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FORMULATION AND EVALUATION OF TIZANIDINE SUSTAINED RELEASE MATRIX TABLETS USING HYDROXY PROPYL METHY CELLULOSE

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Muscle Relaxant,
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ABSTRACT

Tizanidine is a muscle relaxant agent, with the half life of 2.5 hours and requires daily doses to maintain adequate plasma concentrations. The present study was undertaken to with an aim to formulation development and evaluation of Tizanidine hydrochloride sustained release tablets using hydrophilic polymer to sustain the action of Tizanidine. Different batches of Tizanidine hydrochloride were prepared based on preformulation studies using HPMC K100M HPMC K4M and HPMC K100 having different viscosities to calculate the sustained release properties. Tizanidine hydrochloride was analysed by using HPLC using wavelength 240 nm. Results of *in-vitro* study indicate that the trial formulation 5 having considerable sustaining property. From the discussion it is concluded that the trial formulation 5 had considerable *in-vitro* drug release. Trial formulation 5 can be taken as an ideal or optimized formulation of sustained release tablets for 12 hours release and it fulfils all the requirements for sustained.

INTRODUCTION: Oral route of drug administration is the most common and oldest route of drug administration. It poses several advantages. Most of the orally administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other body tissues. For this reason, most systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase circulating blood levels, which in turn, promotes greater concentration of drug at the site of action.

The basic goal of the therapy is to achieve steady state blood level for prolonged period of time. Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make the some drug more effective by slight alteration in the drug delivery. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration often the drug in the body. This article contains the basic information regarding sustained-release formulation and also the different types of the same**.** The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses have been obvious to the pharmaceutical industry for some time.

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The desire to maintain a near constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. Introduction of matrix tablets as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology.

It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in the marketing of new drug entities, has focussed greater attention on development of sustained release drug delivery systems.

Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of drug, that is dissolved or dispersed. In fact a matrix is defined as a well mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time. sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients.

Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/ insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs. Various drug delivery techniques.

MATERIAL AND MEHOD: HPMC K100M,MCC 101, Acrypol 971 G, Instamoistshield, Ludipress, Dicalcium phosphate HPMC, K4M, HPMC K100, PVP K-30, Aerosil, Talc, Magnesium stearate, Stearic acid.

Identification of Tizanidine by U.V.:

Identification of Tizanidine by HPLC:

Tizanidine STD disso: Sample of tizanidine working standard.

Ret. Time: Retention time is the time taken by peak to appear.

Area: Total area covered by the peak.

Height: Is the height of the peak.

Drug and polymer compatibility studies: This can be confirmed by carrying out with Infrared light absorption scanning spectroscopy (IR) studies. Infrared spectra of pure drug, polymer and physical mixture of formulations in ratio 1:1 were recorded by dispersing them in a suitable solvent (KBr) using Fourier Transform Infrared spectrophotometer. A base line correction was made using dried potassium bromide and the spectra of the pure drug, polymer and the formulation mixture were recorded on FTIR. The data are shown in **Fig. 5, 6, 7, 8 and 9**.

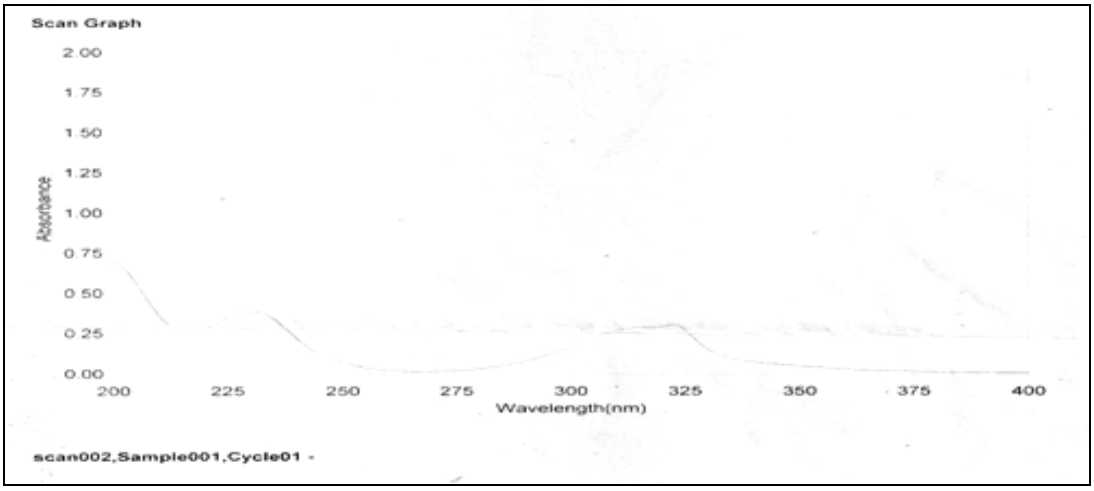
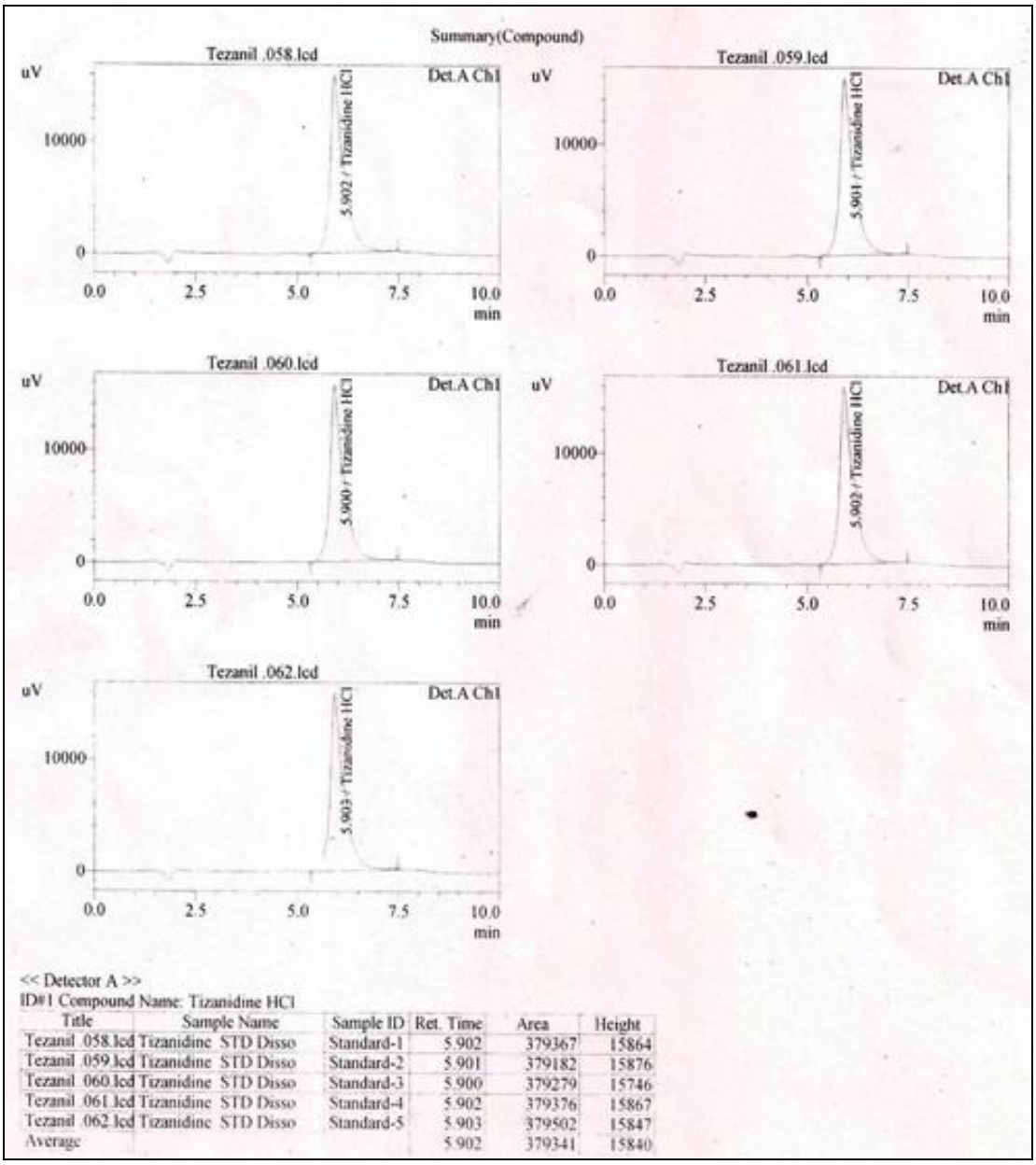


FIG. 1: IDENTIFICATION OF TIZANIDINE BY U.V.



<< Detector A >>
ID#1 Compound Name: Tizanidine HCl

Title	Sample Name	Sample ID	Ret. Time	Area	Height
Tezanil .058.lcd	Tizanidine STD Disso	Standard-1	5.902	379367	15864
Tezanil .059.lcd	Tizanidine STD Disso	Standard-2	5.901	379182	15876
Tezanil .060.lcd	Tizanidine STD Disso	Standard-3	5.900	379279	15746
Tezanil .061.lcd	Tizanidine STD Disso	Standard-4	5.902	379376	15867
Tezanil .062.lcd	Tizanidine STD Disso	Standard-5	5.903	379502	15847
Average			5.902	379341	15840

FIG. 2: IDENTIFICATION OF TIZANIDINE BY HPLC

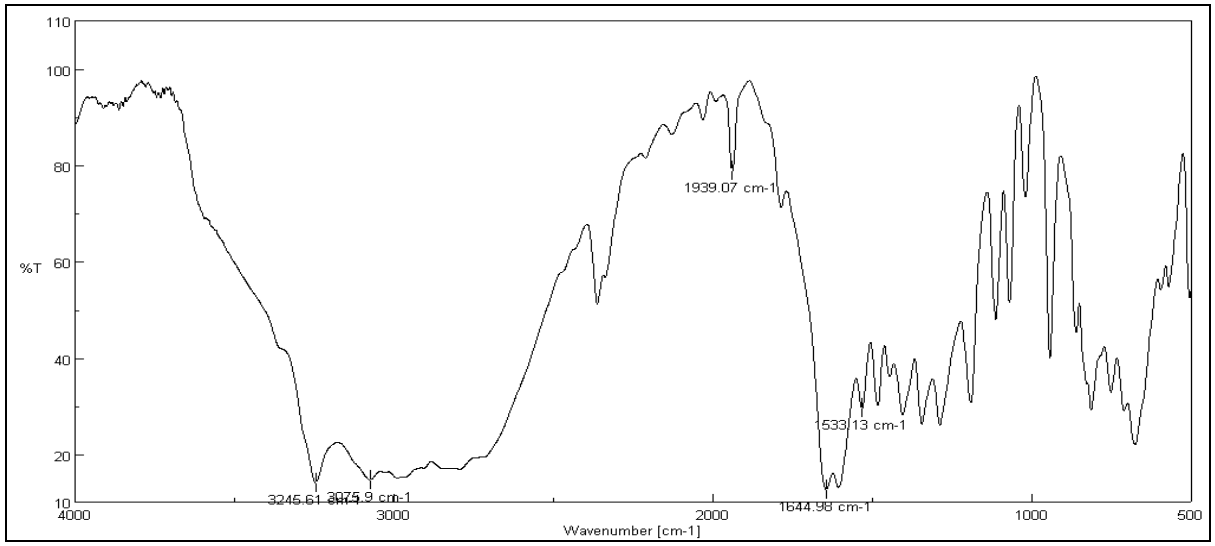


FIG. 3: IR SPECTRA OF PURE TIZANIDINE HCl

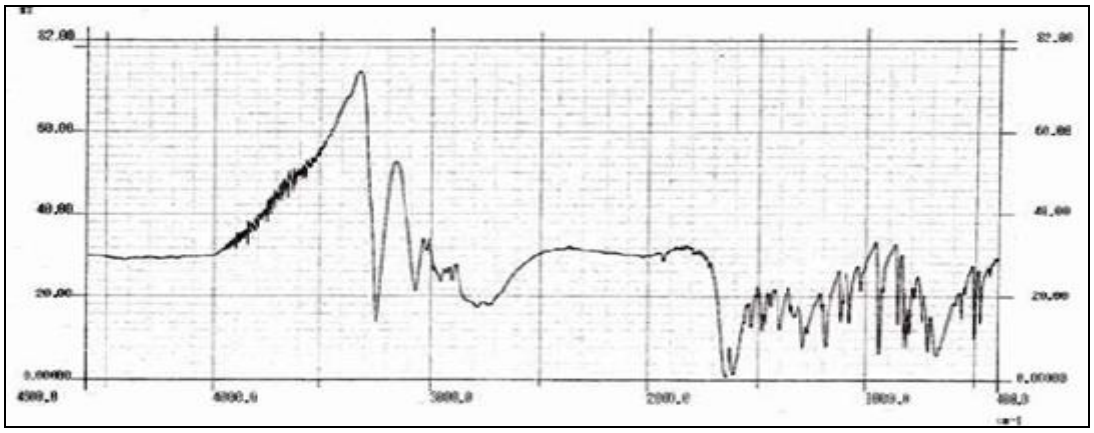


FIG. 4: IR SPECTRA OF SAMPLE TIZANIDINE HCl

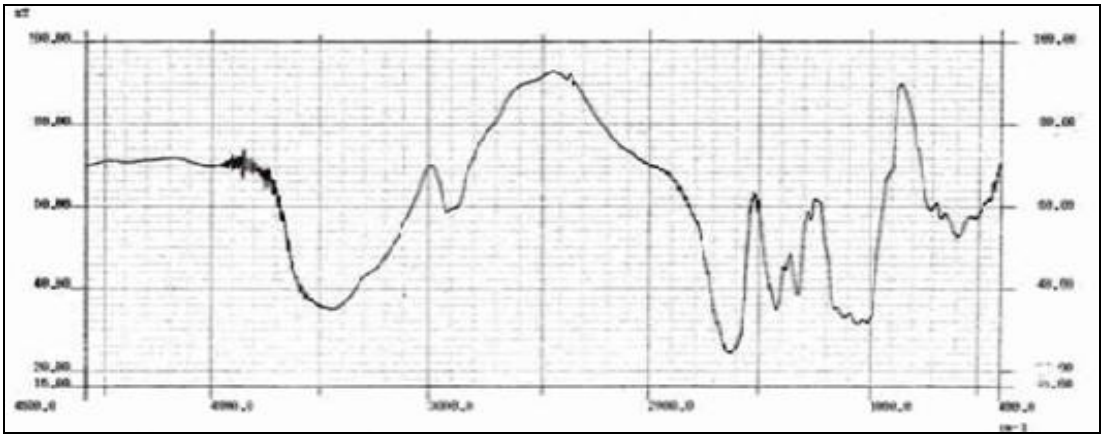


FIG. 5: IR Spectra of HPMC K100M

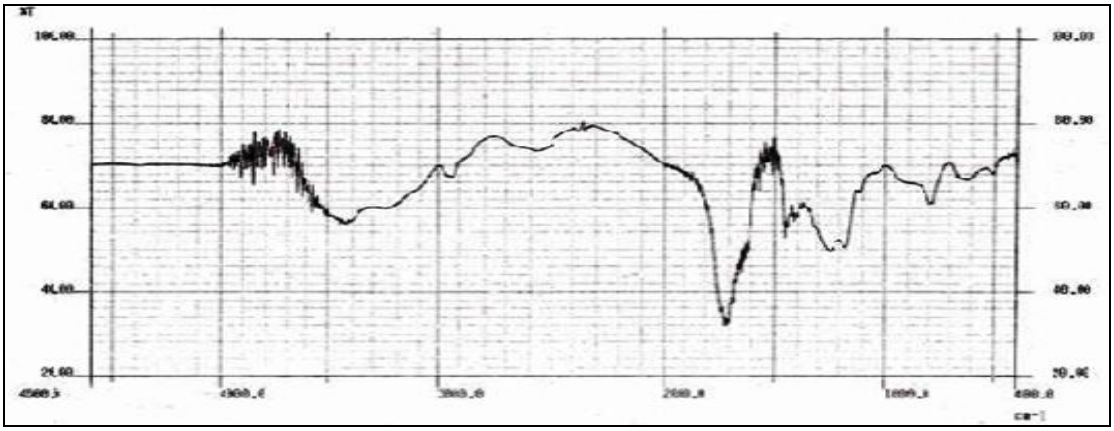


FIG. 6: IR SPECTRA OF HPMCK4M

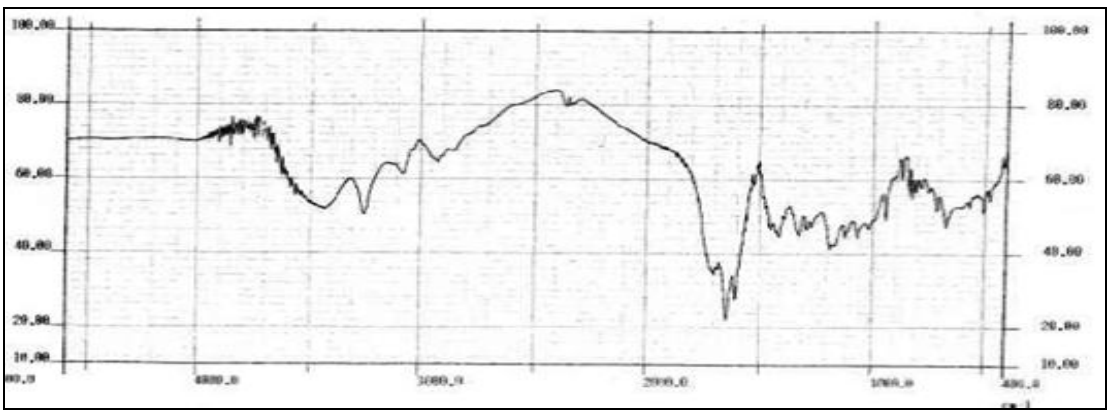


FIG. 7: IR SPECTRA OF PVP K-30

TABLE 1: FORMULATION OF TIZANIDINE SUSTAINED RELEASE TABLETS

Ingredients	F1	F2	F3	F4	F5
Tizanidine HCl	6.87	6.87	6.87	6.87	6.87
MCC 101	56	_	-	-	-
HPMC K100M	20.13	45	20	80	-
Acrypol 971G	-	20	-	-	-
Instamoistshield	-	2	-	-	-
HPMC K100	-	-	-	-	80
HPMC K4M	-	-	50.13	40	40
Ludipress	-	-	15.00		
Dicalcium phosphate	-	-	-	37.13	37.13

Methodology:

Step 1: Weighing and sifting: Weigh all the ingredients accurately and passed through 60 # sieve.

Step 2: Dry mixing: Mix Tizanidine hcl, H.P.M.C. K 100 M, H.P.M.C. K 4 M, and Dicalcium phosphate for 10 minutes.

Step 3: Preparation of binder solution : Take weighed quantity of PVP K-30 and dissolve slowly with constant stirring in quantity sufficient of I.P.A.

Step 4: Granulation: Now granulate the dry mix of step 2 with binder solution with hard binding so that the granules are properly formed.

Step 5: Drying : Now dry the granules in the oven not more than 50°C to 55°C.

Step 6: Sifting and milling: Now after drying check the L.O.D. of the granules which should not be less than 1.65, and sift the granules through 30# sieve. And mill the oversize granules using 1.0 mm screen to get the granules of desired size.

Step 7: Blending : After sifting blend the granules with extragranular ingredients Aerosil and Talc for 10 minutes.

Step 8: Lubrication: Now finally lubricate the blend with stearic acid for 2 minutes.

Step 9: Compression : Compress the blend using 8mm standard round concave punches.

TABLE 2: PHYSICAL PARAMETERS OF BATCHES

FORMULATION CODE	Average Wt. (in mg)	Thickness (in mm)	Hardness (kg/cm^2)
F1	90	3.31	5
F2	95	3.31	5
F3	95	3.41	7
F4	170	3.69	7
F5	170	3.54	8

FIG.1.8: TIZANIDINE SR TABLETS OF TRIAL FORMULATION 5

RESULT AND DISCUSSION:

TABLE 3: DRUG RELEASE FROM MATRIX TABLETS USING HPMC

S. NO	%DRUG RELEASED
Trial formulation 1	Upto 80% after 4 hrs.
Trial formulation 2	Upto 80% - 90% after 6 hrs.
Trial formulation 3	Upto 80% - 90% after 6 hrs.
Trial formulation 4	Upto 80% - 90% after 8 hrs.
Trial formulation 5	Upto 80% - 90% after 12 hrs.

Dissolution Drug Profile: Value of zero order constant k_0 trial batch 4 were found to be 11.4 and value of Regression coefficient is 0.9103.

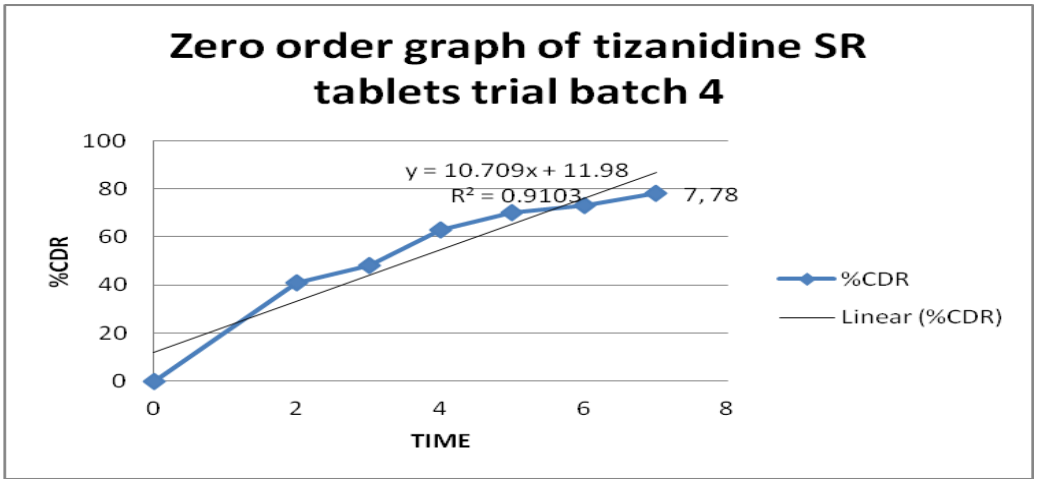


FIG. 9:

Value of first order constant k_1 trial batch 4 were found to be 0.309 and value of Regression coefficient is 0.9891.

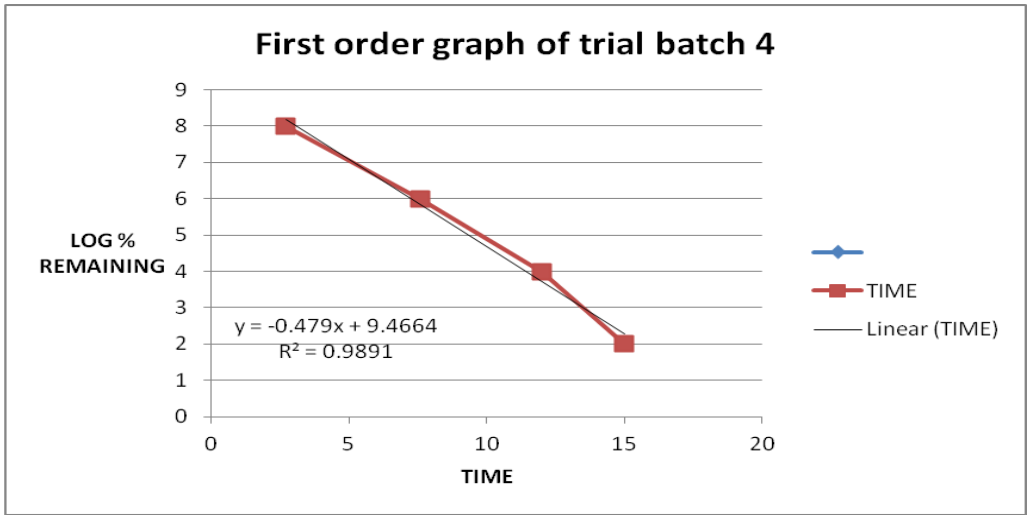


FIG. 10

Value of Higuchi constant k_h of trial batch 4 were found to be 19.5 and value of Regression coefficient is 0.9397.

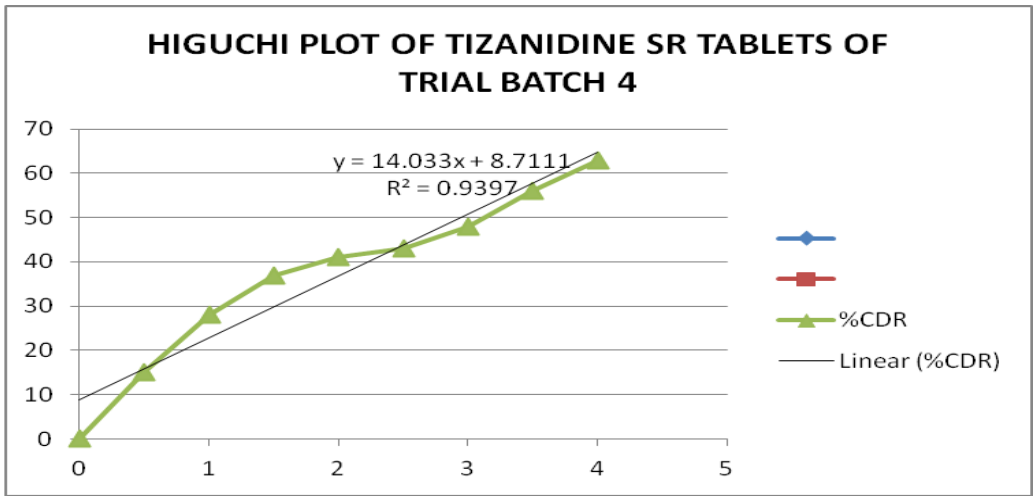


FIG. 11

Value of n found to be 0.88 i.e. the plot follows the non fickian law.

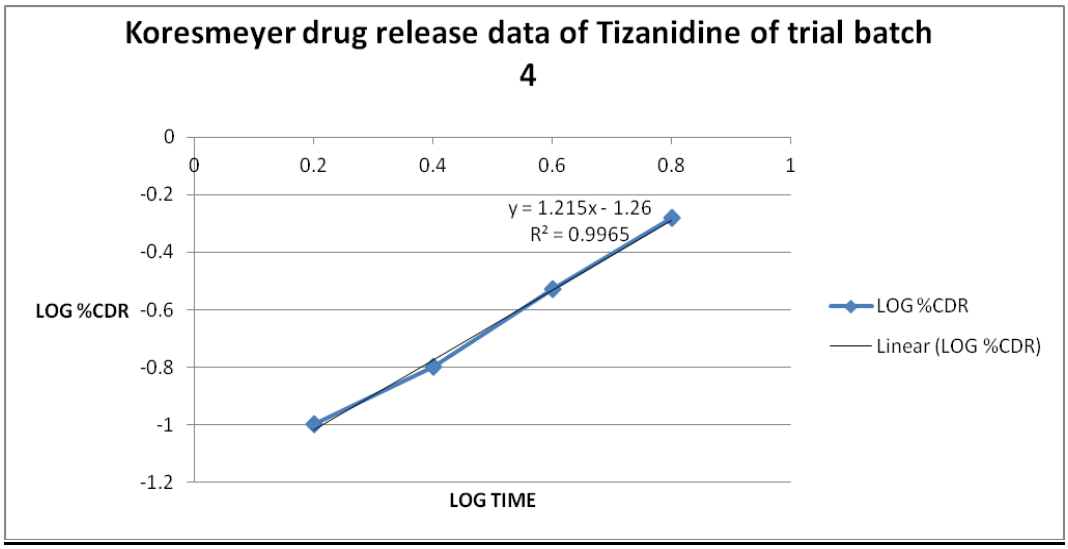


FIG. 12

The value of of zero order constant k_0 optimized batch 5 were found to be 7 and value of Regression coefficient is 0.97.

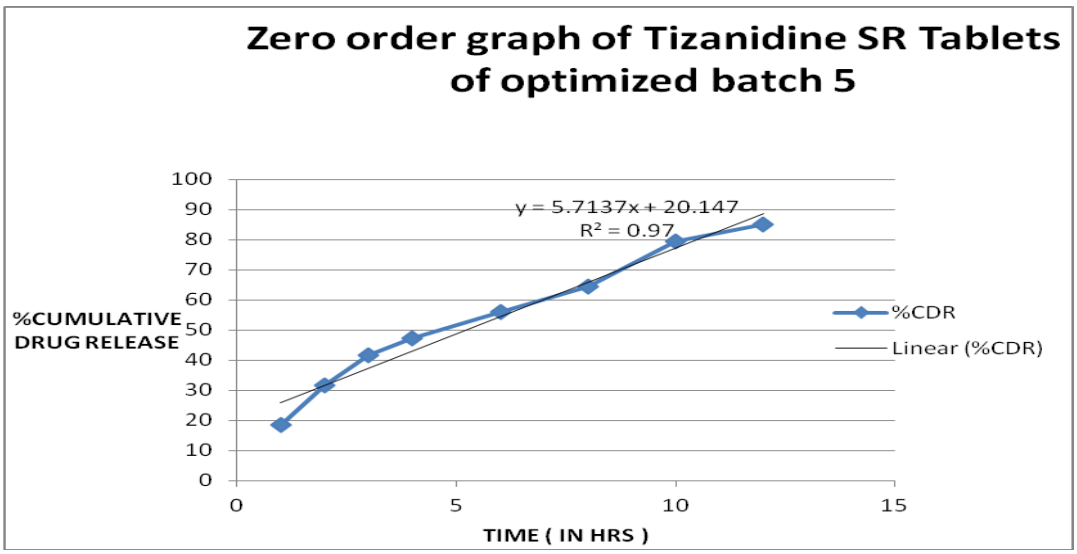


FIG. 13

The value of first order constant k_1 optimized batch were found to be 0.52 and value of Regression is 0.9926.

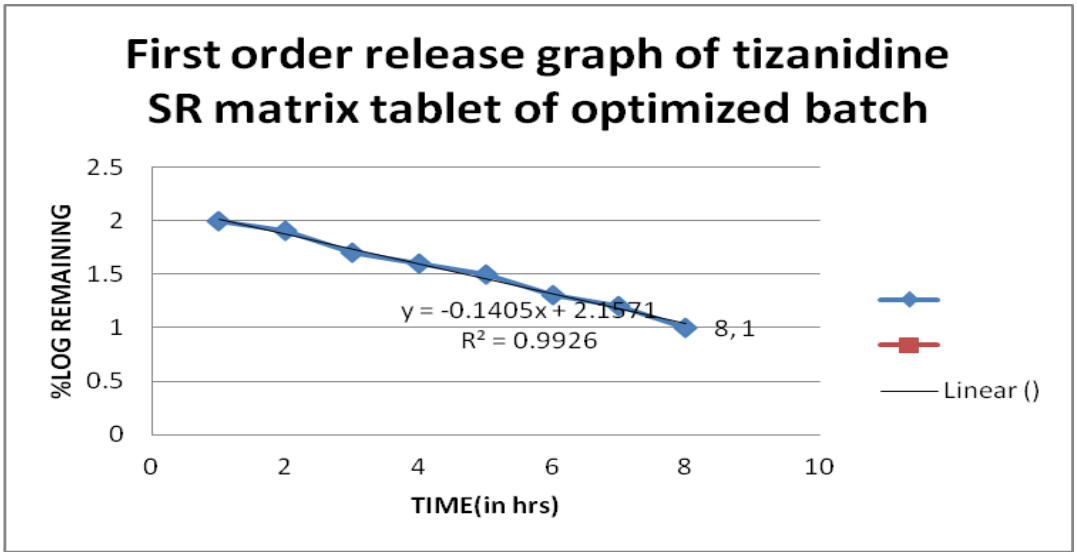


FIG. 14

The value of Higuchi constant k_h optimized batch were found to be 14.166 and value of Regression coefficient is 0.9615.

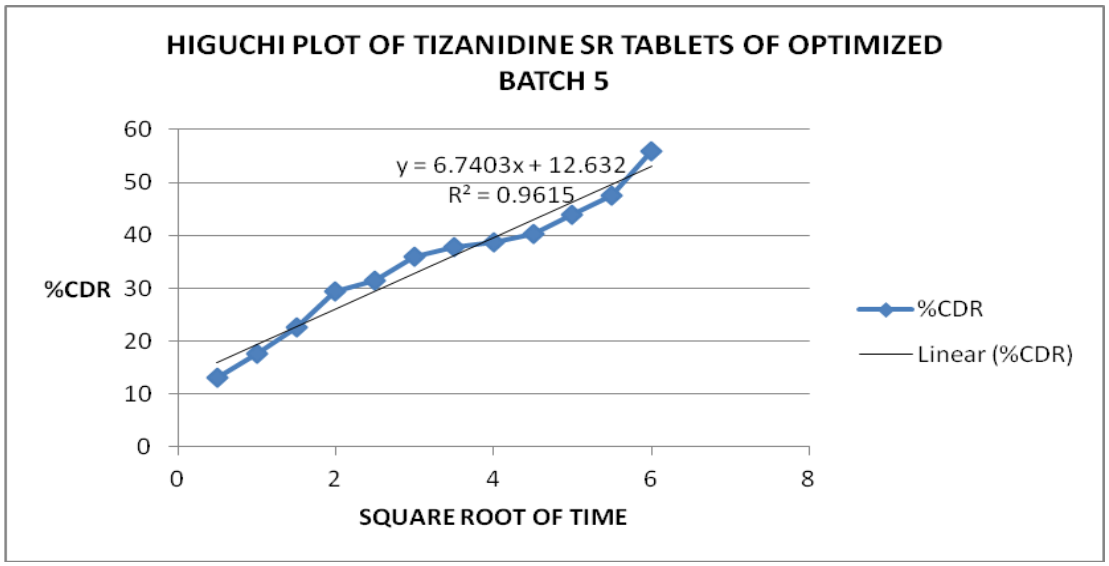


FIG. 15

The value of n found to be 0.86 in the Koresmeyer peppas i.e. the plot follows the non-fickian law.

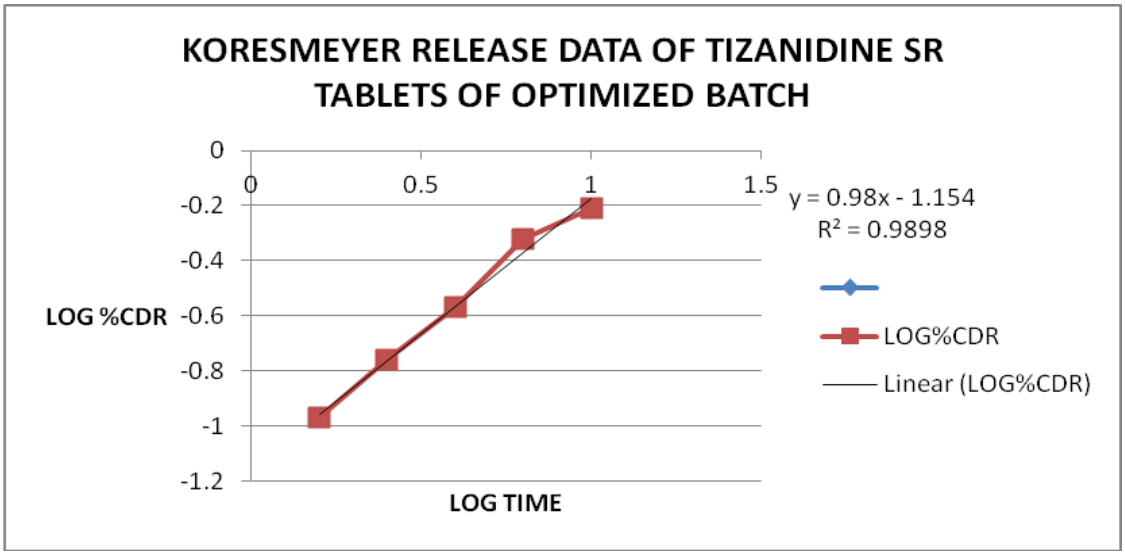


FIG. 16:

The SR tablets of Tizanidine were formulated using Hydroxy propyl methyl cellulose HPMC K100M, HPMC K4M and HPMC K100. It was observed that the therapeutic action of Tizanidine were sustained for more longer time by using two grades of HPMC (K4M and K100) in the optimized batch (Trial batch 5).

The main problem observed during the first three formulation were the unevenness and non-uniformity in the reading when analysed by using U.V. spectrophotometer. The next two batches were analysed using HPLC. The satisfactory result were observed with the HPLC.

So finally, the optimized were formulated by using HPMC K100 and K4M.

CONCLUSION: The action of Tizanidine and its $t_{1/2}$ can be prolonged or sustained by using hydrophilic polymer HPMC to avoid fluctuation in the drug plasma level, to increase patient compliance, to reduce dosing frequency.

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