Sustained release, Pan coating, Wurster type

Correspondence to Author:

D. Vasavi Reddy

Department of Pharmaceutics, Vaageswari College of Pharmacy, Beside L.M.D Police Station, Thimmapur, Karimnagar Dist., 505481, Andhra Pradesh, India

E-mail: vasavisrinivas14@gmail.com

ABSTRACT: The aim of the present investigation is to formulate and evaluate Tizanidine hydrochloride sustained release pellets. Tizanidine hydrochloride is an immadazole α_2-adrenergic agonist used in the management of increase in muscle tone associated with spasticity. It has short biological half-life of 2- 2.5 hrs and is rapidly eliminated from the body. Sustained release dosage form of Tizanidine hydrochloride was developed for reduction in total amount of dose administration, to improve patient compliance, and increase efficiency in the treatment. The pellets were prepared by pan coating and fluidized bed coating technique (Wurster type) using hydroxy propyl methyl cellulose E_5 (HPMC E_5), Ethyl cellulose N-50, Eudragit L-100 as polymers and Isopropyl alcohol, Methylene dichloride as solvents. The pellets are filled in capsules and evaluated for weight variation, content uniformity, moisture content, lock length, disintegration and *in-vitro* dissolution tests and the results were found to be within the limits. A comparative study of dissolution profile of different batches with marketed product was performed. The optimized batch showed good similarity with the marketed product (Zanaflex Capsules). The dissolution data was fitted with various kinetic models, and the optimized formulation followed zero order kinetics by non-Fickian case-II diffusion process. Stability studies were conducted for 3 months according to ICH guidelines and found to have good results.

INTRODUCTION: Oral route is the most frequently used route of drug administration. Oral route dosage forms are usually indicated for systemic effects resulting from drug absorbance through various epithelia and mucosa of the gastro intestinal tract.

QUICK RESPONSE CODE

IJPSR: ICV (2011)- 5.07

Article can be accessed online on: www.ijpsr.com

Comparing with other routes, the oral route is the most convenient and safest means of drug administration. Oral sustained release dosage forms are widely used for delivery of medicament. The dosage forms can be categorized into single and multiple units based on number of unit per dosage form.

The multiple unit dosage forms are preparation that consists of several mini reservoirs [1]. A multiple unit dosage form readily separates into sustained release units throughout the gastrointestinal tract after ingestion.

One of the multiple unit dosage forms is the pellets, which reduces variations in gastric emptying time and transit time, has less susceptible to dose dumping & provides less irritation from high local concentration of drugs [2]. Pellets are small, free flowing, spherical particulates manufactured by agglomeration of fine powders or granules and size ranging from 0.5 mm-1.5 mm.

The most important reason for the wide acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release dosage form. Controlled release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. The above mentioned goals can be obtained through the application of coating materials mainly polymers, providing the desired function or through the formulation of matrix pellets to provide the desired effect [3].

Spasticity is characterized by increased muscle tone and dysfunctional muscle spasm resulting from unregulated brain impulse to the muscles caused by damage to the spinal cord or to portions of the brain that control voluntary movement [4].

Tizanidine HCl reduces spasticity by increasing presynaptic inhibition of motor neurons through agonist action at α_2-adrenergic receptor sites. It has short biological half-life (2-2.5 hrs) and it is rapidly eliminated from the body. For reduction in total amount of dose administration, to improve patient compliance, and improved efficiency in the treatment, we need to develop Tizanidine hydrochloride sustained release pellets. Tizanidine hydrochloride is centrally acting imidazole α_2-adrenergic agonist which is orally administered & indicated for the management of increased muscle tone associated with spasticity [5].

The main objective of the study is to compare the drug release profile of the best with the marketed product. It involves the preparation of sustained release pellets consisting of Tizanidine HCl with different polymer ratios and to perform preformulation studies for drug i.e., drug excipients compatibility studies by FTIR & DSC and to evaluate the drug release profile of Tizanidine HCl and to extend the drug release up to 12 hrs.

MATERIALS AND METHODS:

Materials: Tizanidine hydrochloride is a gift sample from Glukem Pharmaceuticals, Hyderabad. Sugar core of size range 20#24 were used as the initial core for drug loading in coating pan. Sustained release coating was done in fluidized bed coater, using HPMC E-5, Ethyl cellulose N-50, and Eudragit L-100 is obtained from Clariant Chemicals Pvt. Ltd, Mumbai. PVP K-30 is obtained from BASF Chemical Company in India.

Methodology: The formulation development involves the preformulation, drug loading and sustained release coating. Preformulation studies were conducted for pure drug and excipients. Drug and excipients compatibility studies were performed using Fourier transform infra-red spectroscopy (FTIR) and Differential scanning calorimetry (DSC).

Formulation Studies:

Drug Loading: According to the formula (**Table 1**) dispense all the materials as per manufacturing composition. Pulverize the drug i.e., Tizanidine hydrochloride, sugar powder, and talc. Add PVP K-30 in Isopropyl alcohol and stir well to get the clear solution. Transfer the basic core sugar pellets into coating pan, and then spray with the binder solution prepared above. Over wetting of the cores to be avoided as it may cause agglomeration. Add the pulverized powder mixture slowly by spraying the binder solution. The pellets are then dried in a tray dryer for about 45 min at a temperature 45-55^{o}C to attain the moisture content less than 2.5 %. The dried pellets are sized on a sifter to remove agglomerates, broken pellets and fine powder. These pellets are ready for coating [6].

Coating of Tizanidine hydrochloride pellets: According to the formula (**Table 2**) Coating solution was prepared by taking Isopropyl alcohol and Methylene dichloride into a stainless steel container and Hydroxyl propyl methyl cellulose (HPMC E-5), Ethyl cellulose N-50 and Eudragit L-100 were added at different concentrations.

Transfer the drug loaded pellets into the Fluidized bed coater and coated with the above prepared coating solution. Set the inlet temperature to 45-55^{o}C & bed temperature 37-42^{o}C.

Coat the drug loaded pellets with sustained release coating solution by bottom spray (Wurster type) with peristaltic pump 25-30 rpm and atomizing air pressure of 1.5 Kg/cm^2 till the coating solution was completed. Over wetting of drug coated pellets to be avoided as it may cause agglomeration**.** After complete quantity of the coating solution was consumed, reduce the fluidization for a brief post-drying period [6].

TABLE 1: DRUG LOADING COMPOSITION

Drug Loading Composition		
S. No.	**Ingredients**	**Concentration**
1	Drug	3.5%
2	Sugar Core (20#24)	50%
5	Sugar Powder	33%
6	PVP K30	3%
7	Talc	10%
8	Isopropyl alcohol	Qs

TABLE 2: SUSTAINED RELEASE COATING COMPOSITION

Sustained Release Coating Composition									
Ethyl Cellulose N-50	-	1.0%	2.0%	3.0%	4.0%	1.0%	2.0%	3.0%	4.0%
HPMC E5	0.5%	1.0%	2.0%	3.0%	4.0%	-	-	-	-
Eudragit L-100	-	-	-	-	-	1.0%	2.0%	3.0%	4.0%
IPA: MDC	80:20 (4%Dil)	80:20 (4%Dil)	80:20 (4%Dil)	80:20 (4%Dil)	80:20 (4%Dil)	80:20 (4%Dil)	80:20 (4%Dil)	80:20 (4%Dil)	80:20 (4%Dil)

Evaluation of Pellets: The pellets were evaluated for flow properties, moisture content, size distribution and assay.

Bulk density and Tapped density: Accurately weighed quantity of the pellets (W), were taken into the graduated cylinder and the volume (V_o) was measured. Then the graduated cylinder was closed with the lid and set into the density determined apparatus. The density apparatus was set for 500 taps and after that, the volume (V_f) was measured. The bulk density and tapped density were calculated using the following formula [7]:

$$\text{Bulk density } (\rho o) = \frac{M}{Vo}$$

$$\text{Tapped density } (\rho t) = \frac{M}{Vf}$$

Where, M = weight of the pellets, Vo = initial volume Vf = final volume

Compressibility index: The compressibility of a material can be estimated from the tapped and bulk density measurements by using following formula [7]:

$$\text{Compressibility index} = \frac{(\rho t - \rho o)}{\rho t} \times 100$$

Where, ρt = Tapped density and ρo = Bulk density

Hausner's ratio: The Hausner's ratio was calculated using the formula [7]:

$$\text{Hausner's Ratio} = \frac{\rho t}{\rho o}$$

Where, ρt = Tapped density, ρo = Bulk density

Angle of repose: Accurately weighed quantities of pellets were poured into funnel and the height of funnel is adjusted to a height of 2.5 cm and the radius of the circle is measured by taking the diameter values of average of four values. The formula for calculating angle of repose is [7]. The formula for calculating angle of repose is,

$$\theta = \tan^{-1}\frac{h}{r}$$

Where, h =Height of the funnel, r =Half of the diameter of circle

Moisture Content (% w/w): Take suitable quantity of Methanol in titration flask of Karl Fischer Titrator and titrate with Karl Fischer reagent upto end point. Grind the pellets to fine powder in a dry mortar, weigh accurately about 0.5 g of the sample, transfer quickly to the titration flask, and dissolve by stirring and titrate with Karl Fischer reagent upto end point [8].

$$\text{water \%} = \frac{V \times F \times 100}{\text{Weight of sample in mg}}$$

Where, F = Factor of Karl Fischer reagent, V = Volume in ml of Karl Fischer reagent consumed for sample titration.

Size Distribution: Arrange the sample collector, 20 ASTM sieve, 16 ASTM sieve, Weigh and transfer around 100 g of the sample into 16 ASTM sieve and shake for 5 minutes. Collect the 16 ASTM retains (W_{16}) from 16 mesh and pass through 20 ASTM (W_{20}).The sample was collected and the % passed and % retained was calculated using formula [9].

$$\%\text{passed} = \frac{\text{Wt in 16 sieve (gms)}}{\text{wt of sample taken in gms}} \times 100$$

$$\%\text{Retained} = \frac{\text{Wt in 20 sieve (gms)}}{\text{wt of sample taken in gms}} \times 100$$

Assay: Transfer an accurately weighed quantity of the powdered pellets equivalent to about 100 mg Tizanidine hydrochloride into a 100 ml volumetric flask, 60 ml of methanol was added & sonicated for 15 minutes and cool the solution to room temperature and dilute with methanol upto the mark. Transfer 10 ml of above solution to a 100 ml volumetric flask and make upto the mark with methanol. Then transfer the 10 ml of the above solution into a 100 ml volumetric flask and make up the volume to 100 ml with methanol, then absorbance was set to 320 nm in UV visible spectrophotometer. Using calibration curve the drug content was determined from absorbance values of pellets.

Evaluation of Capsules:

Weight variation test: Individual weights of 20 capsules were taken and the average weight was calculated by using the following formula [10].

$$\text{Weight Variation} = \frac{(\text{Weight of the capsule} - \text{Average weight})}{\text{Average weight of capsules}} \times 100$$

Weight variation should not be more than 10%. **Limits:** Less than 300 mg ±10%, more than 300 mg ±7.5%

Lock length: It was tested by using Vernier callipers [11].

Content uniformity: The amount of drug determined by assay is within the range of 85- 105% of the label claim for 9 out of 10 dosage forms and no formulation outside the range of 70 -125% of label claim.

Disintegration: : The capsules are placed in the basket rack assembly which is repeatedly immersed about 30 times per minute into a thermostatically controlled fluid at 37±2°C and observed [12].

***In-vitro* Dissolution Studies:** The dissolution test was carried out for capsules by using USP type-I apparatus (basket type) in 0.1N HCl for first 2 hrs and then continued in 6.8 pH phosphate buffer up to 12 hrs. Capsules contain pellets equivalent to 6 mg of Tizanidine hydrochloride placed in a basket containing 900 ml of dissolution media maintained at 37±0.5°C and rpm was set to 100. Samples of 5 ml were withdrawn at specified time intervals and replaced with fresh medium and analyzed for drug content by using U.V spectrophotometer at 320 nm.

***In-vitro* Release Kinetics:** The dissolution data of optimized batch (F7) were fitted to various kinetic models like zero order, first order, Higuchi's, Korsemeyer- Peppas model and Hixson Crowell to known the kinetics of drug release [13].

Comparison of dissolution profiles by stastical analysis: In order to compare the dissolution profiles, model-independent methods were used. The similarity factor (*f2*) provides a simple measure of similarity between pairs of dissolution profiles. The dissolution profiles of product were compared using the formula *f2*. The similarity factor is calculated using the following formula [14] (**table 3**):

$$f2 = 50 \times \log\{(1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} W_t(R_t - T_t)^2)^{-0.5} \times 100\}$$

n - number of dissolution time points, R_t - reference profile at the time point t, T_t- test profile at the time point t

TABLE 3: SIGNIFICANCE OF SIMILARITY FACTOR (*f2*)

Similarity Factor (f_2)	Significance
<50	The test and reference profiles are dissimilar
50-100	The test and reference profiles are similar
100	Test and reference profiles are identical
>100	Equation yields a negative value

Stability Studies: Stability studies were carried out for 3 months as per ICH guidelines for optimized formulation by placing at different temperatures and evaluated for the parameters assay, disintegration, moisture content, and dissolution [15].

Storage Conditions: The stability samples are stored at accelerated: 40±2°C/75±5% RH**,** Intermediate: 30±2°C/65±5% RH, Long term: 25±2°C/60±5% RH.

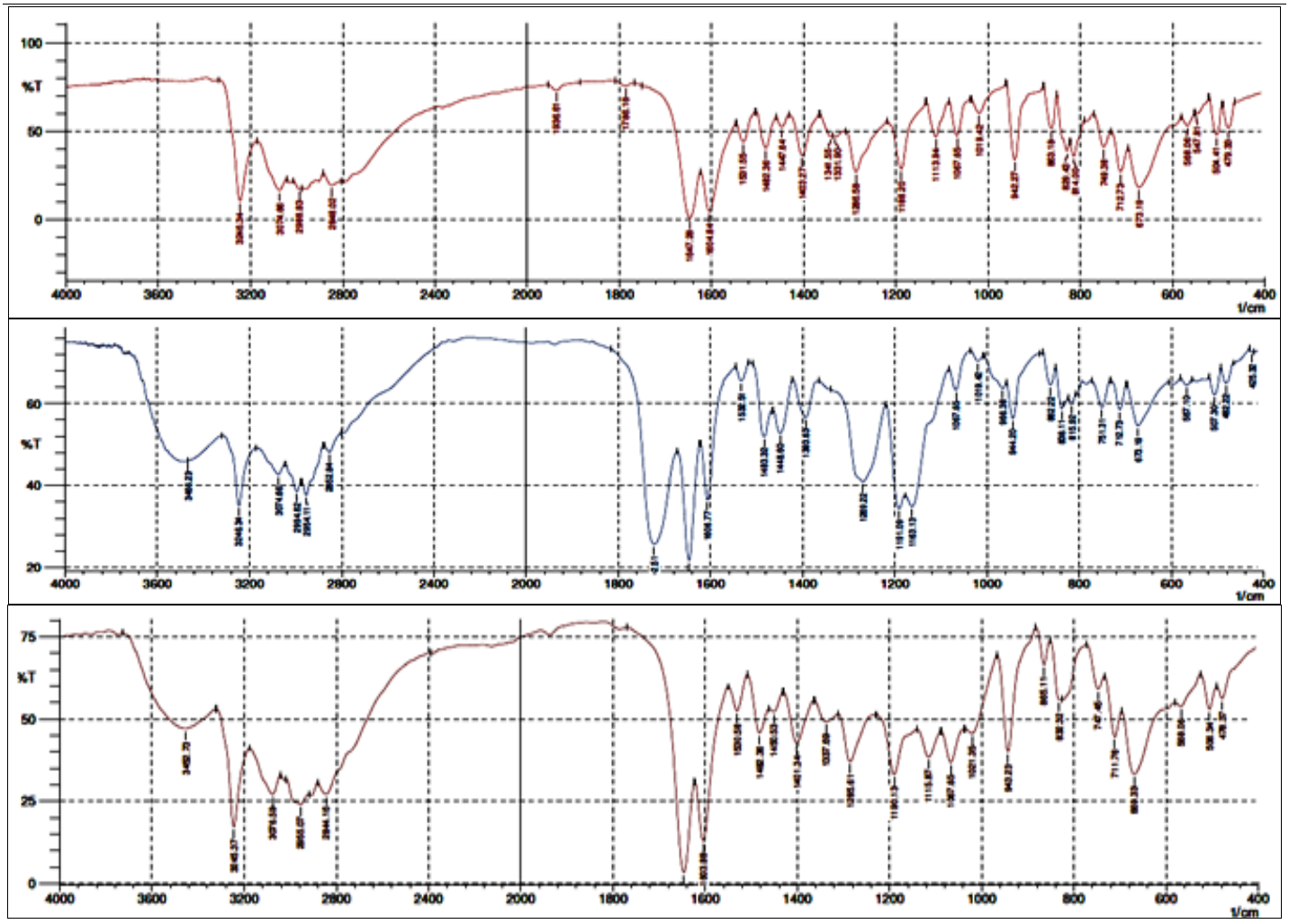
RESULTS AND DISCUSSION: Attempts were made to sustain the release of Tizanidine hydrochloride by pelletization technology. The prepared pellets were optimized and characterized.

Drug-Excipients Compatibility Studies:

FT-IR Studies: The FT-IR studies were carried out for pure drug alone and along with polymers. The results are summarized as follows.

FT-IR spectra of pure drug (Tizanidine hydrochloride) and individual polymers such as HPMC E-5, Ethyl cellulose N-50, and Eudragit L-100 were shown in the **Fig. 1** and peaks were listed in Table 4. The peaks given in the Table 4 matches with that of the literature values for the functional groups present in Tizanidine hydrochloride. This result along with the results of melting point and UV scan confirms that the sample drug under consideration is Tizanidine hydrochloride only.

The peaks listed in the Table 4 for pure drug can be considered as characteristic peaks. The peaks for the drug in the presence of polymers were not affected and prominently observed in FT-IR spectra given in Fig. 1. This indicates that there is no interaction between Tizanidine hydrochloride and polymers and the drug was compatible with the formulation components.



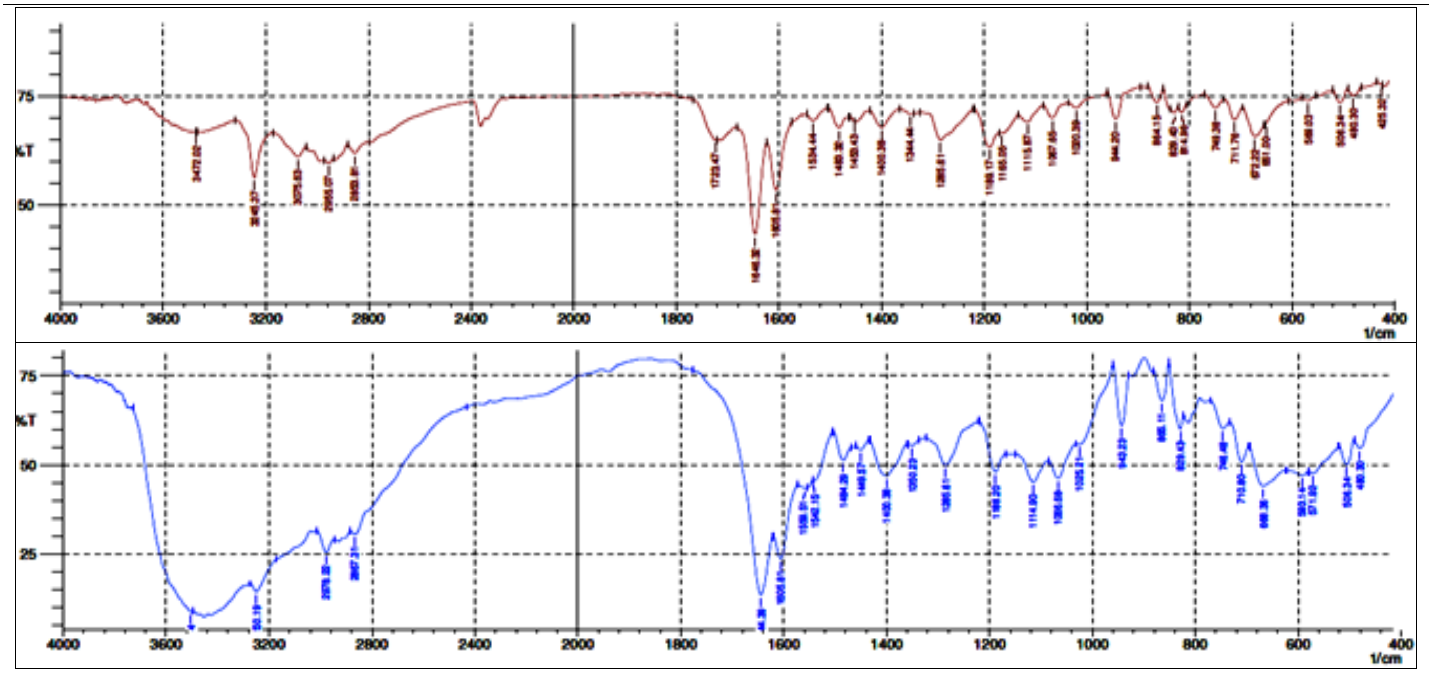
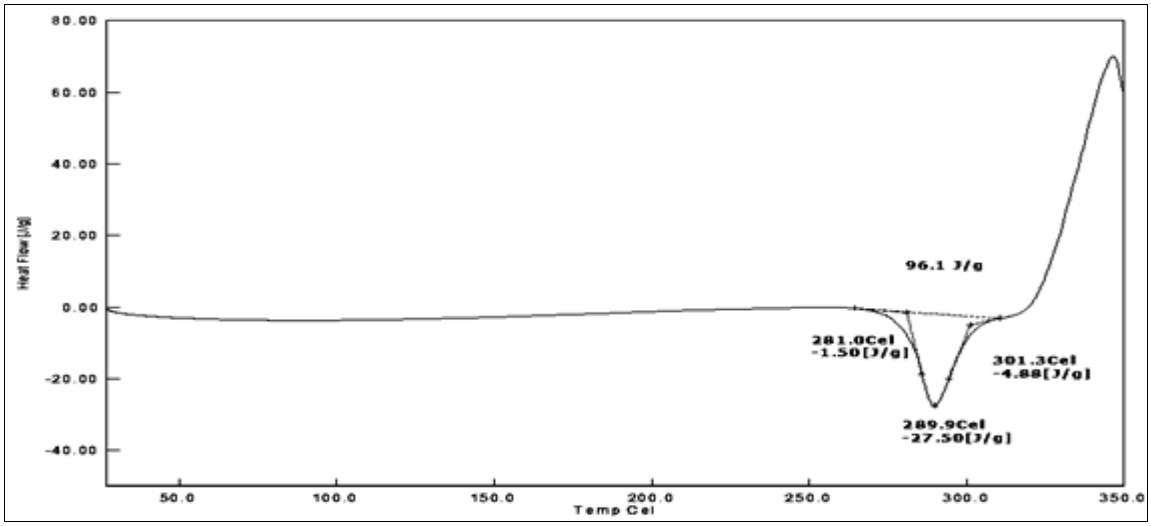


FIGURE 1. A) PURE DRUG B) HPMC E5 C) ETHYL CELLULOSE N-50 D) EUDRAGIT L-100 E) OPTIMIZED PRODUCT

TABLE 4: FTIR DATA OF TIZANIDINE HCl ALONG WITH POLYMERS

FTIR spectra	Peaks of functional groups wavelength (cm^{-1})		
	C=N stretch	C-H stretch	N-H stretch
Pure Drug (Tizanidine HCl)	1647.28	3074.66	3246.34
Drug + HPMC E5	1644.39	2978.22	3250.19
Drug + Ethyl cellulose N-50	1652.42	2955.07	3245.37
Drug + Eudragit L-100	1692.51	2954.11	3246.34
Optimized batch (F7)	1646.32	2955.07	3245.37

Differential Scanning Calorimetry (DSC) Studies: DSC studies for pure drug, and optimized formulation 'F7' was carried out. The thermo grams were shown in **Fig. 2-A & 2-B** respectively for pure drug and optimized formulation 'F7'. Fig. 2-A indicates that the melting of drug has taken place at 289.9°C. It was matching with the literature value 280-290°C. Fig. 2-B indicates that the melting point of the blend (F7) is 270.5°C. Further no more peaks were found in Fig. 2-B. This indicates that there is no interaction between drug and Excipients.



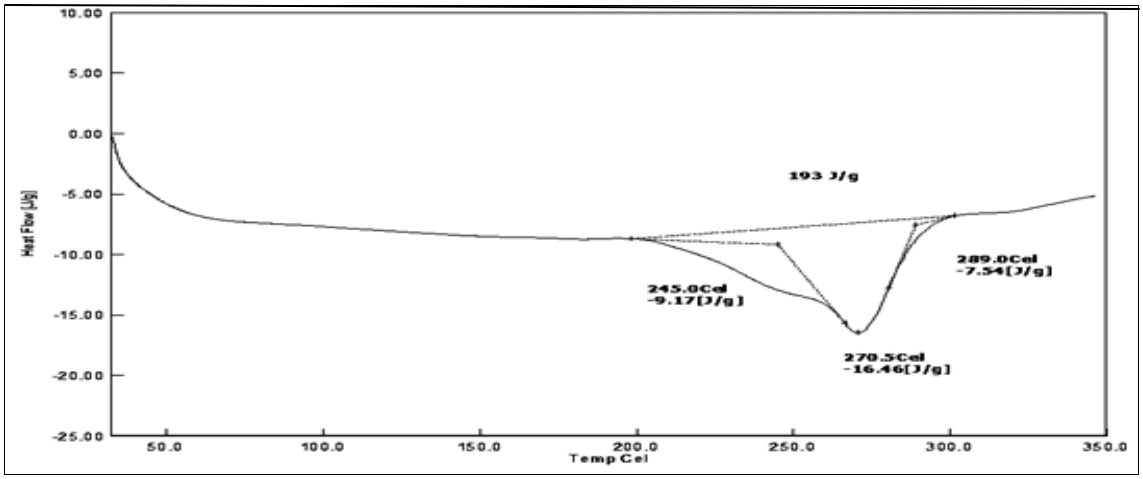


FIGURE 2: DSC OF A) PURE DRUG B) OPTIMIZED PRODUCT

Evaluation of Pellets:

Flow Properties: The formulated pellets from batch F1-F9 have showed the range of Bulk density 0.64-0.76, Tapped density 0.81-0.89, Carr's index was 10.7-21.9, Hausner's ratio 1.10-1.28 and Angle of repose 20-25^{o}. It shows pellets have excellent flow properties. The results are shown in **Table 5**.

Moisture Content: It is determined by using the Karl-Fischer method and all formulations showed <5% moisture.

Size distribution: Initially the sugar core size is 20#24, after drug loading and coating the pellets sizes from F1-F9 batches falling in the range of 16#20.

TABLE 5: EVALUATION OF PELLETS (F1-F9)

Batch	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's Ratio	Angle of Repose (^{o})	Moisture content (%)
F1	0.76±0.92	0.86±0.36	11.6±0.56	1.20±0.27	25±0.64	3.5±0.6
F2	0.74±0.56	0.89±0.32	16.8±0.94	1.17±0.34	21±0.94	3.4±0.4
F3	0.69±0.25	0.81±0.42	14.8±0.54	1.17±0.46	24±0.36	3.0±0.8
F4	0.64±0.43	0.82±0.26	21.9±0.65	1.28±0.75	25±0.58	3.1±0.5
F5	0.74±0.54	0.82±0.47	10.7±0.61	1.10±0.46	20.5±0.64	3.4±0.6
F6	0.72±0.61	0.81±0.75	11.1±0.4	1.12±0.38	22±0.57	3.4±0.5
F7	0.70±0.23	0.82±0.41	17.1±0.41	1.17±0.92	23±0.45	3.9±0.4
F8	0.71±0.75	0.84±0.53	15.4±0.24	1.18±0.59	24.5±0.81	2.9±0.8
F9	0.73±0.54	0.82±0.29	10.9±0.26	1.12±0.61	21±0.62	3.4±0.5

All values are expressed as mean ± SD, n=3

Evaluation of Capsules: Capsules are evaluated for weight variation, content uniformity, moisture permeation, lock length, and disintegration. The results were listed in **Table 6**. All formulated batches showed the drug content within the range of 94.5-102.4%, Weight variation was found to be within the limits, lock length of the capsules were found to be in the range of 15.8-16.1 mm. Disintegration time for capsules found to be in the range of 198-239 sec.

TABLE 6: CAPSULES EVALUATION PARAMETERS

Batch	Content Uniformity (%)	Wt. Variation (mg)	Lock length(mm)	Disintegration Time (sec)
F1	96.8±0.8	188±0.2	15.8±0.3	198±3.52
F2	94.5±0.6	190±0.1	15.9±0.2	214±1.25
F3	101.5±0.5	187±0.5	15.9±0.1	218±2.45
F4	95.9±0.7	192±0.3	15.8±0.2	239±1.22
F5	102.4±0.3	189±0.2	16.1±0.2	232±1.41
F6	98.8±0.5	190±0.1	15.9±0.1	201±1.52
F7	99.5±0.6	191±0.4	15.8±0.3	223±2.93
F8	99.2±0.4	195±0.3	16.1±0.3	235±3.56
F9	98.6±0.5	193±0.2	15.8±0.2	199±3.65

All values are expressed as mean ± SD, n=3

***In-vitro* dissolution studies:** The dissolution profiles of formulated batches were compared with that of the marketed product. The F1 batch pellets were prepared by using HPMC E-5 at a concentration of 0.5% shows 99.9% drug release at the end of 4th hr, and to control the drug release we prepared the pellets with the combination of polymers. From F2-F5 formulations were prepared by using the combination of HPMC-E5, and Ethyl cellulose N-50. Form F6-F9 formulations were prepared by using the combination of Eudragit L-100 and Ethyl cellulose N-50. F2 shows 99.5% drug release at the end of 10th hr. The dissolution result of batch from F3-F6 does not match with the innovator product. The drug release profile was shown below in **Fig. 3, 4, 5**.

The F7 batch were prepared by using 2% of Ethyl cellulose N-50 and 2% Eudragit L-100 match with the dissolution profile of marketed product and the release profile was shown in **Fig. 6**. Further increasing the concentration of polymers from F8-F9 the drug release was decreased.

Scanning Electron Microscopy: Scanning electron microscopy images of the optimized formulation were shown in **Figure 7**.

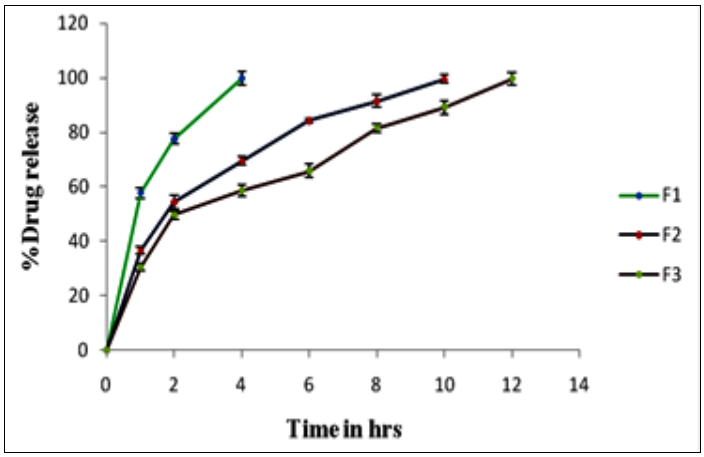


FIGURE 3: DISSOLUTION PROFILES OF F1 TO F3

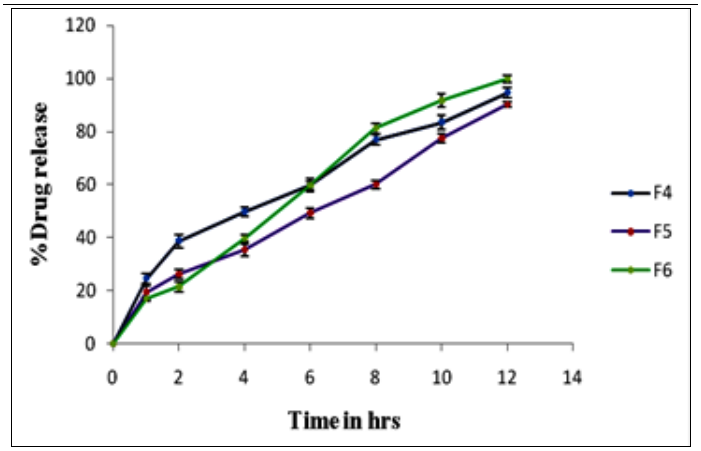


FIGURE 4: DISSOLUTION PROFILES OF F4 TO F6

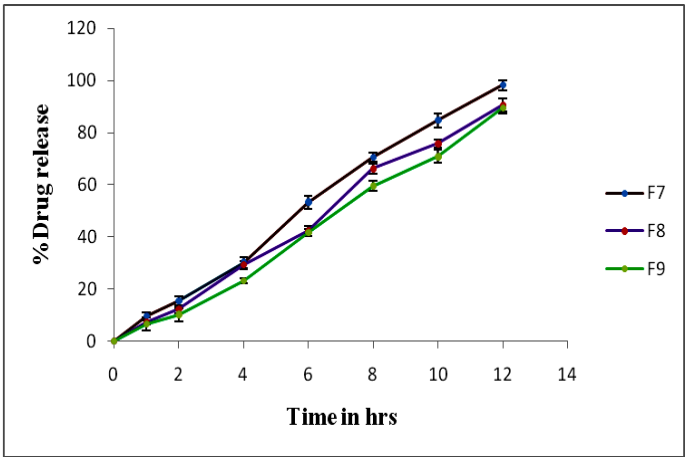


FIGURE 5: DISSOLUTION PROFILES OF F7 TO F9

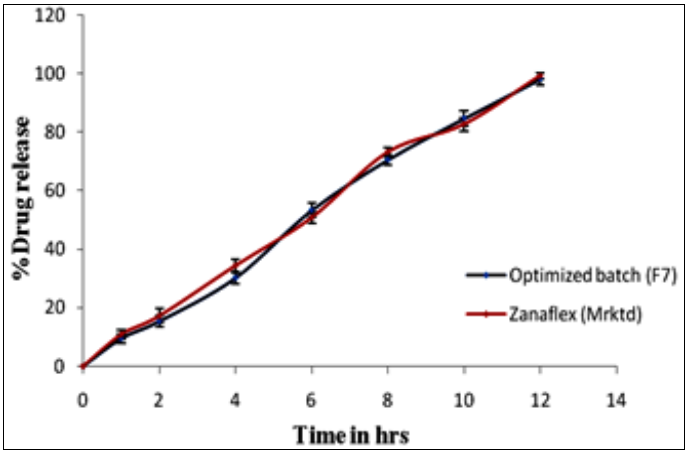
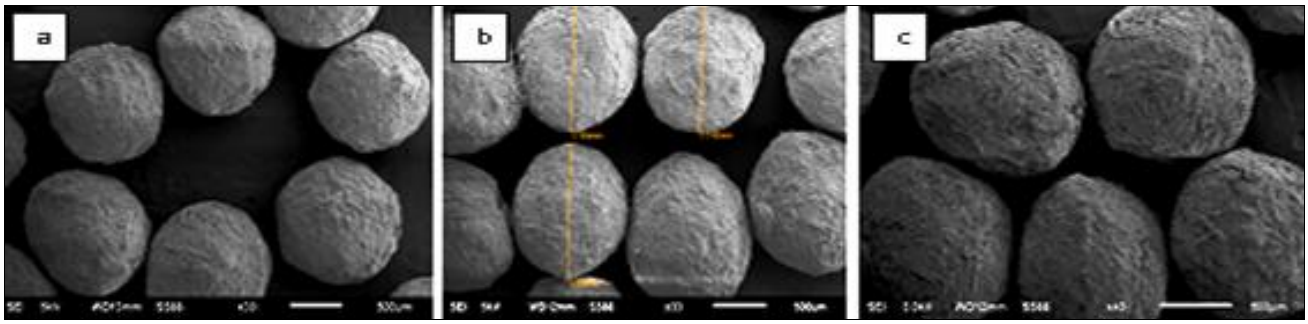


FIGURE 6: DISSOLUTION PROFILES OF OPTIMIZED PRODUCT (F7) WITH MARKETED (ZANAFLEX)



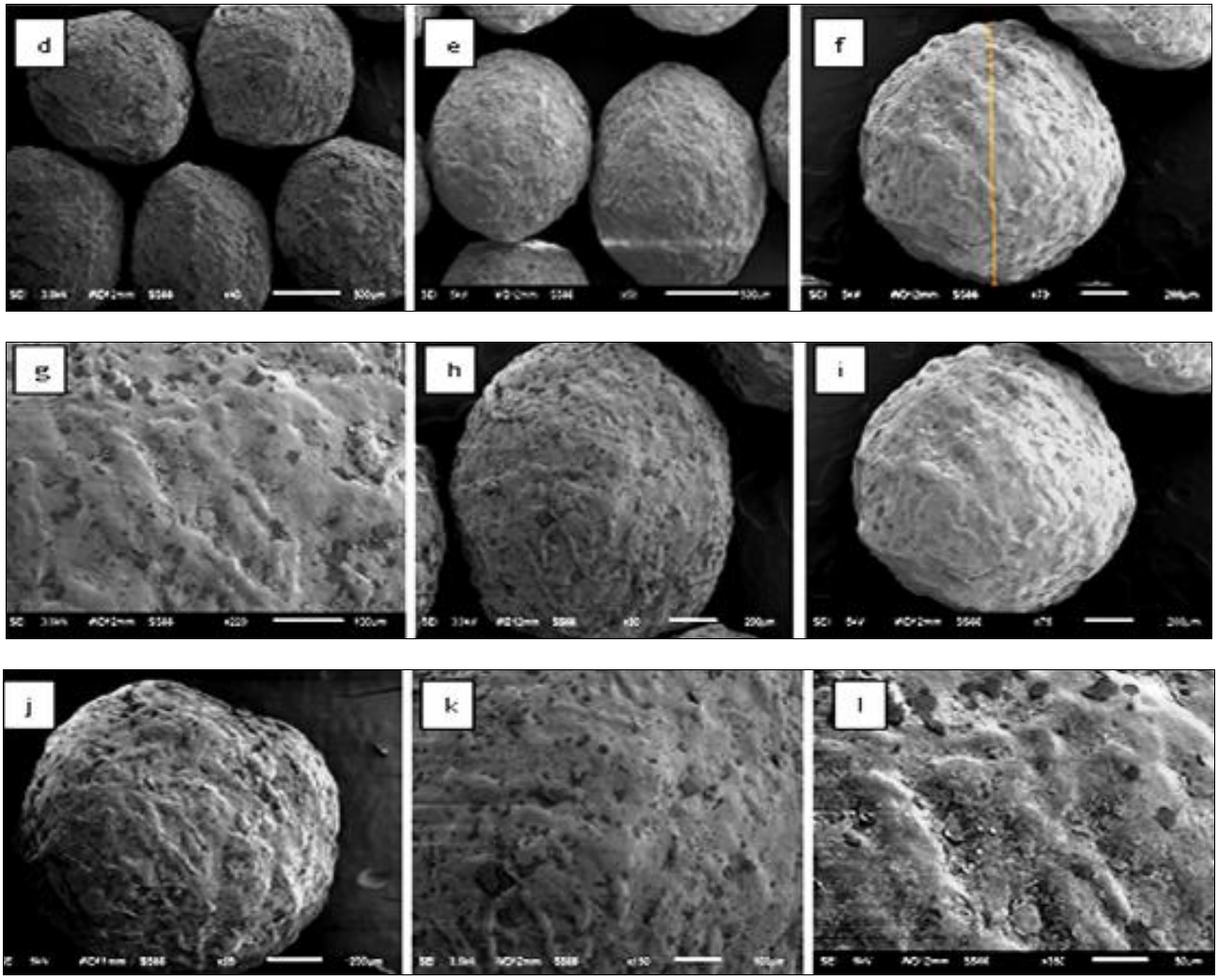


FIGURE 7: IMAGES OF SEM AT DIFFERENT MAGNIFICATIONS a) 30x, b) 33x, c) 40x, d) 43x, e) 50x, f) 70x, g) 75x, h) 80x, i) 85x, j)150x, k) 220x, l) 360x

Drug Release Kinetics: The regression values of optimized formulation were given in **Table 7**. The release kinetics followed zero order kinetics by non-Fickian case-II diffusion process & was shown in **Fig. 8**.

TABLE 7: DRUG RELEASE KINETICS OF FORMULATED PELLETS FOR OPTIMIZED BATCH (F7)

Batch	Zero order		Higuchi		Peppas model			First order		Hixson-Crowell	
	r^2	k	r^2	k	r^2	k	n	r^2	k	r^2	k
F1	0.9278	31.95	0.9980	56.79	0.9889	57.01	0.490	0.7801	2.134	0.9359	1.319
F2	0.8541	8.669	0.9884	31.38	0.9911	38.28	0.425	0.8672	0.444	0.9734	0.341
F3	0.8917	7.064	0.9875	27.59	0.9733	32.35	0.440	0.7634	0.350	0.9274	0.269
F4	0.9396	7.059	0.9930	26.94	0.9899	25.00	0.524	0.9332	0.209	0.9765	0.214
F5	0.9825	6.887	0.9555	25.21	0.9703	17.49	0.615	0.9074	0.168	0.9556	0.186
F6	0.9827	8.476	0.9528	30.98	0.9793	14.72	0.778	0.7586	0.412	0.9415	0.310
F7	0.9956	8.410	0.9213	30.03	0.9919	8.609	0.984	0.8162	0.278	0.9348	0.262
F8	0.9943	7.743	0.9091	27.48	0.9938	6.637	1.058	0.9154	0.179	0.9631	0.202
F9	0.9941	7.528	0.8900	26.44	0.9878	5.649	1.098	0.8882	0.165	0.9455	0.191
M	0.9978	8.251	0.9371	29.68	0.9972	10.02	0.922	0.7741	0.294	0.9192	0.265

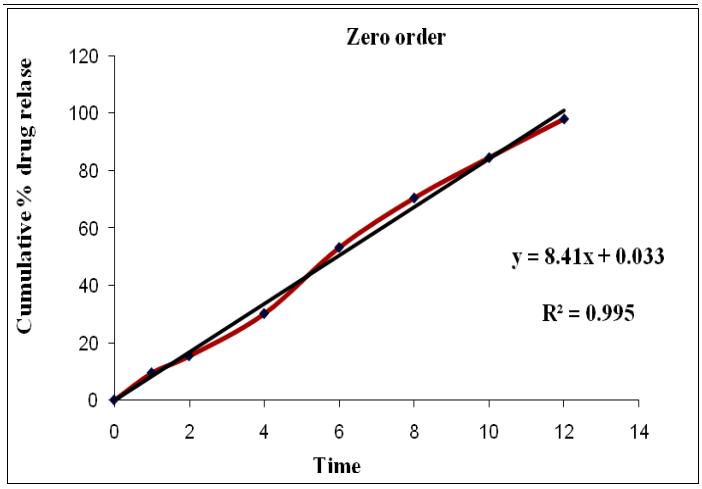


FIGURE 8: PLOT OF CUMULATIVE% DRUG RELEASE VS TIME FOR F7

TABLE 8: CHARACTERISTICS OF PELLETS FOR OPTIMIZED BATCH (F7)

PARAMETERS	RESULTS
Dose	'6' mg
Description	Hard gelatin capsule, with light blue body containing white spherical pellets of 16#20.
Capsule size	'3'
Filled weight of the capsule	188 mg
Sieve analysis for 100g of pellets (16#20)	#16 passed =99g #20 retained =99g
Similarity factor (*f2*)	69

Stability Studies: Stability studies were carried out as per ICH guidelines for F7 batch for 3 months of this product at long term: 25±2°C/60±5% RH, intermediate: 30±2°C/65±5% RH and accelerated: 40±2°C/75±5% RH storage conditions as shown in **Fig. 9, 10, 11**.

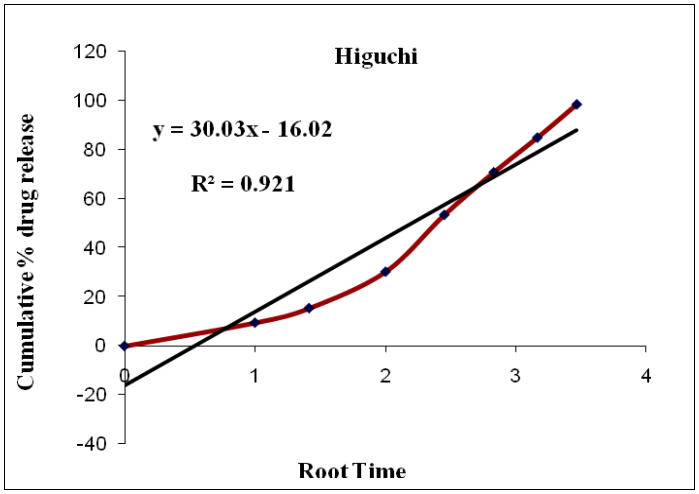


FIGURE 9: PLOT OF CUMULATIVE% DRUG RELEASE VS ROOT TIME FOR F7

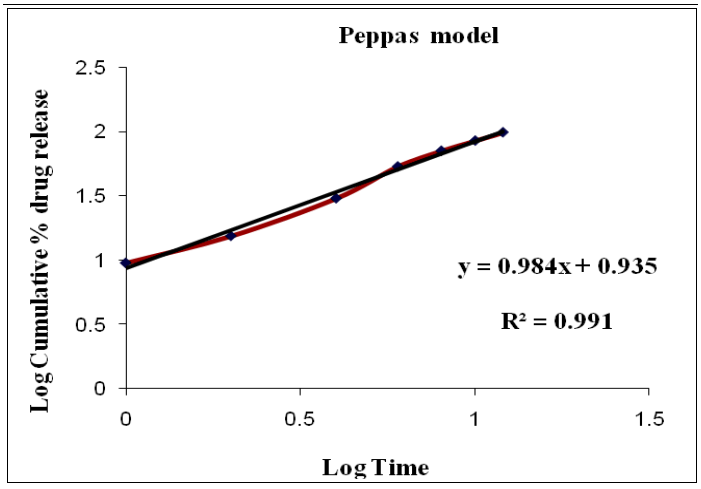


FIGURE 10: PLOT OF LOG CUMULATIVE % DRUG RELEASE VS LOG TIME FOR F7

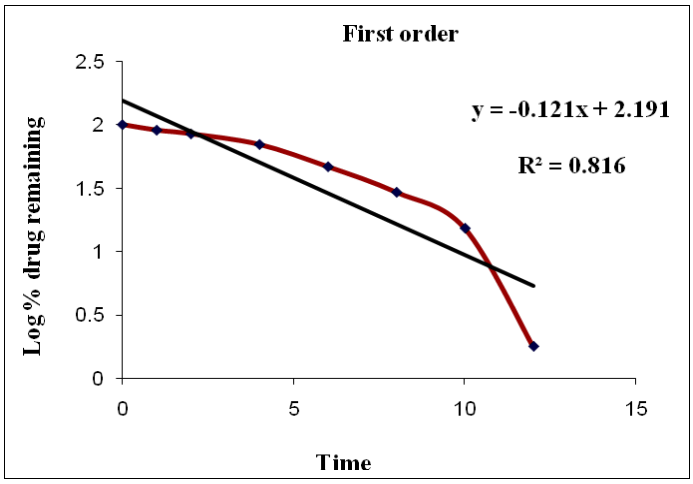


FIGURE 11: PLOT OF LOG % DRUG RELEASE VS TIME FOR F7

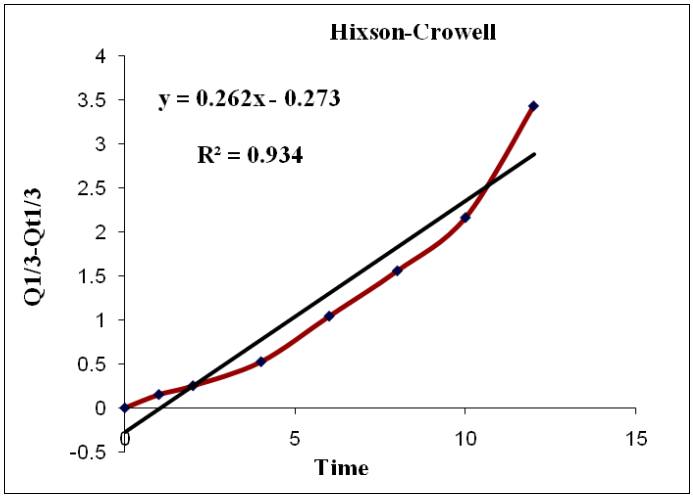


FIGURE 12: PLOT OF Q1/3-QT1/3 VS TIME FOR F7

There was no change observed in the assay, disintegration, moisture content, content uniformity, dissolution profiles were listed in **Table 9**.

TABLE 9: EVALUATION PARAMETER VALUES AT DIFFERENT TEMPERATURE CONDITIONS

Parameters	Stability Conditions		
	25±2°C/60±5%RH	30±2°C/65±5%RH	40±2°C/75±5%RH
	F7	F7	F7
Assay (%)	99.5	98.2	98.0
Moisture Content (%)	3.9	2.9	3.2
Disintegration (sec)	232	220	228

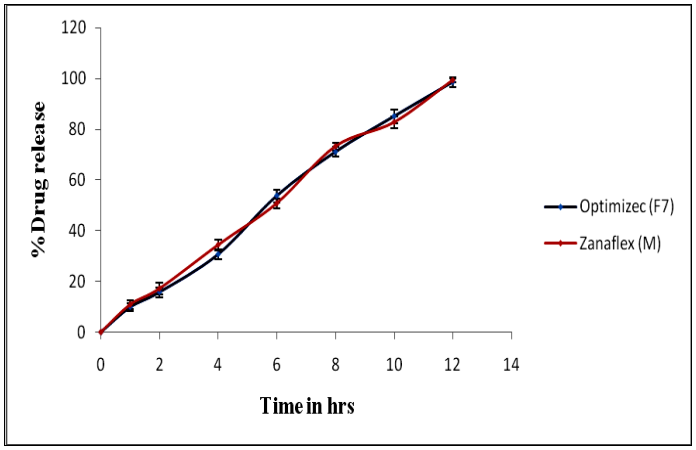


FIGURE 13: *IN-VITRO* DISSOLUTION PROFILE OF F7 AND MARKETED AT 25°C/60% RH

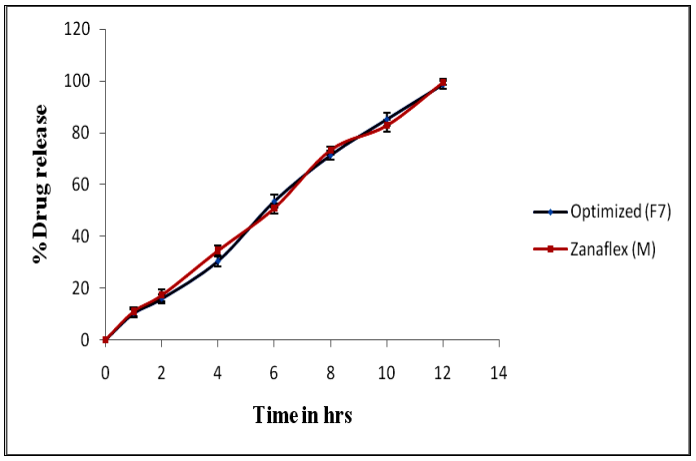


FIGURE 14: *IN-VITRO* DISSOLUTION PROFILE OF F7 AND MARKETED AT 30°C/65% RH

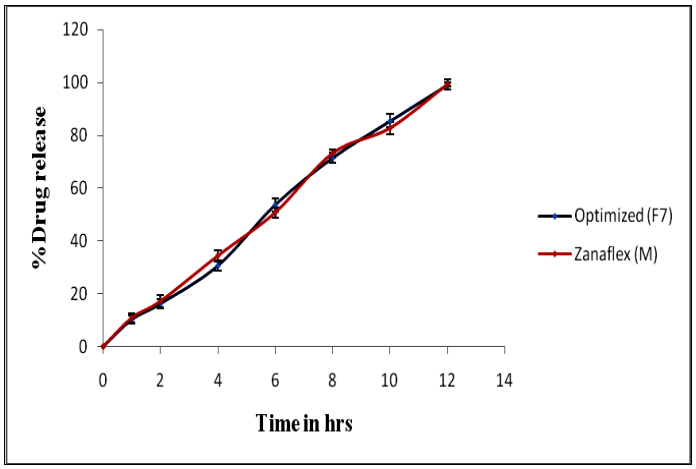


FIGURE 15: *IN-VITRO* DISSOLUTION PROFILE OF F7 AND MARKETED AT 40°C/75% RH

The aim of the present investigation was to design and evaluate sustained release multi particulate system of Tizanidine hydrochloride. The parameters like assay, weight variation, content uniformity, lock length, disintegration test and *in-vitro* dissolution studies were within the limits. The kinetics data of various models revealed that the formulation followed zero order kinetics by non-Fickian case-II diffusion process. Optimized batch (Formulation F7) complies with innovator product (Zanaflex capsules) and thus considered as an ideal formulation.

ACKNOWLEDGEMENTS: The authors are grateful to Mr. Susanta Kumar Hazra, Assistant Director, Glukem Pharmaceuticals, Hyderabad, for providing a gift sample of Tizanidine HCL. They are also indebted to Mrs. D. Vasavi Reddy and Mr. A. Brahma Reddy for their valuable support and suggestions for carrying out this research work.

REFERENCES:

1. Chugh Isha, Seth Nimrata, Rana A.C, Gupta Surbhi. Oral sustained release drug delivery system: An Overview, *International Research Journal of Pharmacy* 2012; 3:57-62.
2. Haritha. VVN. Multi particulate drug delivery system. Pelletization, *American Journal of PharmTech Research* 2012; 2:81-87.
3. Ghebre-Sellassie I, Pellets: An overview. Pharmaceutical Pelletization Technology. Marcel Dekker, Inc. New York 1989; 37:1-13.
4. Van Tulder MW, Touray T, Furlan AD, muscle relaxants for nonspecific low back pain: A systematic review within the framework of the Cochrane Collaboration. Spine 2003; 28:1978-1992.
5. Beard S, Hunn A, Wight J, Treatment for spasticity and pain in multiple sclerosis; a asystematic review. *Health Technology Assessment* 2003; 70:9-3.
6. Abdul Althaf. S, Venkateswarulu. Y & Umal Khair. S Modified release capsules of Ambroxil, Preformulation and evaluation, *Pelagia Research Library* 2011; 2:1-19.
7. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, Tutorial Pharmacy. New Delhi, India: CBS Publishers and Distributors, 1986; 211-233.
8. Muthukumaran M, Senthil Kumar K L, Ratnam B C, formulation and evaluation of delayed release pellets of Rabeprazole Sodium, *International Journal of Pharmacy and Industrial Research* 2011;1:790-793.
9. Mullin J.W. Sieving of pharmaceuticals. In Encyclopedia of Pharmaceutical Technology; Swarbrick, J, Boylan, JC, Marcel Dekker, New York 1996; 14:63-86.
10. Anand Kumar M, Lakshmi PK, Balasubramanium J. Formulation Development and Invitro Evaluation of

Tamsulosin HCl Extended Release Pellets. *International Journal of Pharmaceutical Technology and Research* 2011; 3:968-979.

11. Kotta Kranthi Kumar, N. Dora Babu, A Pasupathi, Design and evaluation of multi particulate system of extended release indomethacin capsules USP, *Research Journal of Pharmaceutical & Biological and Chemical Sciences* 2010; 1:74.
12. Ahmed Abdalla, Karsten Mader, Preparation and characterization of a self-emulsifying pellet formulation, Martin Luther University, Germany. *European Journal of Pharmaceutics and Bio pharmaceutics* 2007; 16:220-226.
13. Prasanta Chowdhury, Padala Narasimha Murthy, Lilakanta Nath and Suvakanta Dash, kinetic modeling on drug release from controlled drug delivery systems, *Acta Poloniae Pharmaceutica-Drug Research* 2010; 69:217-223.
14. Shah V.P, Y. Tsong and P. Sathe, In vitro dissolution profile comparison-statistics and analysis of the similarity factor, *f*2. Center for *Drug Evaluation and Research Food and Drug Administration* 1998; 15:889-896.
15. ICH Harmonized Tripartite guideline, validation of analytical procedures: Text and methodology Q2 (R1), ICH steering committee, 2005.

How to cite this article:
Thriveni M, Reddy AB, Reddy DS and Reddy DV: Design and Evaluation of Sustained Release Multiparticulate system of Tizanidine hydrochloride. *Int J Pharm Sci Res* 2013; 4(4); 1614-1625.