International Journal of Pharmacy and Biological Sciences-IJPBS™ (2020) 10 (2): 238-248
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved

Formulation and Evaluation of Matrix System for Simultaneous Sustained Release of Diclofenac Sodium and Tizanidine Hydrochloride

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Received: 10 Jan 2020 / Accepted: 8 March 2020 / Published online: 01 April 2020
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Abstract

The aim of the present investigation was to formulate and evaluate matrix tablets system for diclofenac sodium and tizanidine to achieve an extended drug release with reduced frequency of drug administration, reduced side effects and improved patient compliance. In the present study, matrix tablets were formulated in which sustained release layer was prepared by using synthetic polymer like ethyl cellulose by wet granulation method. The tablets were evaluated for Physico-Chemical Properties such as Hardness, Friability, Thickness Weight variation, Drug content uniformity. The In vitro release studies were performed in 0.1 N HCl for first two hr. and in 6.8 pH Phosphate buffer up to 12 hr. It was observed that matrix tablets having formulation code F1-F12 which contained 50% ethyl cellulose were successfully sustained the release of drug up to 12hr. FT-IR studies revealed that there was no interaction between the drug and polymer used in the study.

Keywords

DICS-diclofenac sodium, TIZH-tizanidine hydrochloride Sustained release, Ethyl cellulose

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INTRODUCTION

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid) must be developed within the intrinsic characteristics of gastrointestinal physiology, pharmacokinetics and pharmacodynamics as formulation design is essential to achieve a systemic approach to the successful development of an oral dosage form.[1]

To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. [2]

- The physical state of drug.
- The matrix shape and alteration in volume as a function of time.
- The route of administration.
- The release kinetic model.

DICS and TIZH have been used in combination because there are minor differences in the pharmacokinetics of both the drugs. These two drugs are commonly prescribed by the doctors for the relief of pain and inflammations. Sustained release formulation of DICS and TIZH will be able to prolong the release of the both the drugs and reduce the fluctuations in plasma drug concentrations as in case

of conventional dosage form will thus minimize or prevent plasma peak-related adverse events and allow prolongation of the dosing interval enabling a once or twice daily administration with inherent benefits in terms of patient compliance. Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time, thus achieving better patient compliance and allowing a reduction of both the total dose of drug administered and the incidence of adverse side effects. Among the different approaches studied with this aim, matrix systems appear as one of the most attractive; from both the economic, as well as, process development and scale-up point of view[3].

\MATERIALS AND METHOD

Diclofenac sodium (DICS) and Tizanidine hydrochloride (TIZH) was obtained as gift sample from Lupin Research Park, Pune. Methocel- K4M and Avicel PH 101,102 was obtained as gift sample from Colorcon Pvt. Ltd, Goa. Chitosan was obtained as gift sample from Panecea Biotech, Mumbai. Guar gum, Potassium dihydrogen phosphate (AR), Methanol (AR), Methanol (HPLC grade), Water (HPLC grade) were given by SIRT college from company Merck India Ltd., Mumbai. Sodium alginate, sodium hydroxide, magnesium stearate, xanthan gum, ethyl cellulose was given by SIRT college from Loba Chemie Pvt. Ltd., Mumbai. All other chemicals and reagents used were of "analytical reagents" (AR)

Micromeritic characterization of drug[4]

Loose bulk density and Tapped bulk density

10 gm sample was carefully introduced into a 25 mL graduated cylinder. The volume occupied by the powder was recorded and bulk density then calculated, and the cylinder was dropped at 2-second intervals onto a hard wood surface 100 times from a height of 1 inch

$D_f = M / Vp$

$D_o = M / Vp$

Where,

D_f = Loose bulk density

M = Weight of samples in grams

Vp = Final volume of powder in cm^3

D_o = Tapped bulk density.

Compressibility Index and Hausner's ratio

The compressibility index and the Hausner ratio are determined by measuring **both** the bulk density and the tapped density of a powder.

Compressibility= (tapped- loose bulk density)/loose bulk density*100

Hausner's ratio=tapped density/loosed bulk density

Angle of repose

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed.

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

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

Where,

θ = Angle of repose.

h = Height.

r = Radius

UV-VIS spectrophotometric Method for DICS and TIZH

Selection of solvent Study of spectra and selection of analytical wavelengths

The solvent phosphate buffer pH 6.8 was used for the preparation. An amount equivalent to 10 mg of the reference standard DICS and TIZH was added to 100 mL volumetric flasks separately. DICS and TIZH was dissolved separately in around 50 mL Phosphate Buffer Saline (PBS) pH 6.8 in a 100 mL volumetric flask with vigorous shaking followed by ultrasonication for about 5 minutes. The volume was made up to the mark with the same solvent to obtain standard stock solutions of concentration, 100 µg/ mL of both drugs. By appropriate dilution of the standard stock solution, working standard solutions of suitable concentrations (10 µg/ mL) of DICS and TIZH were prepared separately. The standard solutions were then scanned in the spectrum mode of the instrument from 400 nm to 200 nm to determine λ_{max} (wavelength maximum) for both DICS and TIZH.

Study of Beers-Lambert's Law

Preparation of standard stock solutions:

Standard stock solutions (100µg/mL) of DICS and TIZH were prepared separately. 10 mg of drug was dissolved in 50 mL of distilled water in 100 mL volumetric flask with shaking and then volume was made up to the mark with same solvent.

Preparation of standard calibration curves and selection of analytical concentration ranges: For DICS, appropriate aliquots of standard stock solution of the drug were transferred to a series of 10 mL volumetric flasks. The volume was made up to the mark with PBS pH 6.8 to obtain working standard solutions of concentrations of 5, 10, 15, 20….35 µg/mL. TIZH appropriate aliquots of standard stock solution of the drug were transferred to a series of 10 mL volumetric flasks. The volume was made up to the mark with PBS pH 6.8 to obtain working standard solutions of concentrations of 3, 6, 9, 12, 15…21 µg/mL. Similarly, for the absorbance of three replicates of the working standard solutions of each concentration were measured at the selected

analytical wavelengths. The standard calibration curves of absorbance vs. concentration were plotted.

Multicomponent detection analytical method[5,6] (Simultaneous Equation Method)

In this method absorbance were measured at λ_{max} (λ_1 and λ_2) of both the drugs, i.e. DICS (10 µg/mL) and TIZH (10 µg/mL). Two equations were constructed based upon the fact that at λ_1 and λ_2, the absorbance of the mixture is the sum of the individual absorbance of DICS and TIZH.

$$C_{DICS} = A_2ay_1-A_1ay_2 / ax_2ay_1-ax_1ay_2 C_{TIZH} = A_1ax_2-A_2ax_1 / ax_2ay_1-ax_1ay_2$$

Where, A_1 and A_2 are absorbance of mixture at λ_1 and λ_2, ax_1 and ax_2 are absorptivities of DICS at λ_1 and λ_2 respectively. ay_1 and ay_2 are absorptivities of TIZH at λ_1 and λ_2 respectively and C_{Diclo} and C_{Tiza} are concentrations of DICS and TIZH respectively.

Determination of solubility of DICS and TIZH

Saturation solubility of DICS and TIZH was determined in 0.1 N HCl, pH 1.2, pH 4.5 buffer and pH 6.8 phosphate buffer solutions. All media were prepared and excess quantity of DICS and TIZH was individually added to it and kept for shaking on mechanical shaker for 48 hrs. After 48 hrs of shaking, 1 mL of aliquot was taken out from each sample and filtered through whatman filter paper (45µm). Filtrates were diluted with respective solution (i.e. 0.1 N HCl, pH 1.2, pH 4.5 buffer and pH 6.8 phosphate buffer). Absorbance was measured and solubility was determined for both the drugs.

Method Development by HPLC for DICS and TIZH

Selection of mobile phase[8]

The criteria employed for selection of particular solvent system for the analysis was cost, time required for analysis, sensitivity of the assay and solvent noise for the analysis of DICS and TIZH from tablet formulation. various ratios of acetonitrile (ACN): water (HPLC grade) 25mM phosphate buffer pH 7 were tried to develop a sensitive and accurate method like.

1. ACN: Water (70: 30 v/v)
2. ACN: Water (50: 50 v/v)

Then, phosphate buffer pH 7 was used instead of water.

1. ACN: 25mM phosphate buffer pH 7 (70: 30 v/v)
2. ACN: 25mM phosphate buffer pH 7 (50: 50 v/v)

Preparation of standard stock solutions and Selection of analytical Wavelength[8]

Standard stock solutions (100µg/mL) of DICS and TIZH were prepared separately. Dissolve 10 mg of drug in 100 mL of volumetric flask with 50 mL of acetonitrile: water (HPLC grade) (1:1v/v) with shaking and then volume was made up to the mark with same solution.

By appropriate dilution of the standard stock solution with mobile phase, various concentrations of DICS and TIZH were prepared separately. Their spectra were obtained using the double beam UV visible spectrophotometer (Table 1-4).

Table No.1 Concentration and absorbance values for DICS in PBS pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance at 276.2 nm*
1	0	0
2	5	0.1645
3	10	0.2917
4	15	0.4469
5	20	0.6141
6	25	0.7359
7	30	0.8553
8	35	1.015
	R^2	**0.999**
	Slope	**34.7718**
	Intercept	**-0.4222**

Table No.2 Concentration and absorbance values for TIZH in PBS pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance at 321 nm*
1	0	0
2	3	0.1393
3	6	0.290184
4	9	0.41925
5	12	0.5975
6	15	0.747
7	18	0.881
8	21	0

R^2	**0.999**
Slope	**34.7718**
Intercept	**-0.4222**

Table No.3 Concentration and area value for DICS

Sr. No.	Concentration (µg/ml)	AUC at 220.0 nm*
1	0	0
2	6	170493
3	8	233270
4	10	285990
5	12	338344
6	14	384983
7	16	438985
	R^2	**0.998**
	Slope	**27403**
	Intercept	**6207**

Table No.4 Concentration and area value for DICS

Sr. No.	Concentration (µg/ml)	AUC at 220.0 nm*
1	0	0
2	2	113455
3	4	197389
4	6	286789
5	8	370610
6	10	449783
7	12	539245
	R^2	**0.997**
	Slope	**43993**
	Intercept	**15652**

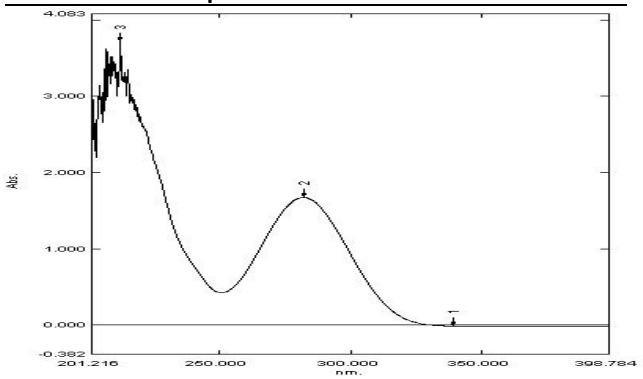

Fig. No. 1 UV spectra of DICS (10µg/mL) in PBS pH 6.8 (λ_{max}=276.2nm)

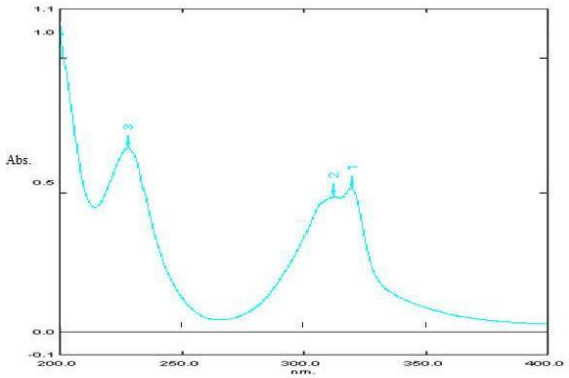

Fig. No. 2 UV spectra of TIZH (10µg/mL) in PBS pH 6.8 (λ_{max}=320nm)

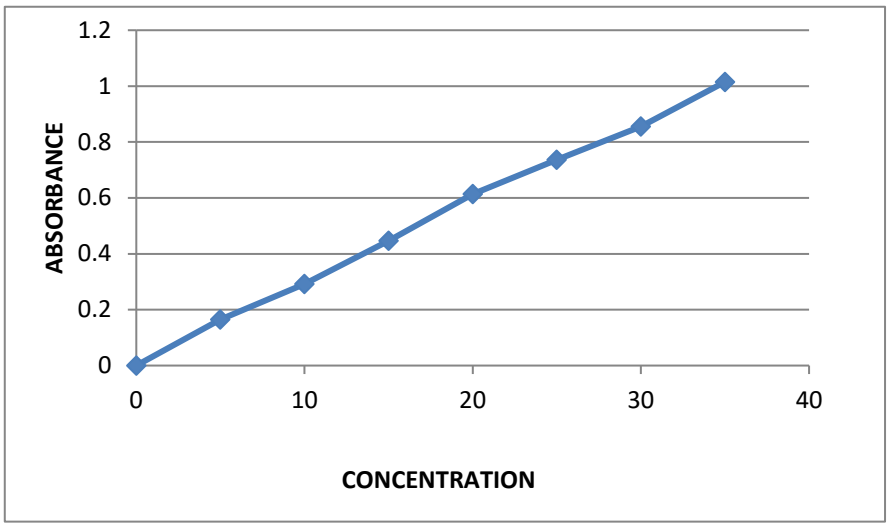

Fig. No. 3 Calibration Curve of DICS

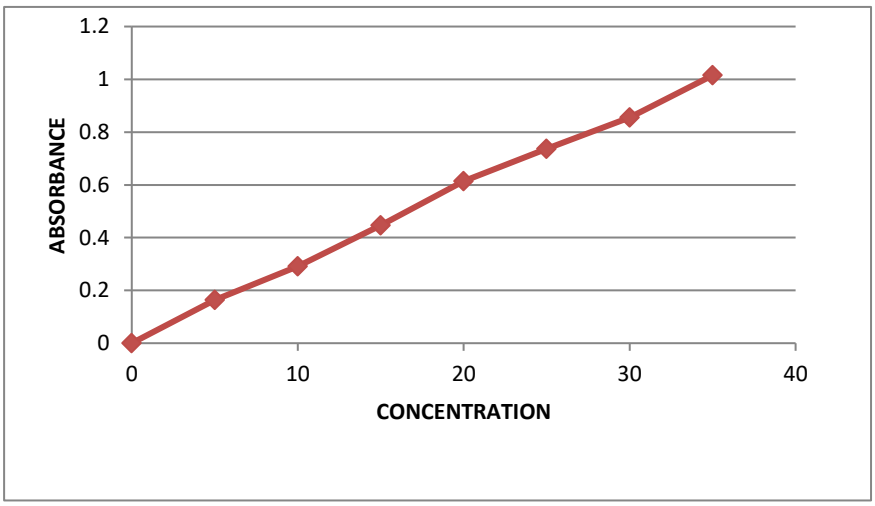

Fig. No. 4 Calibration Curve of TIZH

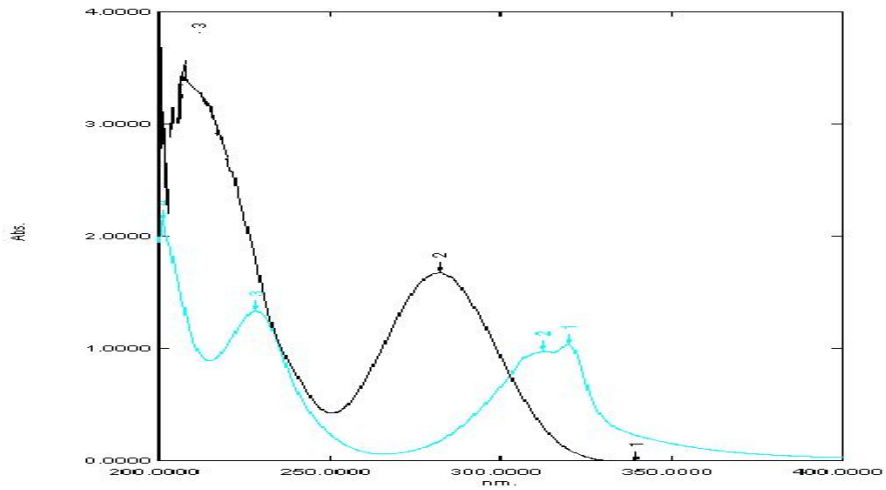

Fig. No. 5 Overlay UV spectra of DICS and TIZH in PBS pH 6.8

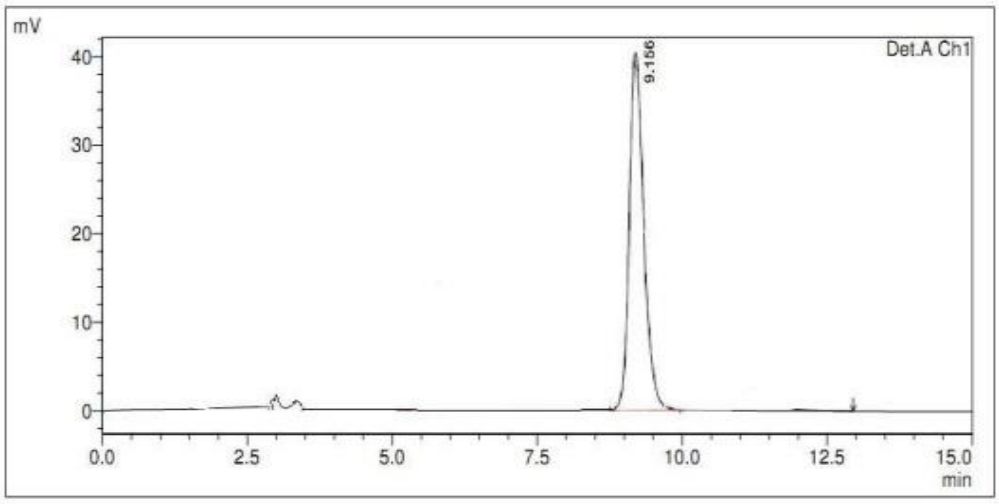

Fig. No. 6 Chromatogram of Pure DICS

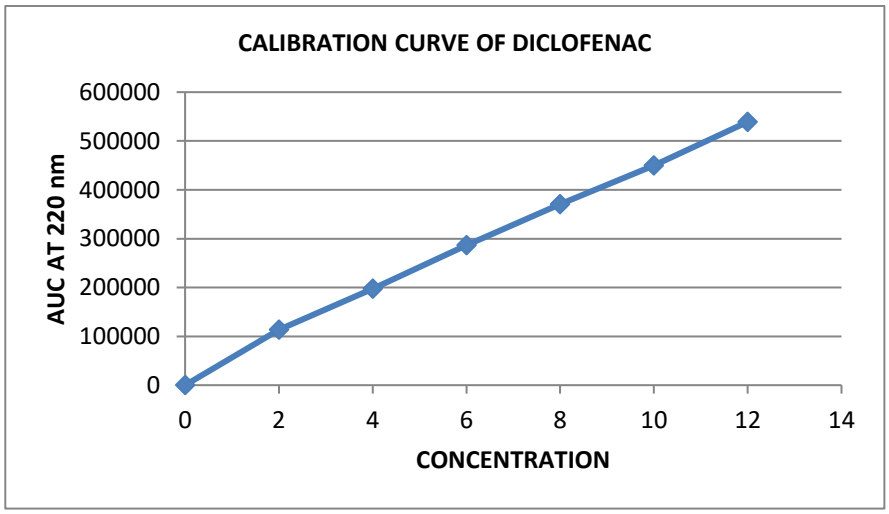

Fig. No. 7 Calibration curve of DICS

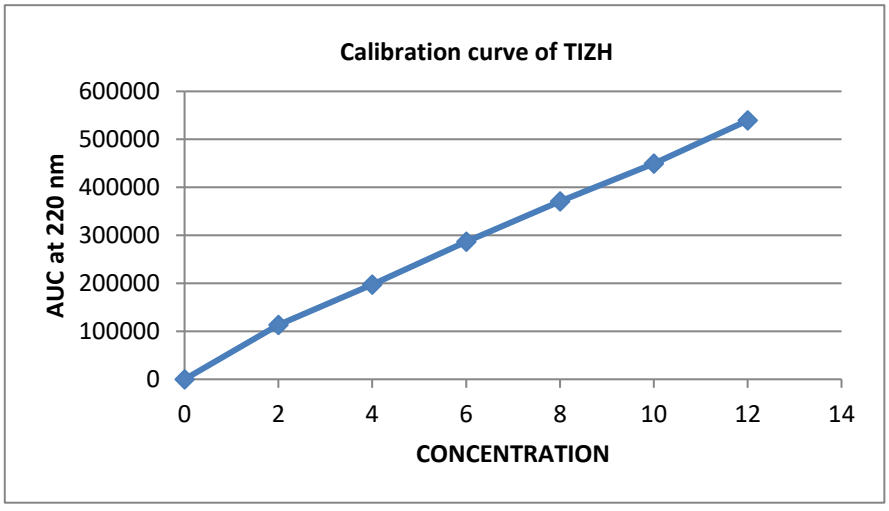

Fig. No. 8 Calibration curve of TIZH

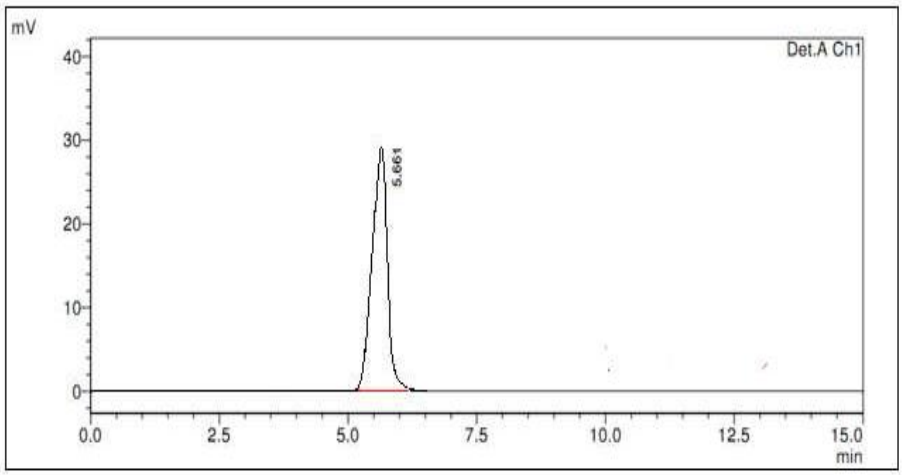

Fig. No. 9 Chromatogram Of TIZH

Preparation of Standard Calibration curves of DICS and TIZH by HPLC Method (Table 3 and Table 4)

Chromatographic conditions[8]

The chromatographic column used was a reverse phase 4.6µ250 mm Hypersil C_{18} HPLC column with 5µm (particles) packing. The column and the HPLC system were kept at ambient conditions. The mobile phase was ACN: Phosphate buffer pH 7.0 (50:50 v/v) delivered at a flow rate of 1.0 mL/min. The injection volume was 25 µL. Elute was analyzed by a UV detector set at 220 nm. For preparation of standard calibration curve, appropriate aliquots were pipette out from stock solutions into a series of 10 mL volumetric flasks. The volume was made up to the mark with mobile phase to obtain a set of solutions of DICS having concentration range 2-10 µg/mL each and 2.5-12.5 µg/mL for TIZH. Triplicate dilutions of each concentration of drug were prepared. From these triplicate solutions, 25µl injection of each concentration of drug was injected into the HPLC system. Evaluation of both drugs was performed with the UV detector set at 220 nm. Peak area was recorded and working calibration curves were plotted separately with peak area Vs the respective concentration of DICS and TIZH.

Formulation Development

All of the formulations contained 100 mg DICS, 6.86 mg of TIZH, 1% (w/w) magnesium stearate, microcrystalline cellulose (MCC) and different amounts of various polymers. The composition of various formulations is listed in Table 5 and 6.

Table No.5 Composition of formulations

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
DICS	100	100	100	100	100	100	100	100	100	100
TIZH	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86
HPMCK4 M	30	45	60	90	120	150	-	-	-	-
HPMCK15 M	-	-	-	-	-	-	90	120	150	-
HPMCK100 M	-	-	-	-	-	-	-	-	-	90
Avical 102	145.14	130.14	100.14	70.14	40.14	100.14	70.14	40.14	100.14	-
Mg. Stearate	3	3	3	3	3	3	3	3	3	3
Total weight	300	300	300	300	300	300	300	300	300	300

(All quantities are in mg)

Table No.6 Composition of formulations

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
DICS	100	100	100	100	100	100	100	100	100	100
TIZH	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86	6.86
Guar gum	15	30	90	200	30	-	-	-	-	-
Chitosan	-	-	-	-	-	60	60	30	-	-
Sodium Alginate	3	3	3	3	3	60	30	60	-	-
Xanthan gum	-	-	-	--	-	-	-	-	30	60

Ethyl cellulose	-	-	-	--	-	-	-	-	30	60
Avical 102					160.14	70.14	100.14	100.14	130.14	70.14
Avicel 101	175.14	160.14	100.14	100.14	-	-	-	-	-	-
Mg.stearate	3	3	3	3	3	3	3	3	3	3
Total weight	300	300	300	300	300	300	300	300	300	300

(All quantities are in mg)

Preparation of Matrix Tablets

Various formulations of tablets were prepared as shown in Table 5 and 6. The drug powder and other ingredients were passed through an 80-mesh sieve before mixing. In order to keep the volume and surface area of tablets relatively constant, the final weight of each tablet was maintained at 300 mg. All of the formulations contained 100 mg of DICS, 6.86 mg of TIZH (6.86 mg of tizanidine hydrochloride equivalent to 6 mg of tizanidine), 1% (w/w) magnesium stearate and different amounts of various polymers and Avicel-102. The composition of various formulations is listed in Table 5 and 6. DICS, TIZH and other ingredients were weighed, and the mixture was then blended with magnesium stearate (1% w/w) as lubricant in a polybag, and then compressed into tablets. All tablets were prepared using six station rotary tablet machine (GMC Mumbai) equipped with standard concave punches of 9-mmdiameter.

Evaluation parameters for tablets[6,7]

Hardness

Although hardness test is not an official, tablet should have sufficient handling during packing and transportation. Hardness of tablet was measured using Monsanto hardness tester. The hardness of 6 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in kg/cm^2.

Weight variation test

Weigh 20 tablets individually, calculating the average weight and compare the individual tablet weight with respect to the USP weight variation test

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose.

The percentage friability was measured using the formula,

Where,

% F = friability in percentage Wo = Initial weight of tablet

W = weight of tablets after revolution

Thickness

The thickness of the tablet was measured using Vernier caliper. Thickness of five tablets from each batch was measured and mean was calculated

Content uniformity

For this at least 30 tablets were randomly selected. Out of 30 tablets, 10 tablets were crushed into fine powder and assayed individually.

***In vitro* dissolution studies**

The *in vitro* dissolution studies were performed using USP-22 type-II dissolution apparatus at 50 rpm. The dissolution medium consisted of phosphate buffer solution pH 6.8 for 12 hours (900 mL), maintained at 37°C ± 0.5°C. An aliquot (10 mL) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrophotometer (UV-1700- Shimadzu Japan) at 276.2 nm and at 320 nm for DICS and TIZH respectively by using simultaneous equation method. At each time of withdrawal, 10 mL of fresh corresponding dissolution medium was replaced into the dissolution flask. It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate.

Matrix integrity

Matrix integrity was observed throughout *in vitro* dissolution studies and the swollen mass of the tablets whether remains intact or not was checked.

Dissolution kinetic study[8,9]

Various mathematical models like; Zero-order model, First-order model, Higuchi (Matrix) model, Hixson and Crowell cube-root equation and Korsmeyer-Peppas Model were evaluated with respect to the dissolution profiles of the optimized formulations of HPMC K4M and guar gum. PCP disso-software was used to fit models to dissolution profiles.

Stability studies

The stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However, the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature.

RESULTS AND DISCUSSION

Micromeritic characterization of drug:

Table 2 shows the relationship between % compressibility and flow property of powder. From

micromeritic characteristics study it was found that both the DICS and TIZH have good flow properties.

UV-VIS spectrophotometric Method for DICS and TIZH: -

UV spectrum for DICS and TIZH are shown in Figure 1 and 2 respectively.

Study of Beers-Lambert's Law: calibration curve for DICS

The calibration curve for DICS and TIZN in PBS pH 6.8 is shown in Figure 3and 4 and Table no 3,4. The graph of absorbance vs. concentration for DICS was found to be linear in the concentration range of 5-35 µg/ml and 3-21 µg/ml at 276.2 nm and 320 nm. The r^2 of the calibration curve was found to be 0.999.

Multicomponent detection for DICS and TIZH (Simultaneous Equation Method)

In this method absorbances were measured at λ_{max} (λ_1 and λ_2) of both the drugs, i.e. diclofenac at λ_{max} of 276.2 nm and tizanidine at λ_{max} of 320 nm. Absorbance of DICS and TIZN was found to be 0.4849 and 0.07465 at 276.2nm and at 320 nm 0.01035 and 0.794 and Figure 5 shows the overlay spectra of DICS and TIZH.

Determination of solubility

The solubility data for DICS and TIZH as observed in 0.1 N HCl and buffers of pH values 4.5 and 6.8 was found to be 0.069, 3.803 and 18.9.

HPLC method development

Calibration curve of diclofenac sodium and tizanidine hydrochloride by HPLC

The chromatogram of pure **diclofenac sodium and tizanidine hydrochloride** at concentration 10 µg/ml and 2 µg/ml. The standard calibration curve and table for DICS and TIZH is shown Figure 6 and 7, Table 5 and 6 respectively. A linear correlation was found between area under the curve and concentration in the ranges 6 to 16 µg/ml and 2 to 12 µg/ml. The retention time was observed as 9.15 min and 5.66 min. The r^2 of the calibration curve was found to be 0.998 and 0.996.

Evaluation of tablets

Hardness of tablets of each formulation was measured and was found in the range of 5-8 kg/cm^2. Average weight of the tablet was found to be 300 ± 3 mg for all formulations. Percentage weight loss of the tablets of each formulation was measured and was found to be less than 1% for all the formulations. Diameter of formulations was found to be 9 ± 0.05 mm. Thickness was found to be 5 ± 0.2 mm for all the formulations. The content uniformity for all tablet formulations was found to be between 98.80 % to 100.40 % for DICS and 98.70 % to 100.20 % for TIZH. All parameter was shown on table 7

Matrix integrity

Integrity of a tablet matrices were studied at time interval of 1, 2, 4, 6, 8, and 12hr by visual observation. Matrices of tablets were found to have good integrity till the end of 12 hr. dissolution study, and as tablet matrices got eroded at controlled rate it was able to release both the drugs in controlled manner.

Dissolution kinetic study

Kinetics treatment

Table 8 shows the Kinetics treatment for the optimized formulations. From drug release kinetic model study, it was found that the **matrix (Higuchi) model** was best fitted for the optimized formulation F1 and F11, for both the drugs i.e., DICS and TIZH. From the regression value (R^2) it was found that Higuchi square root model was best fitted for both the formulations F1 and F11.

Stability study

Formulation F1 and F11 were kept for stability study, tablets were packed in PVC –PVDC coated aluminum - aluminum strip pack of 10 tablets and were kept at 45°C and 75% RH for 3 months. These formulations were evaluated for following parameters after stability study.

Table No.7 Micromeritic Characterization of Drugs

Sr. No.	Parameters	Result of DICS	Result of TIZH
1	Loose bulk density	0.43±0.03g/cm^3	0.51±0.04g/cm^3
2	Tapped density	0.49±0.04g/cm^3	0.58±0.06g/cm^3
3	Carr's Index	13.95±0.05 %	13.72±0.03 %
4	Hausner's ratio	1.139	1.137
5	Angle of Repose	30° 18'	28° 34'

Table No.8 Evaluation Parameter of Tablets

Formulation	Hardness (kg/cm²)*	thickness(mm)*	variation (mg)*	(%)*	DICS	TIZH
F1	6-7	5±0.10	300 ±2	0.60 ±0.02	99.20±0.20	98.90±0.20
F2	6-7	5±0.10	300 ±2	0.60 ±0.05	99.30±0.10	99.40±0.20
F3	6-7	5±0.10	300 ±1	0.60 ±0.05	98.90±0.20	99.30±0.30
F4	6-7	5±0.20	300 ±2	0.50 ±0.06	100.20±.20	98.70±0.30
F5	6-7	5±0.20	300 ±1	0.50 ±0.06	99.60±0.30	100.20±0.20
F6	6-7	5±0.20	300 ±2	0.46±0.04	99.45±0.20	99.80±0.40
F7	6-7	5±0.10	300 ±1	0.41 ±0.03	98.80±0.30	100.10±0.10
F8	6-7	5±0.20	300 ±2	0.50 ±0.06	99.20±0.10	98.70±0.30
F9	6-7	5±0.20	300 ±2	0.66 ±0.04	99.40±0.40	98.80±0.20
F10	6-7	5±0.10	300 ±1	0.61 ±0.04	99.70±0.10	99.20±0.10
F11	7-8	5±0.10	300 ±2	0.61 ±0.05	100.10±0.10	99.90±0.20
F12	7-8	5±0.20	300 ±3	0.56 ±0.03	99.30±0.20	99.70±0.20
F13	7-8	5±0.20	300 ±1	0.46 ±0.03	101.10±0.10	101.20±0.10
F14	5-6	5±0.10	300 ±2	0.51 ±0.06	100.40±0.10	99.60±0.10
F15	6-7	5±0.10	300 ±3	0.54 ±0.04	99.20±0.40	98.90±0.20
F16	5-6	5±0.10	300 ±1	0.41 ±0.04	99.40±0.20	100.20±0.20
F17	5-6	5±0.20	300 ±2	0.61 ±0.04	99.40±0.20	99.80±0.10
F18	5-6	5±0.10	300 ±2	0.66 ±0.03	98.90±0.30	98.70±0.40
F19	6-7	5±0.10	300 ±2	0.51 ±0.04	99.40±0.40	99.70±0.30
F20	6-7	5±0.20	300 ±1	0.60 ±0.03	100.20±0.20	99.70±0.20

Table No.9 *In-vitro* Drug diffusion kinetic study

S.NO	Model	Correlation coefficient (R^2)			
		DICS F1	TIZH F1	DICS F11	TIZH F11
1	Zero order	0.8574	0.8315	0.8582	0.8438
2	First order	0.9257	0.9723	0.8939	0.9638
3	**Matrix**	**0.9989**	**0.9979**	**0.9989**	**0.9987**
4	Peppas	0.9975	0.9970	0.9974	0.9976
5	Hixson Crowell	0. 9826	0.9799	0.9781	0.9852

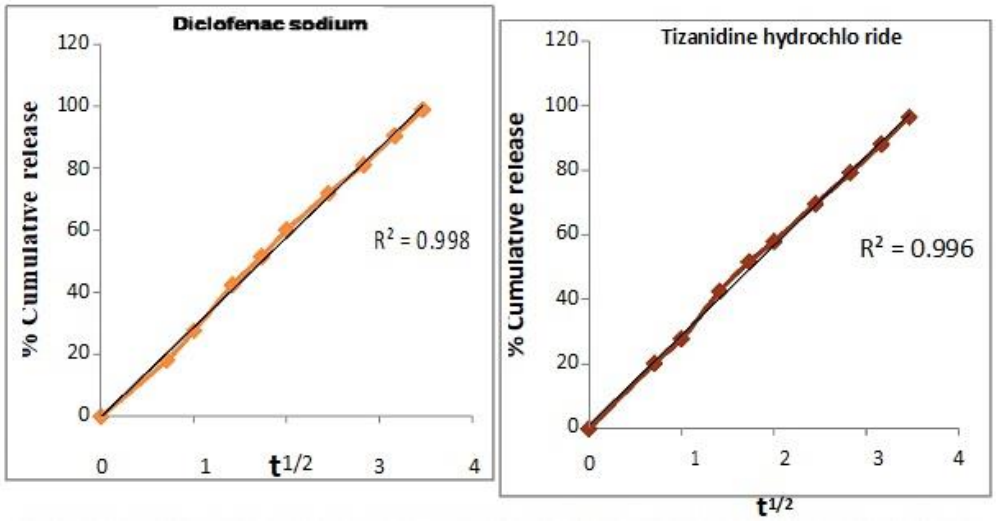

Fig. No. 10 Higuchi square root model study for DICS and TIZH from F1 (HPMC K4M 10%)

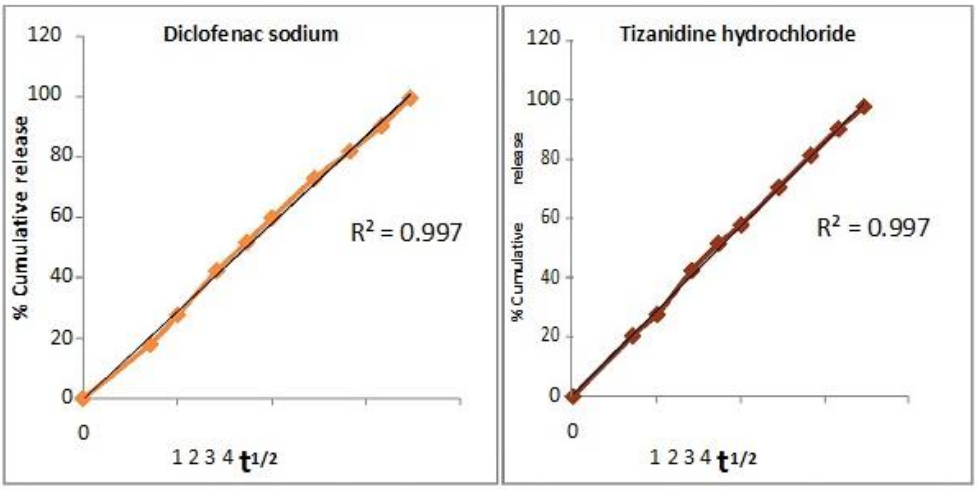

Fig. No. 11 Higuchi square root Model study for DICS and TIZH from F 11 (Guar gum 5%)

CONCLUSION

The prepared tablets were evaluated for various physical parameters of tablet and *in vitro* drug release. It was found that the concentration and type of polymer influences the release and compression characteristics of the sustained release tablets. Increase in concentration of polymer leads to decrease in release rate of both drugs. It was also found that particle size of drug also has considerable effect on drug release from formulation; as particle size decreased drug release increased. matrix systems developed were able to deliver the drugs by matrix (Higuchi) drug release model. This was achieved by a simple strategy of incorporating DICS and TIZH together in a matrix system of HPLC K4M by wet granulation method. This dosage form thus designed would be ideal for patients simultaneously suffering from muscle spasm associated with analgesia and inflammation and where both the drugs would be needed in a sustained manner but being released together from a single unit dosage form.

ACKNOWLEDGEMENT

The authors are very much thankful to Surendra Kumar Jain Director, SIRT College of Pharmacy Bhopal, for his valuable support and providing necessary facilities to carry out the research work.

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