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Formulation and Evaluation of Troxipide Suatained Release Tablets

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ABSTRACT:
The present of this research work to develop sustained release troxipide 200 mg tablets. This is a systemic non-antisecretory gastric cytoprotective agent. In this work six formulations are selected for design troxipide sustained release formulations by using direct compression method and then the formulations are prepared by using different concentrations natural hydrophobic polymer and different ingredients are used as fillers to develop the formula. The granules and tablets are evaluated by pre-compression, post-compression and In-vitro dissolution studies. Based on the dissolution studies F6 was selected as an optimized formula because of it gives best results in sustained by drug release manner and best fitted to order of kinetics.

Key Words: Troxipide, HPMC K15M, Abelmochus Mucilage, Micro Crystalline Cellulose (MCC), Sustained Release Tablets.

I. INTRODUCTION:

Controlled Release Drug Therapy:

For many decades treatment of acute diseases or chronic illnesses have been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, liquids, aerosols and inject able. Present nova a day's these controlled release dosage forms most use full technology for the improve the release rate.

In the oral route the control drug delivery drug delivery systems are well recognized to give on time release of the drug. So to achieve to maintain the drug concentration and therapeutically more effective. Different types of drug delivery systems are available nova a days but the controlled drug delivery system is more affect for the compare the other drug delivery systems. This results in a significant fluctuation in drug levels often with a sub-therapeutic and or toxic levels and wastage of drug. Recently several technical advancements have resulted in the development of new systems of drug delivery capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the delivery of drug to a tissue[1].

Troxipide is well absorbed throughout the gastrointestinal tract with a relative bioavailability of 99.6%. At any time, a mean concentration of 5.3- 8.9 µg of troxipide is present per gram of tissue, which is capable of inhibiting the chemo tactic migration and superoxide generation in the gastric mucosa. Thus, even 3 hrs after attaining peak serum levels, troxipide is found in therapeutically active concentrations in the small intestine, liver and stomach. The elimination half-life of troxipide is 7.5 hours, and is mainly excreted in urine (96% as metabolites)

II. MATERIALS AND METHODS:

Troxipide (Hetero Drugs Limited, Hyderabad) , Abelmochus esculentus mucilage (Isolated in lab), HPMC K15M (Chemiloids, Vijayawada), Micro crystalline cellulose (Chemiloids, Vijayawada) Sodium Stearyl Fumarate (S.D. Fine-Chem limited, Mumbai), Talc (Reidel Chemicals, Hapur) and Magnesium stearate (S.D. Fine-Chem limited, Mumbai.)

METHODS:

Pre- formulation studies:

Bulk Density (Db):

It is the ratio of the mass of powder to the bulk volume of powder. It was measured by pouring the weight powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

Db = M/Vb

Where,M= mass of powder. Vb=bulk volume of the powder.

Tapped density (Dt):

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

Dt = M/Vt

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Where, M=mass of powder.V_t=tapped volume of the powder.

Carr's Index (I):

It in dictates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

I= Dt-Db/Dt*100

Where, D_t = tapped density of the powder. D_b = bulk density of the powder.

Angle of Repose (θ):

The friction force sin loose powder can be measured by the angle of repose θ.It is defined as maximum angle possible between the surface of a pile of powder and the horizontal plane.

$\tan\theta = h/r$

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

Where θ = is the angle of repose, h = is the height, r = is the radius.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

FT-IR Spectral studies:

The IR spectra for the formulation excipients and pure drugs were recorded onJasco FT-Infrared spectrophotometer using KBr palette technique (1:100) at their solution rate of 4cm-1. Spectrum was integrated in transmittance mode at the wave number range 400-4000 cm-1utions were.

Differential scanning calorimetry:

Conventional DSC and MTDSC experiments were performed using DSC Q200 (TA Instruments, NJ, USA) with a refrigerated cooling assembly (RCS) and a modulated capability. The DSC cell was purged with 50 ml/min dry nitrogen, and the RCS was purged with 150 ml/min nitrogen. The DSC cell was calibrated for baseline using empty pans of matched weight and for temperature using three temperature standards (cyclohexane, $T_m = 279.54^o$ K; indium, $T_m = 429.61^o$ K; tin $T_m = 504.93^o$ K). About 3-5 mg of samples was exposed to the desired heating rates from the desired starting temperature to above the melting point of Dolutegravir under dry nitrogen purging (50 ml/min) in hermetically sealed aluminum pans. The data was analyzed using Universal Analysis Software from TA Instruments

Analytical method development for Troxipide:

U. V Spectrophotometer:

Calibration curve of the pure drug Troxipide was prepared in the concentration range from 2-10 µg/ml at the wave length of 258 nm by using 6.8 phosphate buffer solutions. A graph of absorbance vs concentration was plotted which indicated in compliance to Beer's law in the concentration range.

Preparation of standard Stock solution of Troxipide:

100 mg of Troxipide sodium was dissolved in 100 ml of 6.8 phosphate buffer in a100 ml volumetric flask and made up to the volume with 6.8 phosphate buffer. From this 1 ml of solution was taken and made to 100 ml with 6.8 phosphate buffer.

Method

For the estimation of Troxipide sodium in 6.8 phosphate buffer the stock solution has to be diluted subsequently with 6.8 phosphate buffer to get a series of dilutions containing 2, 4, 6, 8, 10 µg/ml of solution. The absorbance of the solution was measured at 258 nm against blank. The calibration curve was constructed.

Method of isolation of Abelmochus esculentus mucilage:

Fresh okara fruits were collected and washed with water to remove dirt and debris. Incisions were made on the fruits & left over night. The fruits were crushed and soaked in water for 6-7hrs. Boil for 30min and left to withstand for 1hr to allow complete release of the mucilage into the water. The mucilage was extracted using a multilayer muslin cloth bag to remove marc from the solution. Acetone (3times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40ºc for 10min. The dried mucilage was collected, ground into powder, passed through a # 80 sieve and stored in a desiccators at 30ºc and 45% relative humidity before use.

Formulation of Troxipide sodium sustained release tablets:

Troxipide sodium sustained release tablets were prepared by direct compression method. Six formulations of tablets each containing 200 mg dose of Troxipide. Were prepared with different concentrations of various excipients which were shown in given below. Troxipide and polymers such as HPMC k15M and Abelmocus Esculentus were accurately weighed, mixed uniformly and passed through # 40 meshes. Microcrystalline Cellulose is used as diluents were weighed accurately and passed through #40 meshes. Both

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were mixed properly and the mixture of Talc and magnesium stearate 1:1 ratio was added and mix for few minutes. Then the above mixture was compressed in to tablets by using station rotary compressed machine with punch size of 8 mm.

Table.11: **Formulation of Troxipide sustained release tablets**

Ingredients mg/tab	**Formulation**					
	F1	F2	F3	F4	F5	F6
API (Troxipide)	100	100	100	100	100	100
HPMC k15 M	30	40	50	---	---	---
Abelmocus Esculentus	---	---	---	30	40	50
Microcrystalline Cellulose	66	56	46	66	56	46
Talc	2	2	2	2	2	2
Mg stearate	2	2	2	2	2	2
Total weight (mg)	200	200	200	200	200	200

Evaluation of Troxipide sustained release tablets

Weight variation test:

The weight variation test is performed by taking 20 tablets from each formulation and weighing the individual tablets by using electronic balance. Their average weight was calculated as

% Weight variation = (WA- WI) ×100/ WI

Where,

WI = Individual weight of the tablets

WA = Average weight of the tablet

Table 12: Weight variation specifications (B.P)

Average Wt of the Tablets	**Maximum difference allowed**
Less than 130	5
130-324	7.5
More than 324	10

Table 13: Weight variation specifications (I.P)

Average weight of tablet(mg)	**Percentage deviation**
130 or less	10
130 to 324	7.5
More than 324	5

Thickness:

Thickness of the tablets was determined using vernier calipers. Five tablets from each batch were used, and an average value was calculated.

Hardness (kg/cm^2):

Hardness of the tablets was tested using a Monsanto hardness tester. Five tablets from each batch were tested for hardness.

% Friability:

Friability of the tablets was determined in a roche friabilator. Ten tablets were weighed initially (w_1) and placed in the friabilator that revolves at a speed of 25 RPM, dropping those tablets at a distance of six inches height with each revolution and rotated in the friabilator for 100 revolutions. After completion of rotations, the tablets were dedusted and weighed (w_2). The percent loss in weight or friability (f) is calculated by using the formula.

% Friability= (Initial weight- Final weight)/ Initial weight × 100

Drug content:

Ten tablets were taken and amount of drug present in each tablet was determined as follows: Tablet was crushed in mortar and transferred to a 100 ml flask. The powder was dissolved buffer medium. The sample was mixed by using Sonicated for 5 minutes, after which it was filtered

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through what man's filter paper. The filtered solutions after appropriate dilution (1to10 ml) with P^H 6.8 phosphate buffer were analyzed by the validated UV Spectrophotometric method at λ_{max} 254 nm.

In-vitro dissolution studies:

In-vitro dissolution study was performed by using USP type II dissolution test apparatus (paddle type) [Lab, India (DS-8000, Mumbai)] at 100 RPM. 900ml of phosphate buffer of pH 6.8was used as the dissolution medium which was maintained at 37±0.5°C. Aliquots of dissolution medium (5mL) were withdrawn at specific time intervals (1hr, 2hr, 4hr, 8hr, 12hr, 16hrand 24 hr) and were filtered. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 258 nm.

III. RESULTS AND DISCUSSION:

Formulation of sustained release tablets of Troxipide utilizing the natural polymers like HPMCK15and Abelmocus Esculentus impact on In- Vitro dissolution rate.

Pre-formulation studies: Active pharmaceutical and excipients were blended and evaluated for different parameters as clarified before. Bulk density was found in the limit of 0.610 - 0.633 g/cm3 and the tapped density between 0.635 - 0.688 g/cm3. By using both density data Carr's compressibility was determined. The compressibility record was found between 19.56 – 21.35 %, and the Hausner's ratio was found to be 1.14-1.35. The result shows good flow properties of blend. The good flow properties of powder were also evident from angle of repose that range from 27.56-30.21°. In the present examination all powder mixes indicated excellent flow property. The outcomes are appeared in Table no 2.

Table 2: Micromeritic properties of the granules of Troxipide formulation

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Angle of repose(ɵ)	Compressibility Index (%)
F1	0.610	0.688	1.21	28.56	19.56
F2	0.621	0.669	1.35	28.44	20.36
F3	0.614	0.656	1.26	29.56	21.35
F4	0.632	0.678	1.24	30.21	20.36
F5	0.625	0.645	1.14	27.56	20.14
F6	0.633	0.635	1.22	29.12	20.15

FT-IR Spectral studies:

FT-IR studies:

From the FT-IR spectra, it was concluded that similar characteristic peaks with minor difference for the drug and the FT-IR formulation. Hence, it appears that there was no chemical interaction between the drugs and excipients used**.** The IR Spectra of with, HPMCK15, Abelmocus Esculentus shown. The following peaks were observed in as well as nebivolol with excipients.

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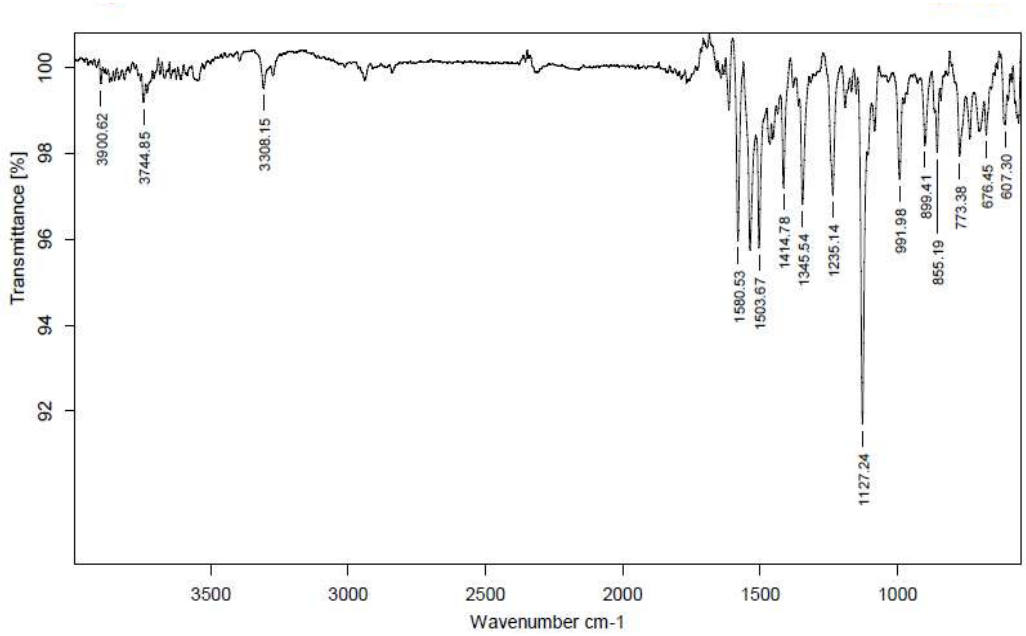

Fig 1: FT-IR Reports of Troxipide

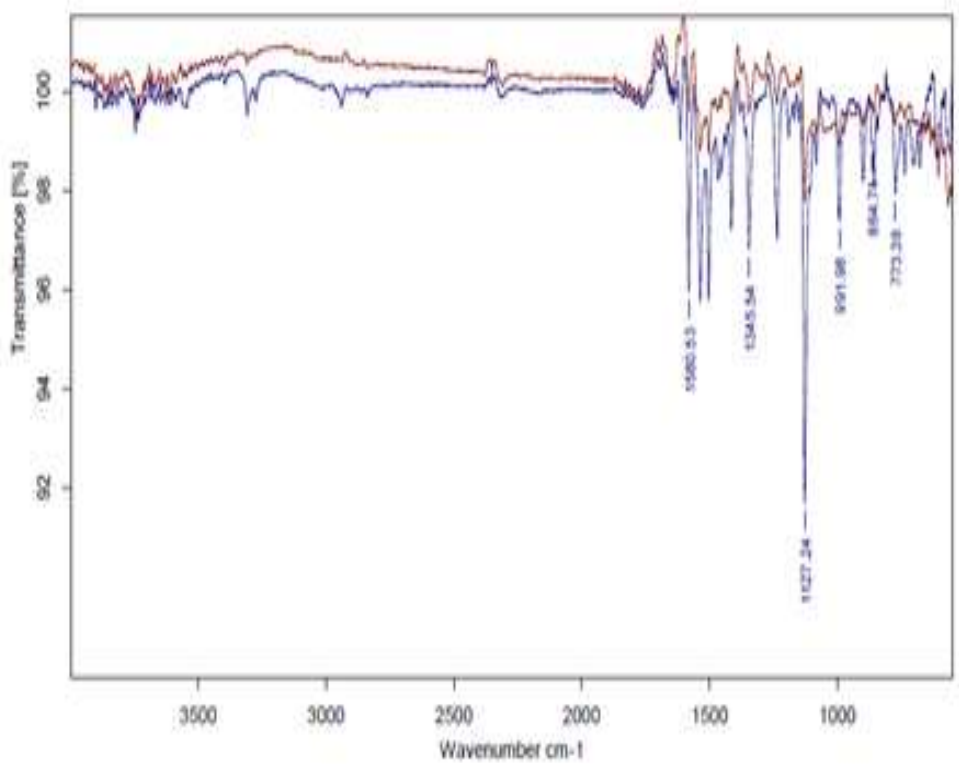

Fig 2: FT-IR Reports for optimized formula

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Differential scanning calorimetry:

DSC indicated better drug stability presence of hydrophobic polymers. A stronger drug amorphization and entrapment in hydrophobic polymers was observed.

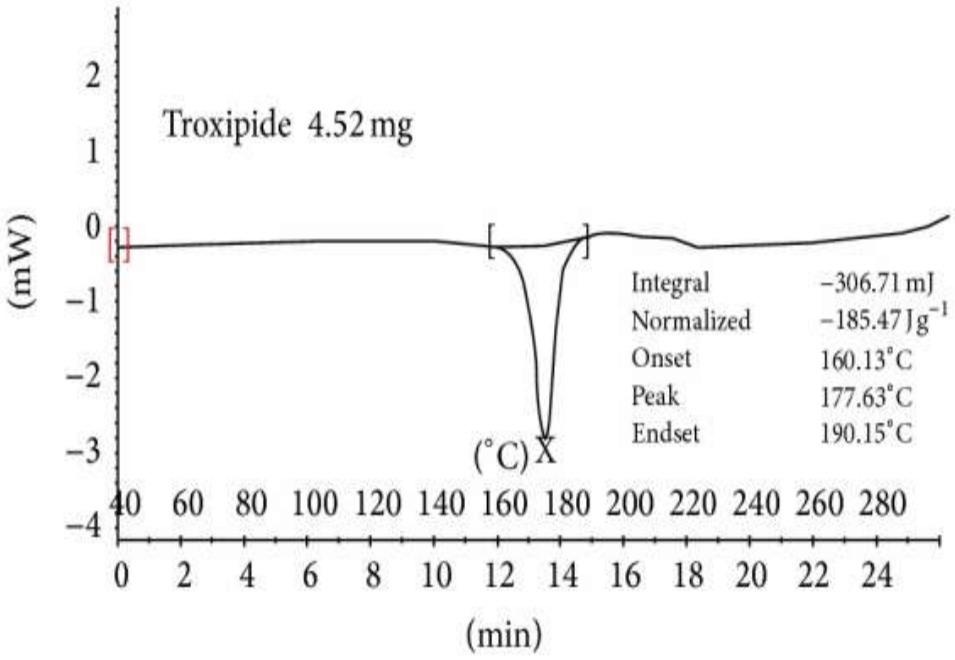

Fig 3: DSC Reports for Troxipide

Analytical method development:

Troxipide was estimation using UV/VIS spectrophotometer method. It was found that under UV/VIS spectrophotometer standard absorbance of the peak of Troxipide was 0.719 µg/ml,

Table : 18 Standard Calibration Curve for the Troxipide in 6.8 pH phosphate buffer.

S. No	Concentration (µg/ml)	Absorbance
1	2(µg/ml)	0.102
2	4(µg/ml)	0.206
3	6(µg/ml)	0.311
4	8(µg/ml)	0.424
5	10(µg/ml)	0.538

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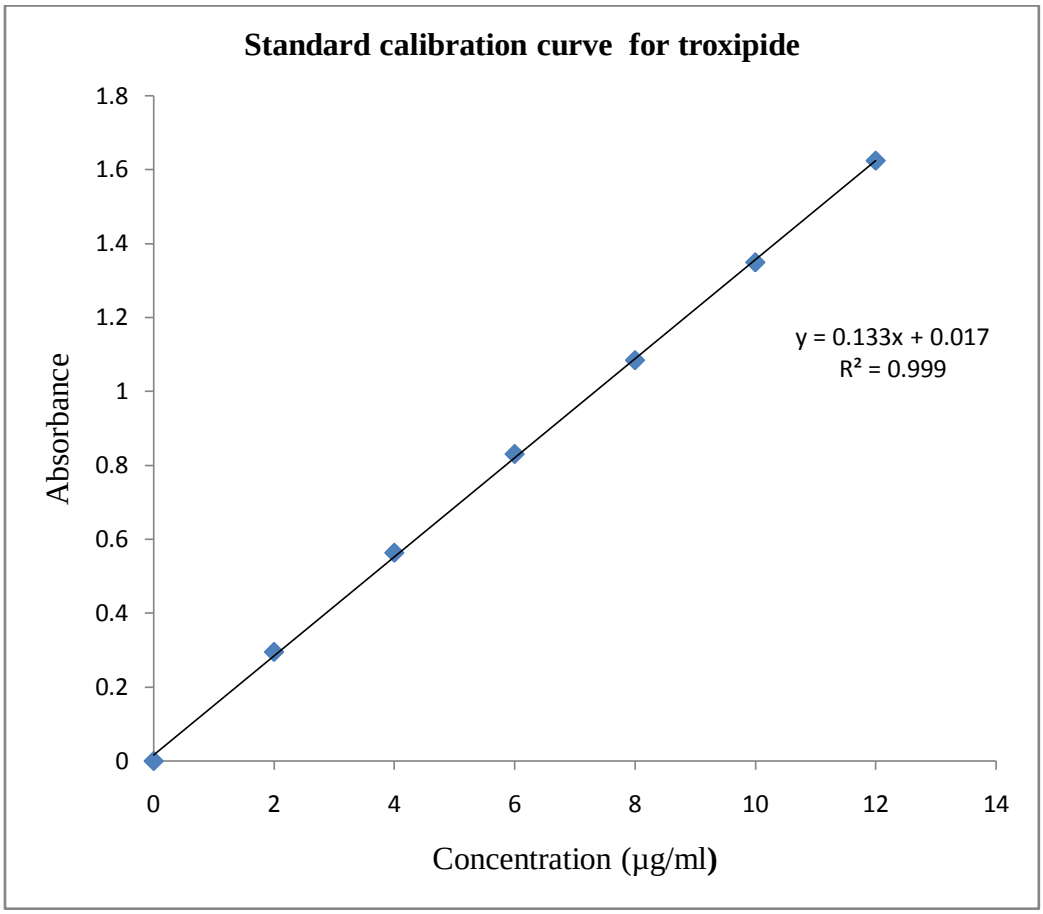

Fig 4: Calibration curve of Nebivolol 0.1N HCl

Post – compression parameters:

The preliminary studies were carried out by preparing various formulations with different process variable and subjecting the formulation to all post-compression parameters has fulfilled according to IP standards.

Weight variation: Average weight of 20 tablets of Nebivolol was calculated for each formulation which varied from mg 1.13 ± 0.23 to 2.51 ± 0.19mg. the complied the official requirements as per IP.

Tablet thickness: The thickness of the Nebivolol formulation varied from 3.26 ± 0.06 mm to 3.65 ± 0.06mm

Tablet hardness (kg/cm^2): The hardness ofthe tablet developed formulation shows 6.9 ± 0.9 kg/cm^2 to 8.0 ± 0.3 kg/cm^2.

% Friability: The friability of the developed formulation varied from 0.39 ± 0.03 % to 0.86 ± 0.03 % loss which was less than 1%as per official requirement of IP.

Drug content: Ten tablets were taken and amount of drug present in each tablet was determined as follows: Tablet was crushed in mortar and transferred to a 100 ml flask. The powder was dissolved buffer medium. The sample was mixed by using Sonicated for 5 minutes, after which it was filtered through what man's filter paper. The filtered solutions after appropriate dilution (1to10 ml) with P^H 6.8 phosphate buffer were analyzed by the validated UV Spectro photometric method at λ_{max} 254 nm. The drug content 98.2 ± 0.65 to 99.6 ± 0.65.

Post – compression parameters:

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Table: 20 Post compression parameters of Troxipide sustained release tablets

Formula	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	% Friability (% loss)	Drug content
F1	1.50±0.22	3.26	7.5 ± 0.5	0.39 ± 0.03	99.3 ± 0.65
F2	2.49±0.19	3.56	8.0 ± 0.3	0.75 ± 0.07	98.2 ± 0.65
F3	2.49±o.27	3.65	6.9 ± 0.9	0.66 ± 0.03	99.6 ± 0.65
F4	1.13±0.23	3.45	7.3 ± 0.5	0.43 ± 0.05	99.5 ± 0.65
F5	1.96±0.21	3.58	7.8 ± 0.4	0.39 ± 0.06	99.4 ± 0.65
F6	2.51±0.19	3.52	7.2 ± 0.3	0.86 ± 0.03	99.3 ± 0.65

In-Vitro Dissolution studies of Troxipide sustained release tablets:

In-vitro dissolution studies:

In-vitro dissolution study was performed by using USP type II dissolution test apparatus (paddle type) [Lab, India (DS-8000, Mumbai)] at 100 RPM. 900ml of phosphate buffer of pH 6.8was used as the dissolution medium which was maintained at 37±0.5°C. Aliquots of dissolution medium (5mL) were withdrawn at specific time intervals (1hr, 2hr, 4hr, 8hr, 12hr, 16hrand 24 hr) and were filtered. The amount of drug dissolved was determined by UV spectrophotometer by measuring the absorbance of the sample at 258 nm.

The all six formulation are prepared by using different concentrations of polymers like HPMC-K4 and Abelmochus Esculentus. f1,f2 and f3 contains the HPMC-K4 was prepared in Troxipide sustained release tablets formulation f1 is 73.21 % in 24 hr, f2 is 97.33 % in 24hr and f3 formulation drug released is 83.89 % in 24hr, f4 formulation the drug released was 94.23 % in 24 hr, f5 formulation the drug released was 92.30 % in 24 hr and f6 formulation the drug released was 100.1 % in 24 hr .The optimized formulation f1 the prepared with PEG-400 the dissolution medium was 0.1 N HCL the drug released in formulation f6 is 100.1% in 24 hr.

In-vitro dissolution studies:

Table: 21 Dissolution studies for Troxipide sustained release tablets

Dissolution with pH 6.8 phosphate buffer, 900ml, RPM 100, λ max 254 nm							
% Cumulative Drug Release							
S.NO	Time (hr)	F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	1hr	6.04	15.26	14.73	25.05	18.15	12.20
3.	2hr	8.67	18.36	16.59	36.24	40.20	36.21
4	3hr	12.92	25.89	18.91	51.33	53.35	58.36
5	4hr	17.24	37.26	20.33	63.21	65.57	69.61
6	8hr	20.67	58.944	34.083	78.90	71.96	78.83
7	12hr	35.92	73.394	50.32	82.32	79.46	85.39
8	16hr	61.37	88.66	71.927	89.81	84.76	93.88
9	24 hr	73.21	97.33	83.899	94.23	92.30	100.1

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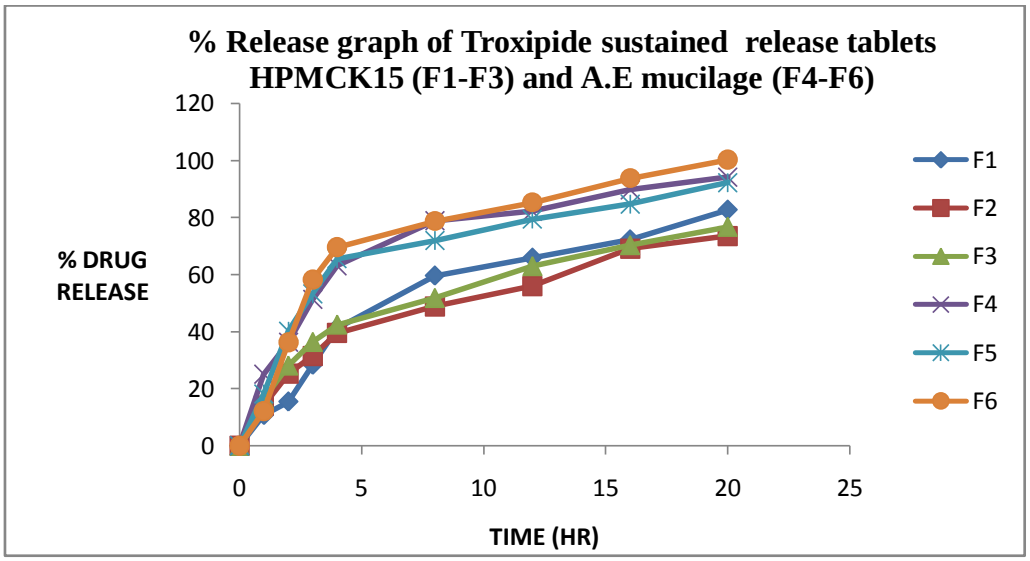

Fig 11: % Release graph of Troxipide sustained release tablets HPMCK15 (F1-F3) and A.E mucilage (F4-F6).

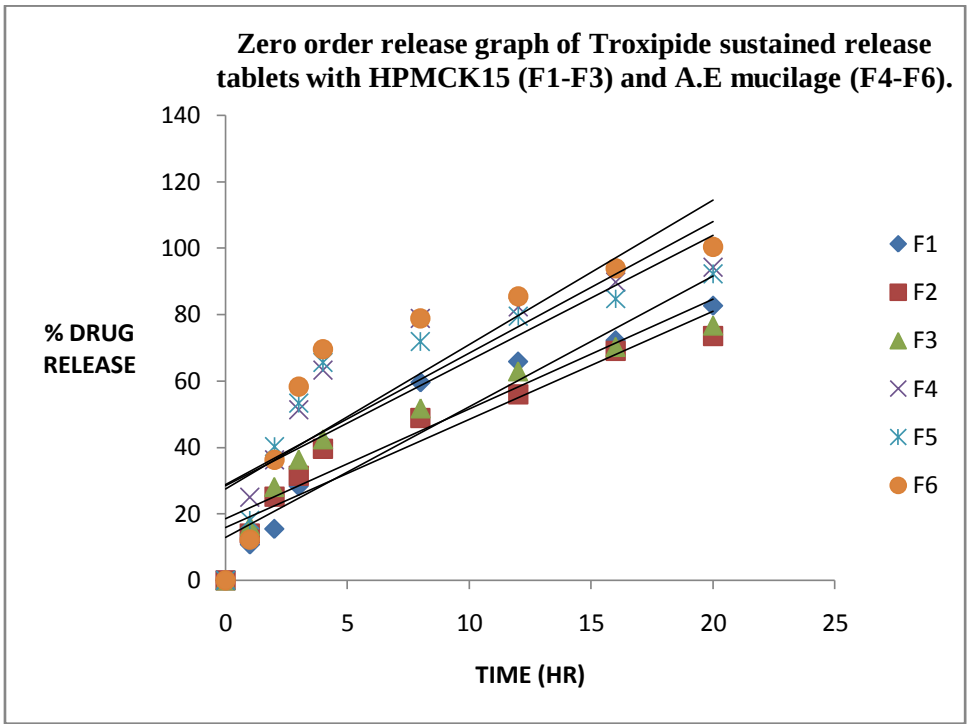

Fig 12: Zero order release graph of Troxipide sustained release tablets with HPMCK15 (F1-F3) and A.E mucilage (F4-F6).

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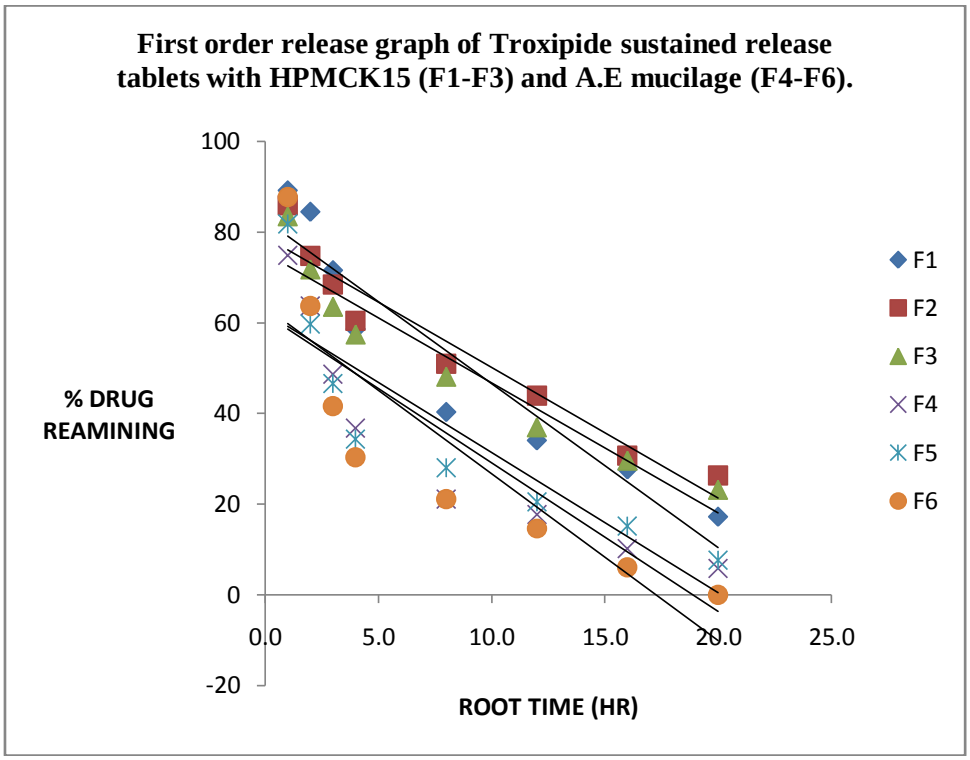

Fig 13: First order release graph of Troxipide sustained release tablets with HPMCK15 (F1-F3) and A.E mucilage (F4-F6).

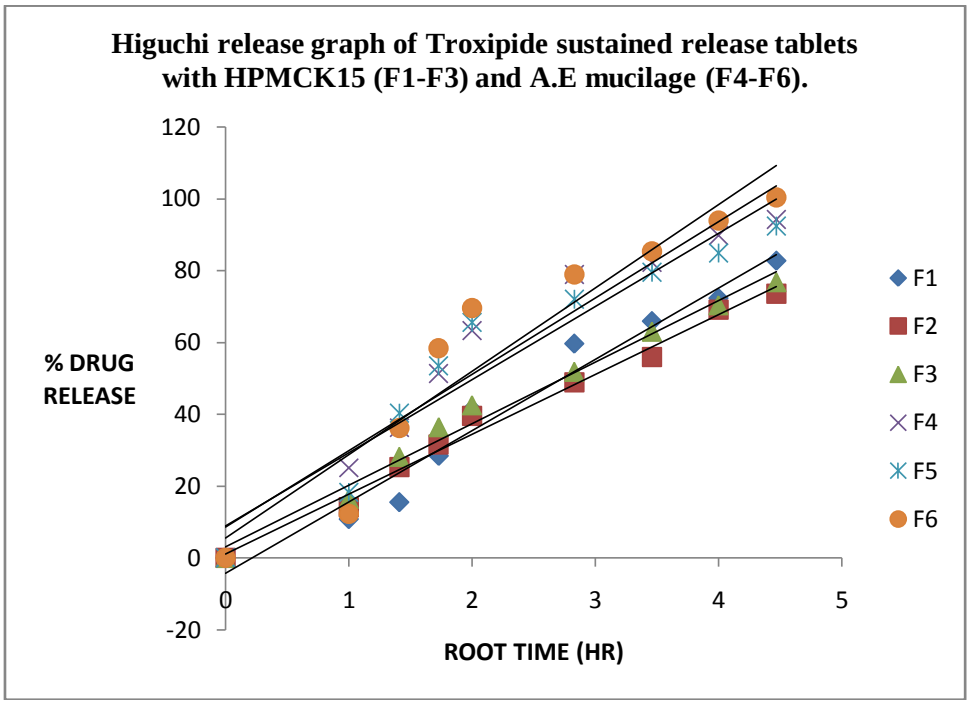

Fig 14: Higuchi release graph of Troxipide sustained release tablets with HPMCK15 (F1-F3) and A.E mucilage (F4-F6).

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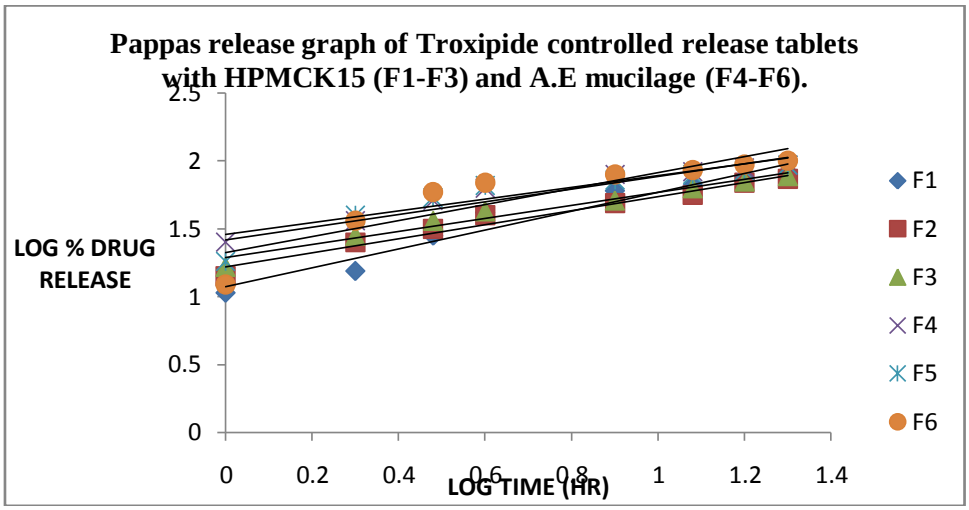

Fig 15: Pappas release graph of Troxipide sustained release tablets with HPMCK15 (F1-F3) and A.E mucilage (F4-F6).

Table 22: Dissolution kinetics of Troxipide sustained release tablets with HPMCK15 (F1-F3) and A.E mucilage (F4-F6).

Correlation co-efficient				
Formulation	**Zero order**	**First order**	**Higuchi**	**Pappas**
F1	0.851	0.621	0.652	0.917
F2	0.867	0.646	0.693	0.92
F3	0.815	0.665	0.732	0.922
F4	0.895	0.742	0.798	0.935
F5	0.922	0.704	0.739	0.957
F6	0.843	0.661	0.753	0.905

IV. CONCLUSION:

From the present research, it can be concluded that among all the formulations A.E mucilage and HPMCk15M combination formula F6 was found to release drug in slow, 100.1% sustained manner. A.E mucilage slow releases the drug when compared to HPMCk15M alone. The combination form was shown better sustained.

The Abelmochus esculent mucilage was available cheap when compared to synthetic polymers. Interaction is very less with drug. The A.E mucilage very well controls the drug release from formulations. Drug – excipients compatibility studies were conducted by FT-IR spectroscopy, results indicated that the troxipide and polymers were found to be compatible.

The micromeritic properties of granules were evaluated, all the formulations exhibited good flow properties. The evaluation parameters for the prepared tablets such as % weight variation, hardness, % friability, thickness and drug content were found to be in satisfactory limits. The maximum drug release was found to be 100.1% over a period of 24 hours in A.E mucilage tablets. This indicates combination of A.E mucilage required preparing the sustained release tablets of troxipide. All the formulations were also subjected to model fitting analysis to know the order and mechanism of drug release from the formulations by treating the data according to Zero order, First order, Higuchi and Peppas Equations, The data clearly shows that, the release kinetics revealed that the formulations containing A.E mucilage and HPMCK15 follows zero order release kinetics and release rate was sustained by Non-Fickian diffusion. It can be concluded that A.E mucilage can be used as an effective former to sustain the release of of troxipide for the period of 24 Hours.

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