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FORMULATION DEVELOPMENT AND OPTIMIZATION OF ZOLMITRIPTAN TABLETS BY DIRECT COMPRESSION METHOD

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Keywords:

Zolmitriptan matrix tablet, anti migraine agents, Natural and synthetic polymer.

Abstract

The aim of the present study is to develop a robust formulation of Zolmitriptan Anti Migraine Analgesic drug as a Sustained release Matrix Tablets by direct compression method. The polymers like Karayagum, Guargum, and HPMC K100M and were used as sustained release polymer to retard the drug release. The tablets prepared were evaluated for various parameters like various density parameters, thickness, hardness, friability, disintegration time, wetting time and In-vitro dissolution time. All the parameters were found to be within limits. The invitro release pattern of final formulation was compared with the innovator. Zolmitriptan sustained-release formulation provides continual drug delivery over 12hours and reduces fluctuations in serum drug concentrations. This delayed release minimizes side effects related to high serum levels that occur with immediate-release formulations. It is effective, safe, and relatively well tolerated. An sustained release model drug tablet can lead to the reduction of the number of doses administered, leading to better patient compliance and less chances of overdose, in addition to which it can reduce the cost associated with treating pain symptoms.

Introduction

Sustained Release Dosage Form Sustained release dosage form is defined as well characterized and reproducible dosage form, which is designed to control drug release profile at a specified rate to achieve desired drug concentration either in blood plasma or at target site13.

This system will provide actual therapeutic
control that would be temporal (time related),
spatial (site related) or both6,14.

Advantages of sustained drug delivery system

- Reduced see-saw fluctuations.
- Total amount of dose decreases.
- Improved patient compliance.
- Increased safety of drugs15-19.

Disadvantages of sustained drug delivery system

- Chances of dose dumping.
- Dose retrieval is difficult.
- High cost of formulation.
- Need for additional patient education.
- Reduced potential for accurate dose adjustment20,

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Formulation Strategies for Oral Sustained Release System

- Diffusion Sustained Release
- Dissolution Sustained Release
- pH Dependent System Altered Density System
- Osmotic Pump System
- Ion Exchange System31

Types of diffusion sustained system

• Swellable matrix.
• Reservoir/Laminate matrix.
Types of dissolution sustained system:
• Matrix/Monolith Dissolution System.
• Encapsulation/Coating/Reservoir System.
Types of altered density system:
• High Density System.
• Low Density System.
• Muco Adhesive System8,32.

Diffusion sustained system

These systems are those where the rate controlling step is not the dissolution rate of the drug but diffusion of the dissolved drug molecule. Depending upon the mechanism such system can be classified as: Porous membrane controlled system: In these type of system the rate controlling element is a water insoluble non swellable polymer like ethyl cellulose, polymethaacrylate etc. which controls the drug release through the micro pores present in their membrane or matrix structure

Advantages

• Can provide zero order drug releases.

Disadvantages

• High cost per dosage unit.
• In case of dose dumping toxicity can take place.

Porous matrix controlled system

In these type of system the rate controlling element is a water swellable material (hydrophilic polymers and gums) like alginates, xanthan gum, locust bean gum, HPMC etc. or a non swellable water insoluble polymer like ethyl cellulose.

Advantages

• Cost effective.
• Easy to fabricate.
• Drug could be protected from hydrolysis orother changes in GIT, so enhanced stability.
• Compounds with high molecular weight could be formulated.

Disadvantages

• Release rate is affected by presence of food.
• Matrix must be removed after the release of drug. Dissolution sustained system The drugs with slow solubility are suitable candidates for this system and for the drugs having high solubility the dissolution is decreased by conversion into a suitable salt or derivative.

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Design of sustained release products

Principle behind SR drug release
Dissolution and diffusion controlled systems have classically been of primary importance in oral delivery of medication because of their relative ease of production and cost compared with other methods of sustained or controlled delivery [4]. Most of these systems are solids, although a few liquids and suspension have been recently introduced. The classifications of such systems are as follows:
1 Dissolution-controlled release system.
1.3.4.2. Diffusion-controlled release system.

1.3.4.3. Osmotic pump system.

1.3.4.4. Erosion controlled release systems.

Materials and methods

Materials
Zolmitriptan was obtained as a gift sample from drugs india, hyderabad. Hpmc k 100m , drugs india, hyderabad Guargum , drugs india, hyderabad karayagum, drugs india, hyderabad microcrystalline cellulose drugs india, hyderabad magnesium stearate drugs india, hyderabad

Methods

Preformulation Studies
Determination of solubility of Zolmitriptan The solubility of zolmitriptan was tested in various solvents such as distilled water, ethyl alcohol, phosphate buffer, propanol and acetone. Solubility experiments were conducted in triplets.

Melting point determination
The melting point of drug was determined by taking a small amount of drug in capillary tube closed at one end and placed in melting point apparatus and the temperature at which drug melts was recorded. This was performed in triplets and average value noted.

Analytical method used in the determination of zolmitriptan
The UV-Spectrophotometer method was developed for the analysis of the drug using double beam Shimadzu 1601Spectrophotometer.

Determination of λ max
Zolmitriptan was dissolved in phosphate buffer and further diluted with the same. A solution of concentration of 5mcg/ml was prepared and scanned for maximum absorbance in double beam UV-Spectrophotometer in range 200-400nm, phosphate buffer pH 6.8 as a blank. The λ max of the drug was found to be 225.4nm.13

Preparation of Standard curve for Zolmitriptan

8 UV method developments for estimation of drug

7.8.1 Preparation of different buffer media

7.8.3 pH 1.2 buffers**:** 85 ml of 0.2 M HCl was added to 50 ml of 0.2 M potassium chloride solution and volume was made up to 200 ml.

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7.8.2Phosphate Buffer pH **6.8**
Place 6.8g of potassium di hydrogen phosphate and 0.896g of sodium hydroxide in a 1000ml volumetric flask, and then add water to volume and mix.

Standard Stock
100 mg of model drug was taken and added to respective media in a 100 ml volumetric flask and volume was made up to 100 ml, resulting in a standard stock solution of 1 mg/ml.

Working Stock

From the above standard stock solution 10 ml was taken and added to respective buffer media in a 100 ml volumetric flask and volume was made up to 100 ml toobtain 100 mcg/ml solution. From the working stock dilutions were prepared using respective media.

7.8.3Determination of absorption maxima

10 µg/ml solution was taken to determine absorption maxima. Initially blank buffer solution was kept and scanned in the region of 200-400 nm. Then sample was kept for analysis and scanned in the same region. Absorption maxima were found to be 225 nm. Hence all further analysis was carried out at 225nm for P^H 1.2, P^H 6.8 buffers.

7.8.4Determination of Beer's law range and plotting of calibration curv

From the working stock solution 1,2,3,4,5,6,7,8,9,10 ml of sample was taken and diluted up to 10 ml using respective buffer media in a 10 ml volumetric flask resulting in concentrations of 10,20,30,40,50,60,70,80,90 and 100 µg/ml solutions. These were analyzed at 225 nm and calibration curve was plotted taking concentration in µg/ml on X-axis and absorbance units on Y-axis.

METHOD OF PREPARATION

Development Strategy

Following ingredients were selected for formulation development of model drug based on the literature search and Preformulation studies.

Selection of formulation method

Sustained release tablets of model drug were formulated using following methods they are:

1. Direct compression
2. Wet granulation.

1. Direct compression

In this process the tablets are compressed directly from powder blends of active ingredient and suitable excipients, which will flow uniformly in to the die cavity and forms a firm compact.

Brief manufacturing procedure for the preparation of tablets

Step 1- Weighed all the ingredients separately.
Step 2- The model drug and the other excipients were passed through 40# sieve together and blended for 10 minutes.
Step 3- The magnesium stearate was passed through 60# sieve and added to the blend of step2 and blended for 5 minutes.
Step 4- Compressed the blend of step 3 in to tablets by using 8.5mm, round punches.

Preformulation studies

Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rationale development of the dosage forms.

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Pre-formulation studies yield necessary knowledge to develop suitable formulation. It gives information needed to define the nature of the drug substance and provide a dosage form. Hence, the following pre-formulation studies were performed for the obtained sample of drug.

1. Organoleptic evaluation
2. Particle size distribution.
3. Bulk density.
4. Tapped density.
5. Carr's index.
6. Hausner's ratio.
7. Angle of repose.
8. Particle size determination.
9. Drug-excipient compatibility study.
10. UV method development for estimation of drug.
11. Saturation solubility.

The methods are described below.

7.1. Organoleptic evaluation

The color, odor and taste of the model drug were evaluated and tabulated using descriptive terminology.

7.2 Particle size distribution

10.35 grams of sample was taken and added to an assembly of sieves consisting ASTM sieve numbers # 30, 40, 60, 80,100,120 base plate. Then assembly was closed and kept on sieve shaker and started analysis. Weights retained were checked for every 5 minutes and process was continued until variation in weights retained was not more than 5% or 0.1 gram. 20 minutes was set as end point based on the observation. Calculations were made to obtain cumulative percentage weight retained and tabulated.

7.3 Bulk density

Bulk density was determined by pouring 15 grams of drug (previously passed through 18# sieve to remove any lumps) into a graduated cylinder inclined at 45^0 to horizontal surface. The cylinder was then brought to standing position and measured the volume occupied by material to the nearest possible and calculated BD using following formula.

Bulk density = Weight / Bulk volume.

7.4 Tapped density

Tapped density is determined by using ELECTROLAB TD TESTER according to USP method I. A 50 ml measuring cylinder was taken and the weight of the cylinder was noted. 15 g of drug was weighed and added to the cylinder and weight and volume of the cylinder was noted. The measuring cylinder was subjected to 500 taps in TD apparatus, then Volume was noted, then again subjected to 750 taps and volume (V_a)was noted, then the tapping was continued for 1250 taps and volume(V_b)was noted, the difference between V_a and V_b was less than 1 % so V_a was selected as final tapped volume. Tapped density was calculated using following formula.

Tapped density = Weight / Tapped volume

Carr's Index: Carr's index was calculated using the following equation:

CI = (Tapped density-Bulk density) / Tapped density x100

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7.5 Hausner's Ratio

The Hausner's ratio is another index of the flow-ability of the pharmaceutical powders. It was calculated using following equation:

Hausner's Ratio = Tapped density/Bulk density

7.6 Angle of Repose

Angle of repose was measured by passing Drug through a funnel on graph paper until the pile touches the tip of the funnel. The funnel was kept at a fixed height of 2cm, from the horizontal surface to the tip of funnel. The radius 'r' of the cone base formed was determined. The angle of repose (θ) was calculated as follows:

Drug-Excipients compatibility study

Physical observation

Physical mixtures of drug and excipients were prepared by grinding specific ratios of drug and excipients in a mortar. Sample of 3-4 grams was taken and loaded in a glass vial, covered with rubber stopper, sealed with aluminum cap and labeled properly. Samples were observed and color was recorded for initial evaluation and loaded into stability chamber 40^0 c temperature and 75 % relative humidity for 4 week Compatibility study. Samples were removed at 1 week interval for four weeks and observed for any color change.

7.8 UV method development for estimation of drug

7.8.1 Preparation of different buffer media:7.8.3 pH 1.2 buffer**:** 85 ml of 0.2 M HCl was added to 50 ml of 0.2 M potassium chloride solution and volume was made up to 200 ml.

7.8.2Phosphate Buffer pH **6.8** : Place 6.8g of potassium di hydrogen phosphate and 0.896g of sodium hydroxide in a 1000ml volumetric flask, and then add water to volume and mix.

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7.8.4Determination of Beer's law range and plotting of calibration curve

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2 FT-IR spectroscopy study

In the present study FT-IR data of drug and excipient was compared with standard spectrum of pure Zolmitriptan drug. The characteristic peaks associated with specific functional groups and bonds of the molecule and their presence/absence in the polymer carrier formulation were noted. The IR spectra showed that there is no significant evidence for interaction the drug and the excipients. The figure shows the IR spectrum of pure Zolmitriptan while figures show the compatibility the drug and, Hpmck100m, Guargum, karayagum,Mcc Magnesium stearate respectively.

Zolmitriptan:

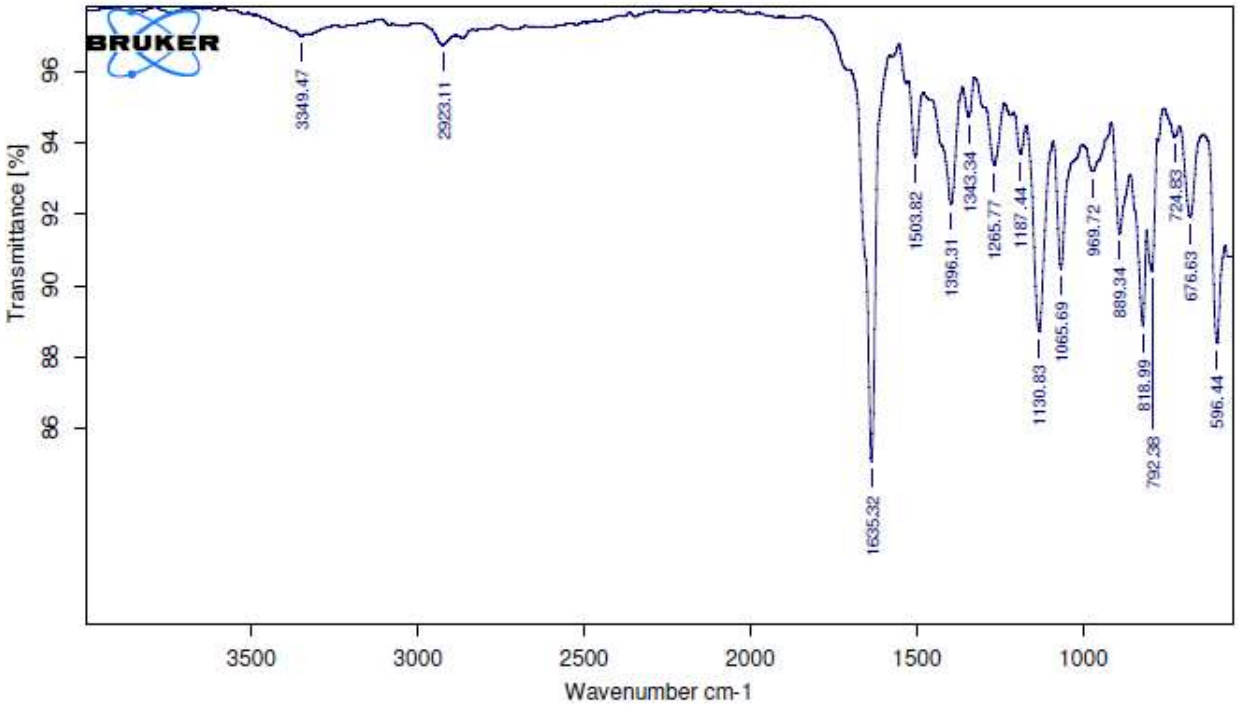

Figure 7:FTIR spectra of Zolmitriptan

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HPMCK100

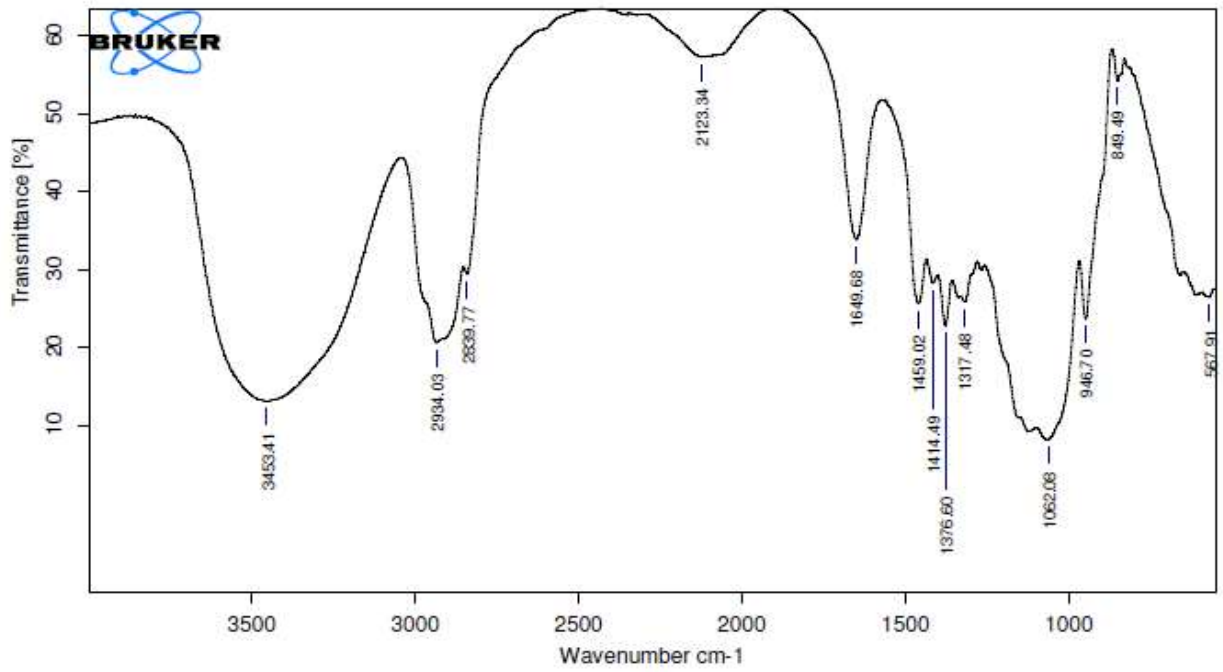

Figure 8: Ftir Spectra Hpmck100

KARAYAGUM

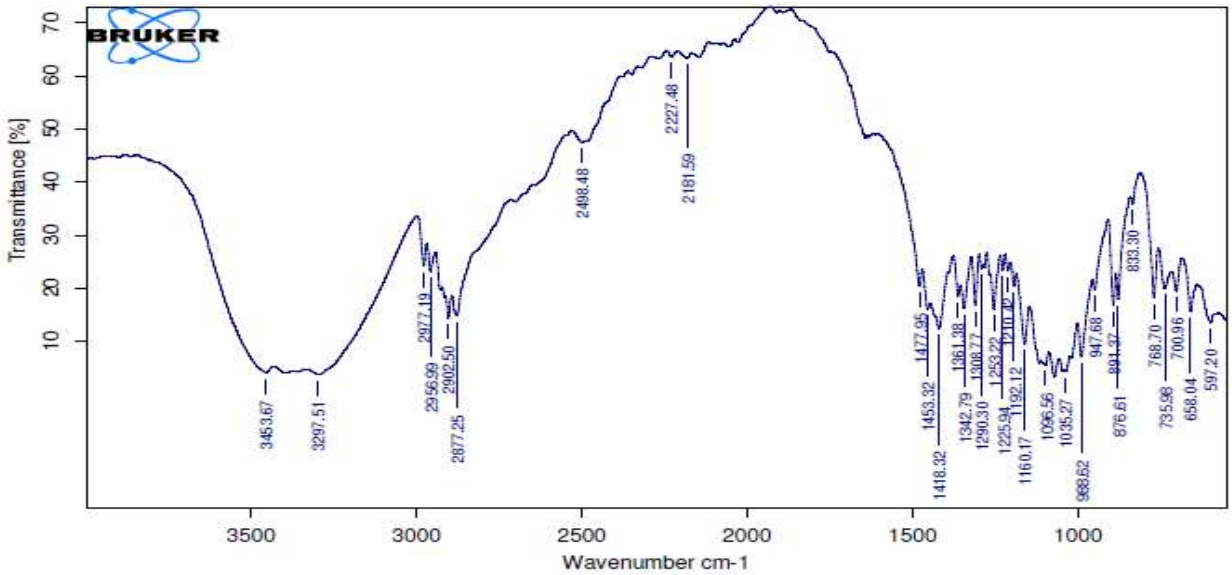

Figure 8: Ftir Spectra Karayagum

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GUARGUM

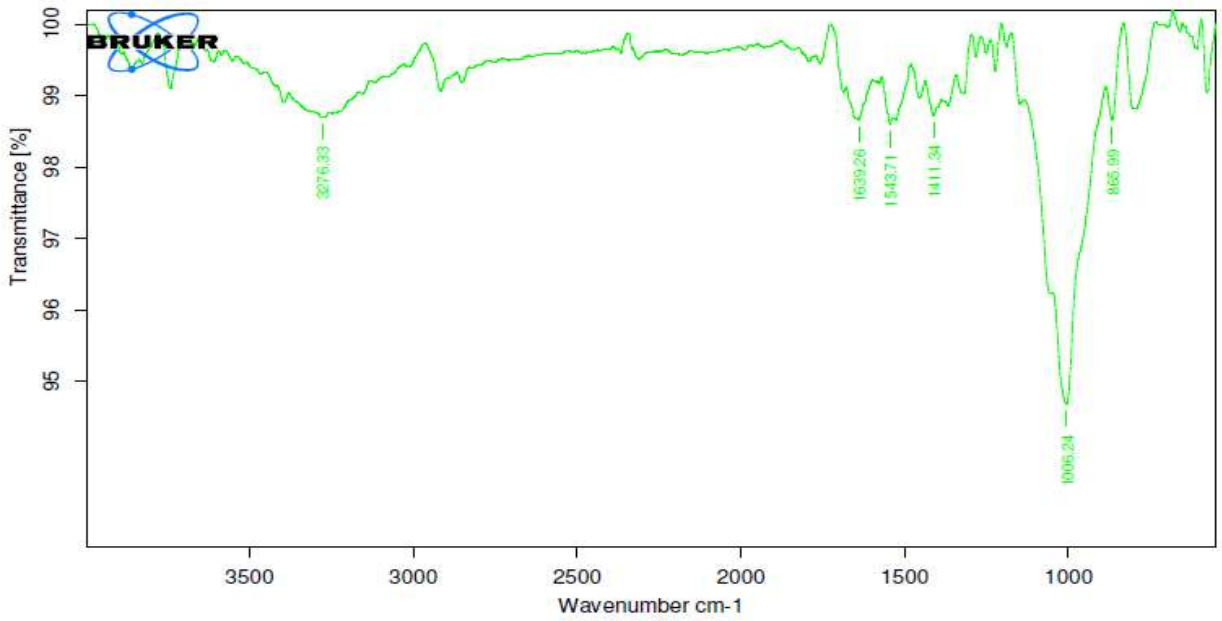

Figure 9: Ftir Spectra Guargum

MCC

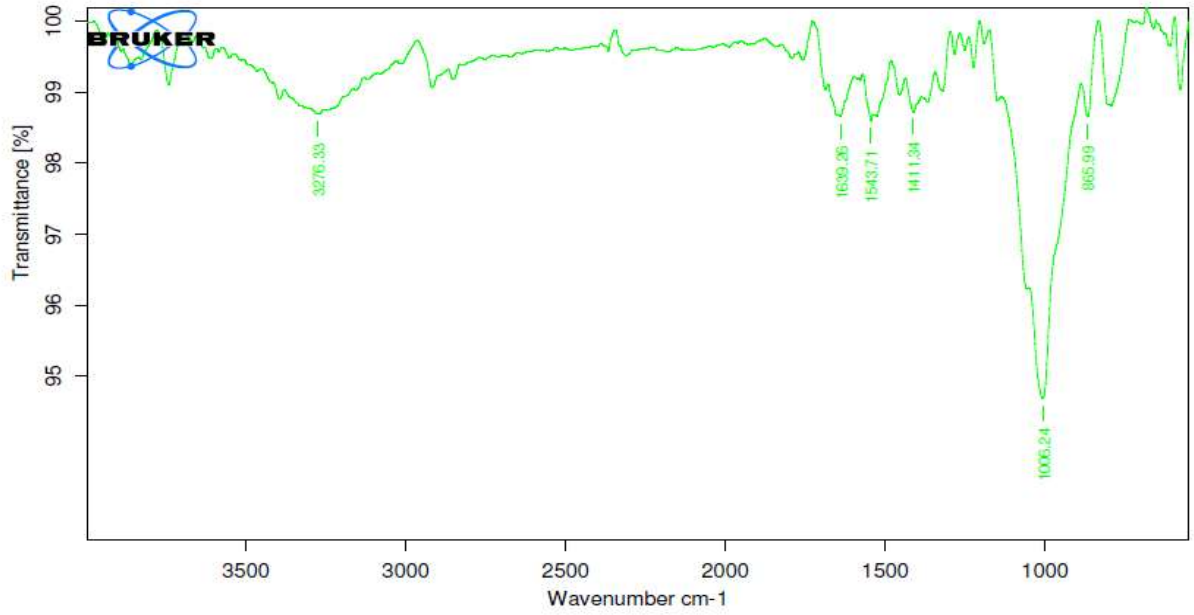

Figure 10: Ftir Spectra MCC

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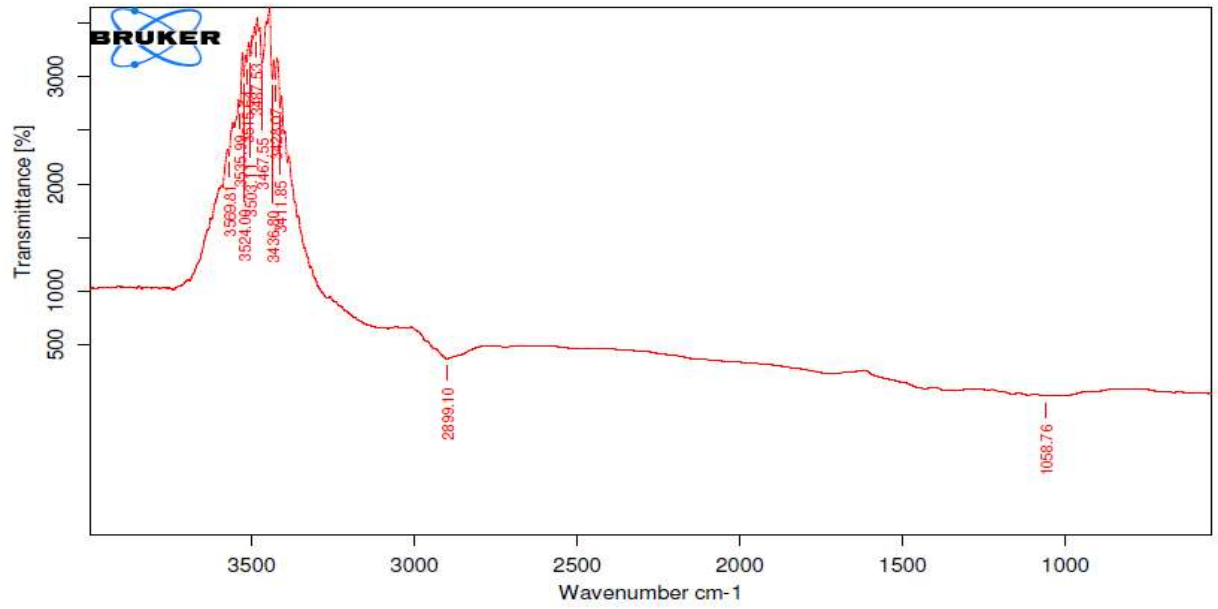

Figure 11: Ftir Spectra TALC

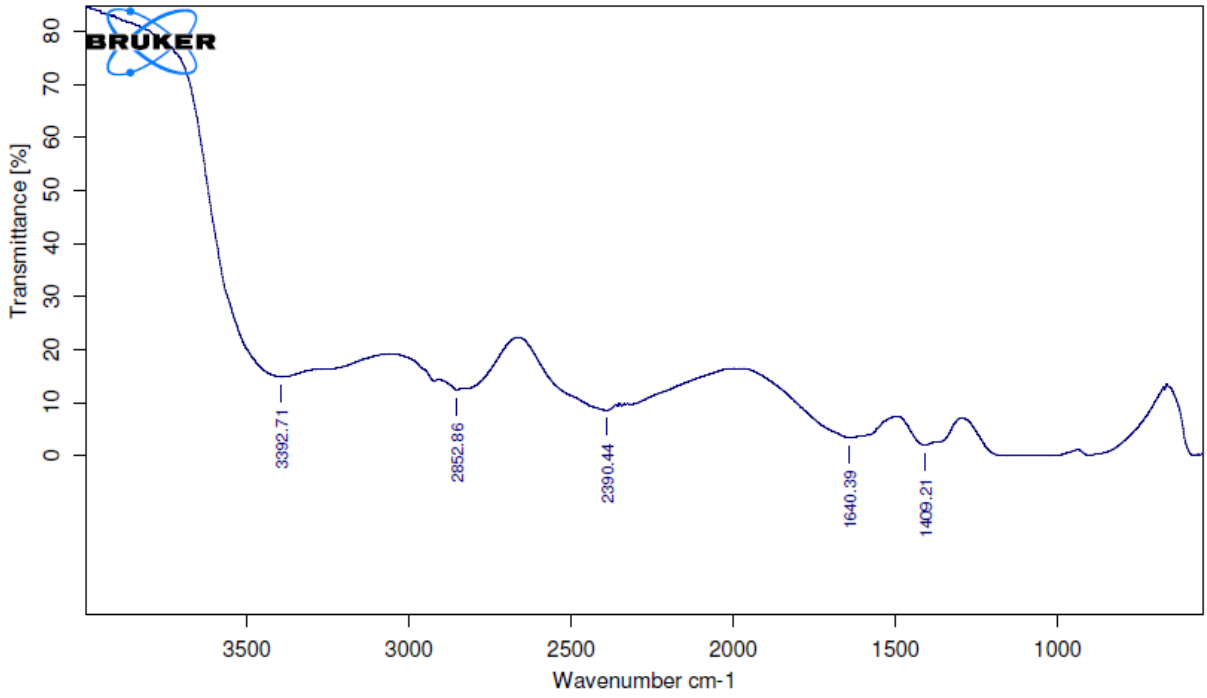

Figure 11: Ftir Spectra Mg Stearate

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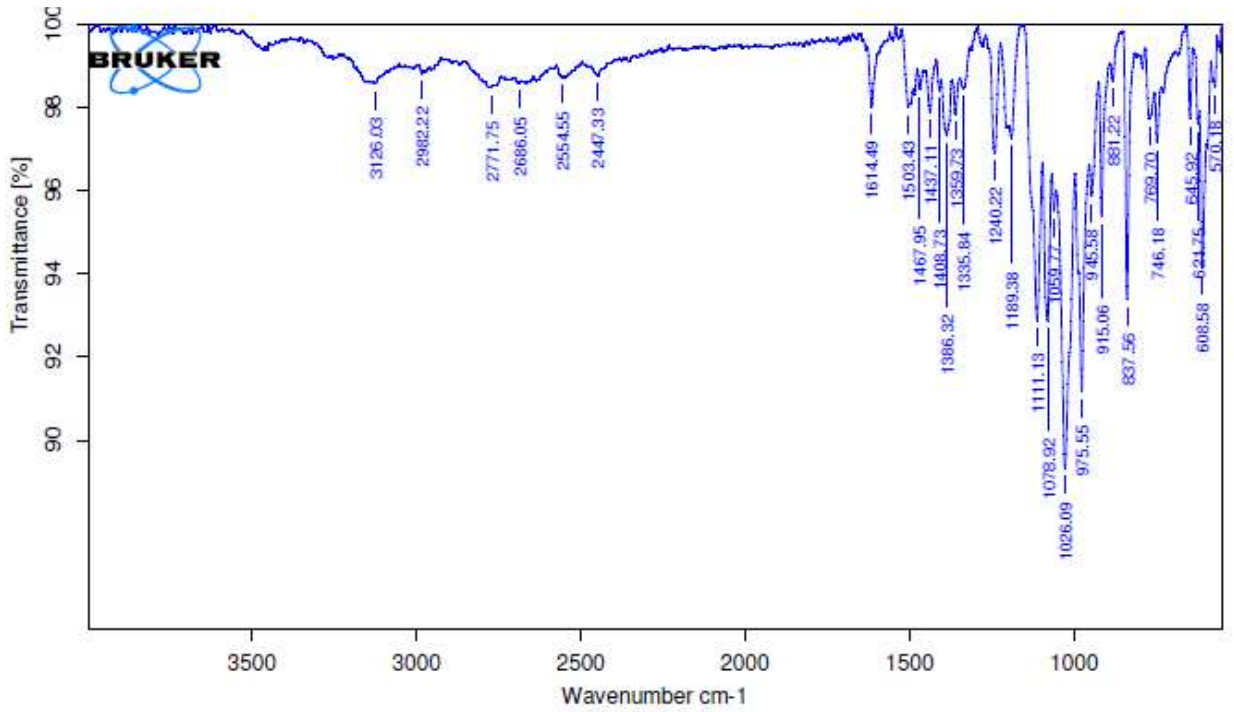

Figure 12: Ftir Spectra of optimised Formulation

9.5 Standard calibration curves of Zolmitriptan

Table 21: Calibration data of model drug in 0.1N HCl

Calibration curve of Zolmitriptan in 0.1N HCl(wave length 225nm)

Concentration(mcg/ml)	**Absorbance**
0	0
10	0.081
20	0.160
30	0.242
40	0.335
50	0.406
60	0.595
70	0.563
80	0.618
90	0.706

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100	0.784
120	0.953

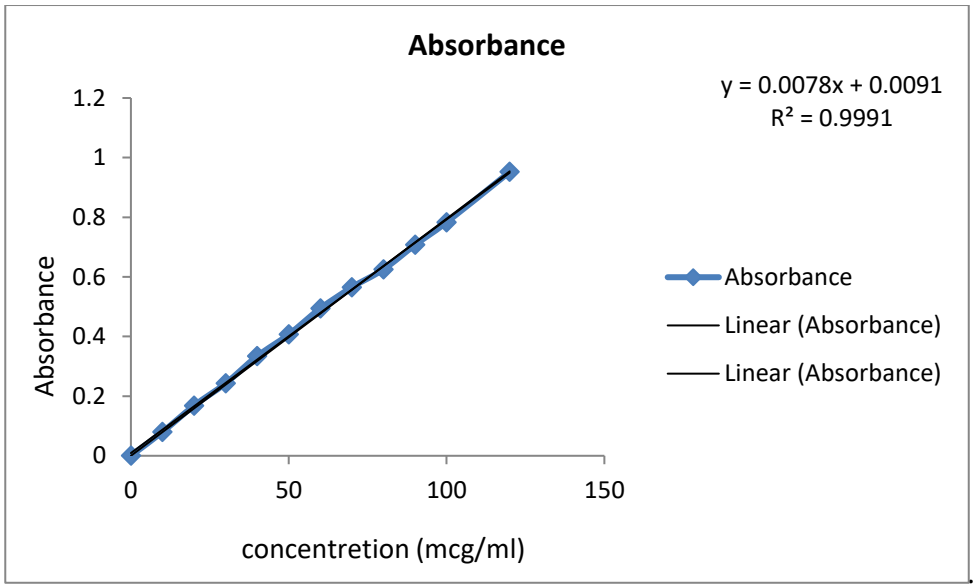

Figure 15: Standard graph of model drug in 0.1 N HCl

Table 22: Calibration data of model drug in 6.8 pH buffer

Calibration data of Zolmitriptan in 6.8pH buffer(wave length 225nm)

Concentration(mcg/ml)	**Absorbance**
0	0
20	0.067
40	0.110
60	0.162
80	0.233
100	0.279
120	0.336
140	0.392
160	0.446
180	0.507

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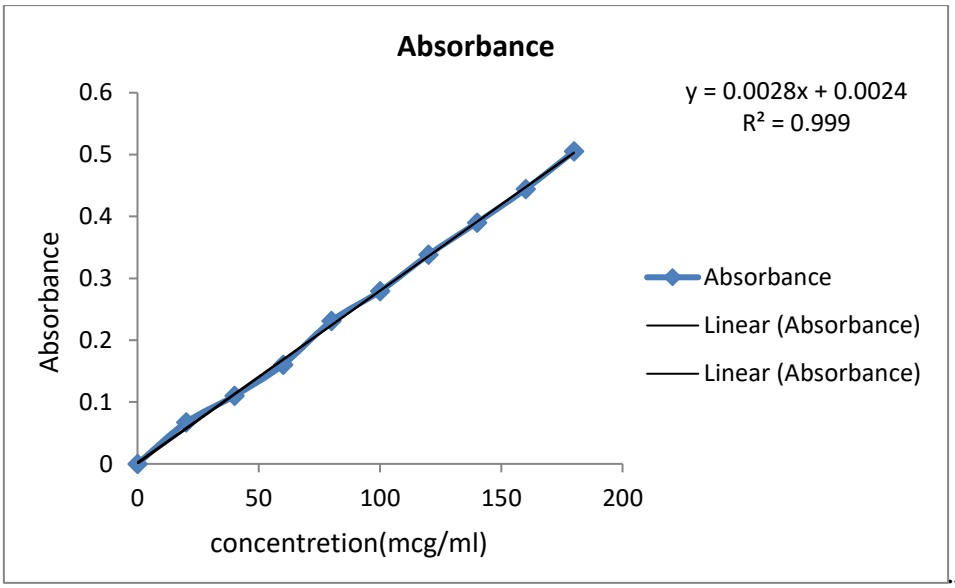

Figure 16:Standard graph of model drug in 6.8 pH buffer

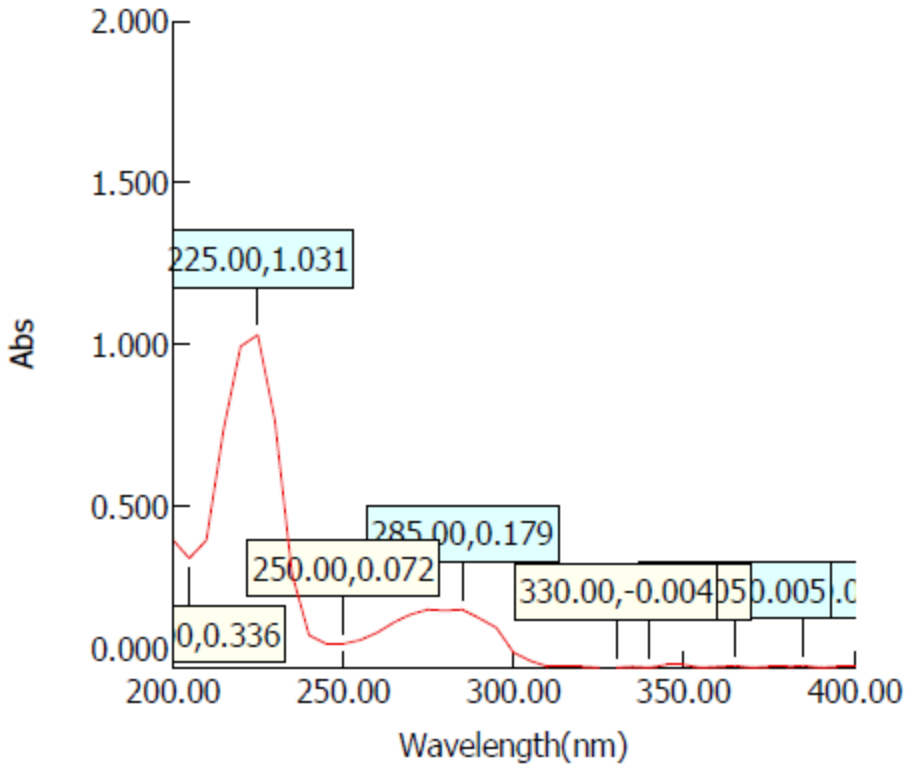

Figure17: Spectrum of Zolmitriptan: 225 nm

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9.6 Characterization of blend

Table 23: 9.6.1 Pre Compression parameters

Formulation code	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
F1	32.59±1.06	0.58±0.36	0.68±0.31	13.46±0.44	1.18±0.37
F2	33.37±1.02	0.63±0.26	0.73±0.29	11.52±0.28	1.15±0.56
F3	29.67±0.87	0.65±0.44	0.76±0.18	14.0±0.19	1.16±0.2
F4	27.6±0.88	0.68±0.28	0.74±0.55	10.48±0.12	1.11±0.36
F5	31.16±0.95	0.63±0.52	0.73±0.25	13.17±0.34	1.16±0.26
F6	32.55±0.88	0.62±0.14	0.75±0.18	14.63±0.32	1.18±0.64
F7	33.27±0.98	0.61±0.24	0.70±0.54	10.29±0.43	1.13±0.15
F8	32.48±0.97	0.67±0.48	0.76±0.83	10.21±0.33	1.12±0.44
F9	31.6±0.65	0.64±0.17	0.69±0.25	12.05±0.54	1.16±0.27

Inference
The angle of repose of different formulations was ≤ 33.48 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing.

The bulk density of blend was found between 0.58g/cm^3 to 0.68 g/cm^3.Tapped density was found between 0.68g/cm^3 to 0.76 g/cm^3.These values indicate that the blends had good flow property.

Carr's index for all the formulations was found to be between 10.21-14.63 and Hausner's ratio from 1.11-1.18 which reveals that the blends have good flow character.

9.7 Characterization of tablets

9.7.1 Post Compression parameters
All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table24.

Table 24: Characterization Zolmitriptan tablets

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Drug content(%)
F1	150±1.08	2.24±0.4	3.6	0.19±0.03	99.34±0.46
F2	149±0.93	2.23±0.3	3.2	0.16±0.02	98.54±0.62
F3	149±0.58	2.26±0.5	3.4	0.14±0.01	97.87±1.06
F4	150±1.02	2.12±0.3	3.8	0.31±0.02	99.7±0.53
F5	150±1.37	2.63±0.5	3.3	0.13±0.01	100.13±0.52

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F6	149±1.58	2.12±0.4	3.2	0.22±0.02	97.64±0.16
F7	149±0.47	2.23±0.7	3.1	0.19±0.05	98.73±0.92
F8	150±1.48	2.18±0.9	3.2	0.16±0.03	99.55±1.46
F9	150±0.97	2.28±0.8	3.6	0.19±0.08	100.23±1.21

Inference
Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3.1-3.8kg/cm^2.

All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the tablet weight.

Friability values were found to be less than 1% in all the formulations F1 – F9 and considered to be satisfactory ensuring that all the formulations are mechanically stable.

The % drug content for all the formulations were close to 100 and varied between 97.87 to 100.23%.

9.8 In vitro dissolution studies

9.8.1 Dissolution studies

9.8.1.1: Table 26: % Cumulative drug release of formulations F1-F4

	% drug release			
Time(hr)	**F1**	**F2**	**F3**	**F4**
1	11.12±0.4	9.18±0.6	7.89±0.2	8.12±0.6
2	29.48±0.6	10.87±0.5	11.12±0.4	16.53±0.5
3	32.89±0.5	14.35±0.5	18.23±0.9	17.06±0.4
4	37.23±0.8	19.10±0.5	29.67±0.5	23.42±0.3
5	38.93±0.4	32.55±0.6	37.13±0.5	28.89±0.3
6	43.90±0.2	41.42±0.2	42.02±0.2	36.12±0.4
7	62.29±0.6	58.60±0.4	49.32±0.3	43.89±0.2
8	75.80±0.4	73.23±0.5	54.12±0.6	49.65±0.5
9	89.12±0.9	78.19±0.3	64.58±0.2	58.32±0.3
10	97.88±0.3	92.32±0.2	72.32±0.4	63.12±0.6
11	_	99.12±0.5	79.52±0.3	75.77±0.3
12	_	_	84.12±0.5	79.83±0.9

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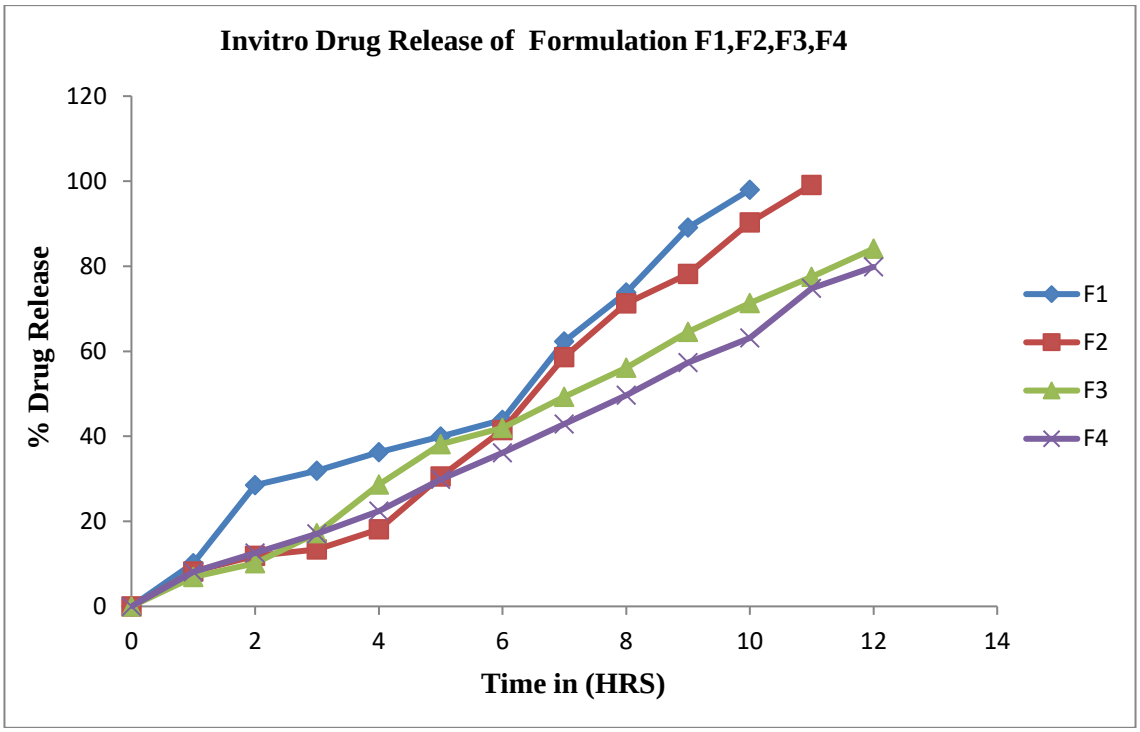

Figure 19:In vitro drug release study of F1,F2,F3,F4

Inference: Above dissolution studies indicate that Formulation F4 containing guar gum as 25% of the polymer has extended the model drug release up to 12 hours. But formulations F1,F2 and F3 containing 25%,50%,75% concentrations of karayagum as the polymer showed drug release and they released drug within 10 to 12 hours only.

9.8:% Cumulative drug release of formulations F5-F9

Table 27: % Cumulative drug release of formulations F5-F9

Time(hr)	% drug release				
	F5	F6	F7	F8	F9
1	7.93±0.4	4.65±0.8	19.12±0.2	18.43±0.6	18.19±0.8
2	15.04±0.6	12.23±0.6	26.80±0.4	21.12±0.7	19.93±0.6
3	22.13±0.4	18.12±0.5	37.39±0.8	29.80±0.6	28.24±0.5
4	32.02±0.6	27.59±0.5	51.12±0.5	35.42±0.5	35.13±0.5
5	38.42±0.5	33.93±0.5	69.37±0.5	48.23±0.3	39.75±0.7
6	43.13±0.8	34.41±0.2	78.02±0.2	66.07±0.7	51.02±0.4
7	9.68±0.6	38.67±0.2	85.25±0.4	69.41±0.3	56.24±0.6
8	54.32±0.5	41.83±0.4	90.33±0.8	79.13±0.2	65.26±0.4
9	58.83±0.5	48.24±0.8	97.59±0.6	86.53±0.4	72.18±0.6
10	63.41±0.7	56.18±0.5	_	95.12±0.8	79.13±0.5
11	69.13±0.6	58.03±0.5	_	97.59±0.7	84.26±0.2
12	72.93±0.5	63.68±0.3	_	_	88.80±0.4

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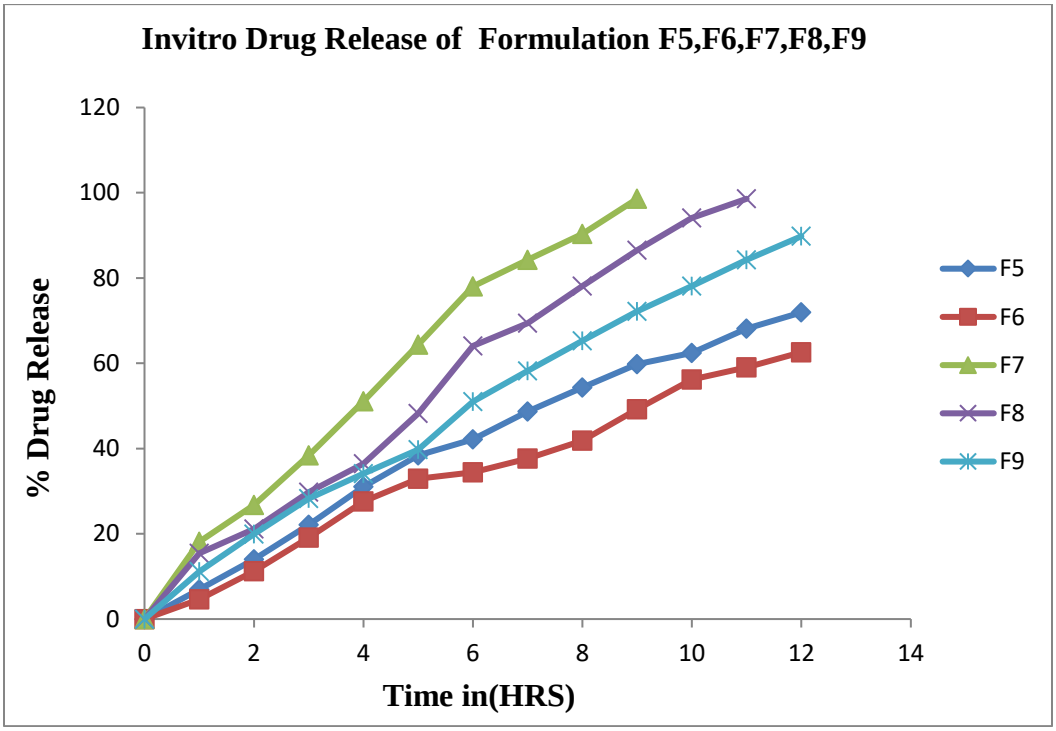

Figure 20:In vitro drug release study of F5,F6,F7,F8,F9

Inference: Above dissolution studies indicate that Formulation F7, F8 & F9 containing HPMC K100M as 25%, 50% and 75% concentration of the polymer has extended the model drug release up 10 to 12 hours. But formulations F5 and F6 containing 75%, 100% concentrations of Guar gum as the polymer showed faster drug release and they released drug within 12 hours only.

9.8.5 Evaluation of drug release kinetics

Release kinetic study

The kinetic release data was computed from the release data obtained from the *in-vitro* dissolution study of the best formulation F6 and reference and fitted to the mathematical models; Zero order equation, First order, Higuchi release and Korsmeyer- Peppas models . The best fit was calculated and the graphs are shown in figures

Table 33:In Vitro Drug Release kinetics for optimized formulation

KINETIC VALUES:				
Formulation F-6	**Zero order**	**First order**	**Higuchi**	**Korsmeyer – Peppas**
R^2 values	0.984	0.980	0.943	0.874

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The invitro dissolution data for best formulation F6were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation in peppas F6 shows R^2 value 0.874. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot.

9.8. Kinetic models for optimized formulationF6

Time(hrs)	%cdr	Log%cdr remain	SQRT(time)	Log time(hrs)	Log%cdr
0	**0**		**0**	**0**	**0**
1	4.65	1.979320697	1	0	0.667452953
2	12.23	1.943346098	1.414213562	0.301029996	1.087426457
3	18.12	1.913177834	1.732050808	0.477121255	1.258158193
4	27.59	1.859798547	2	0.602059991	1.4407517
5	33.93	1.820004307	2.236067977	0.698970004	1.53058386
6	34.41	1.816837631	2.449489743	0.77815125	1.536684673
7	38.67	1.787672965	2.645751311	0.84509804	1.587374172
8	41.83	1.764699064	2.828427125	0.903089987	1.621487865
9	48.24	1.713994268	3	0.954242509	1.683407299
10	56.18	1.641672373	3.16227766	1	1.749581735
11	58.03	1.622258969	3.31662479	1.041392685	1.763652571
12	63.68	1.56014584	3.464101615	1.079181246	1.804003055

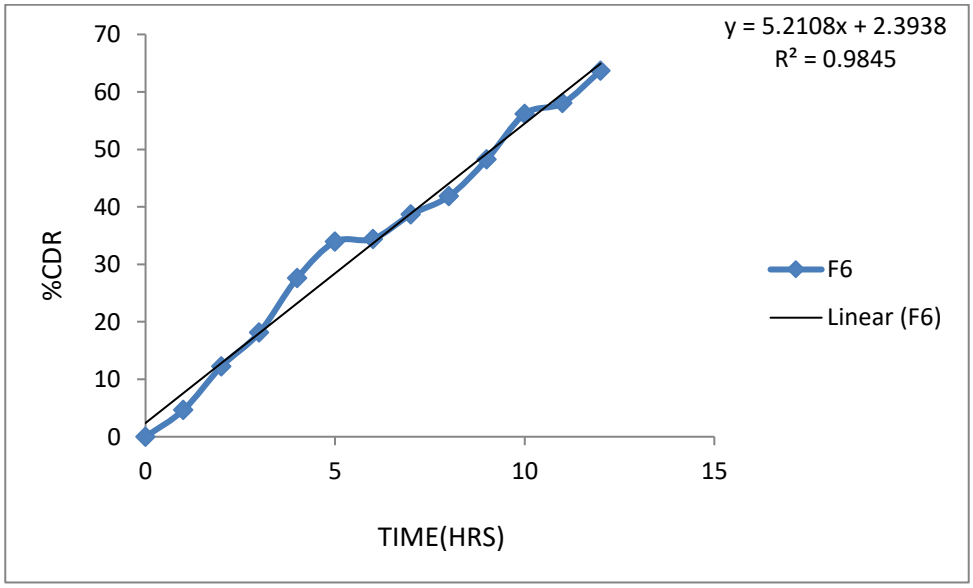

Figure 30: Zero order plot of F6

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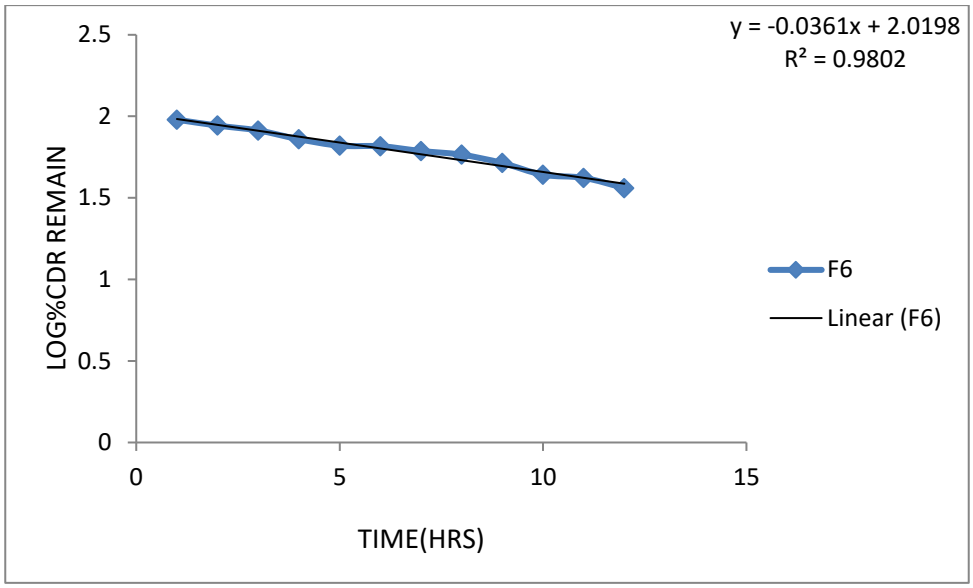

Figure 31:First order plot of F6

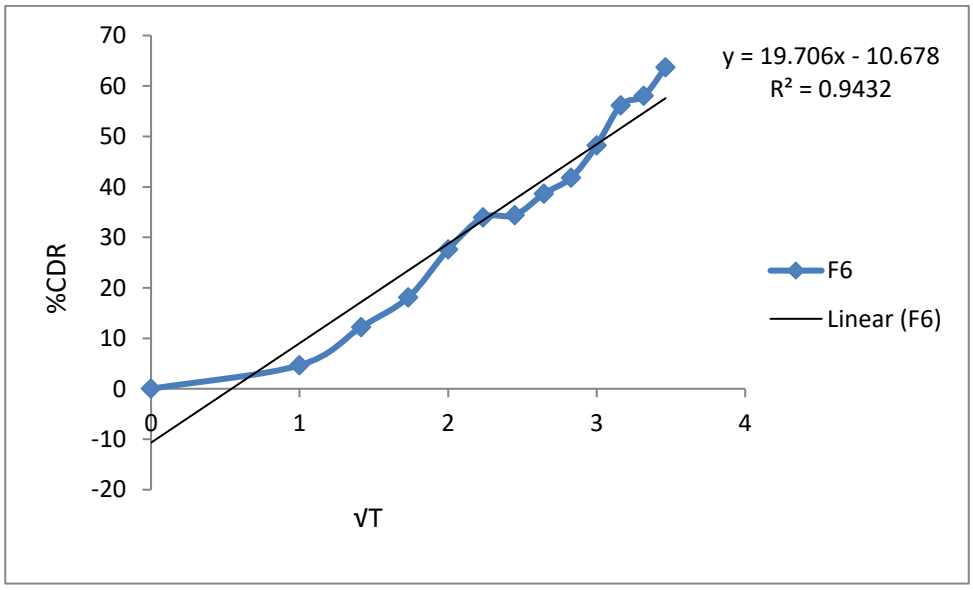

Figure 32: Higuchi plot of F6

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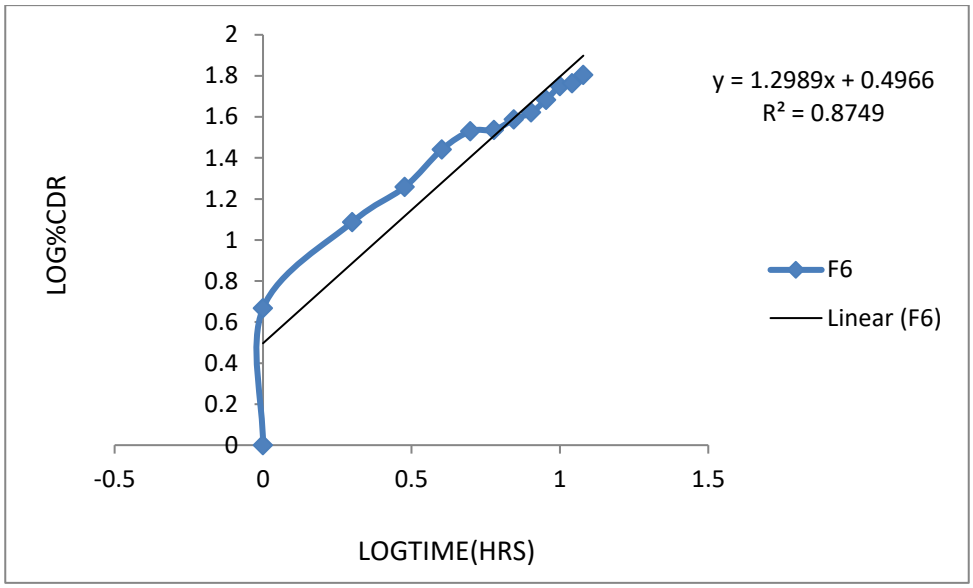

Figure 33:Korsmeyer-peppasplot of F6

9.9 Stability data of formulation (F6)

The tablets were stored at 40 ± 2˚C/75 ± 5% RH for three months to assess their stability. At the end of three months, tablets were withdrawn, evaluated for tablet characteristics and invitro drug release and results were shown in table .

Dissolution studies of formulation F6 after 12weeks at 40^0 c /75% RH

Table 34:Dissolution studies of formulation F6 after 12weeks at 40^0 c /75% RH

Time(hrs)	% drug release F6
1	5.25±0.8
2	11.99±0.6
3	19.22±0.5
4	28.66±0.5
5	31.86±0.5
6	34.51±0.2
7	38.67±0.2
8	42.73±0.4
9	50.32±0.8
10	57.32±0.5
11	59.05±0.5
12	61.63±0.3

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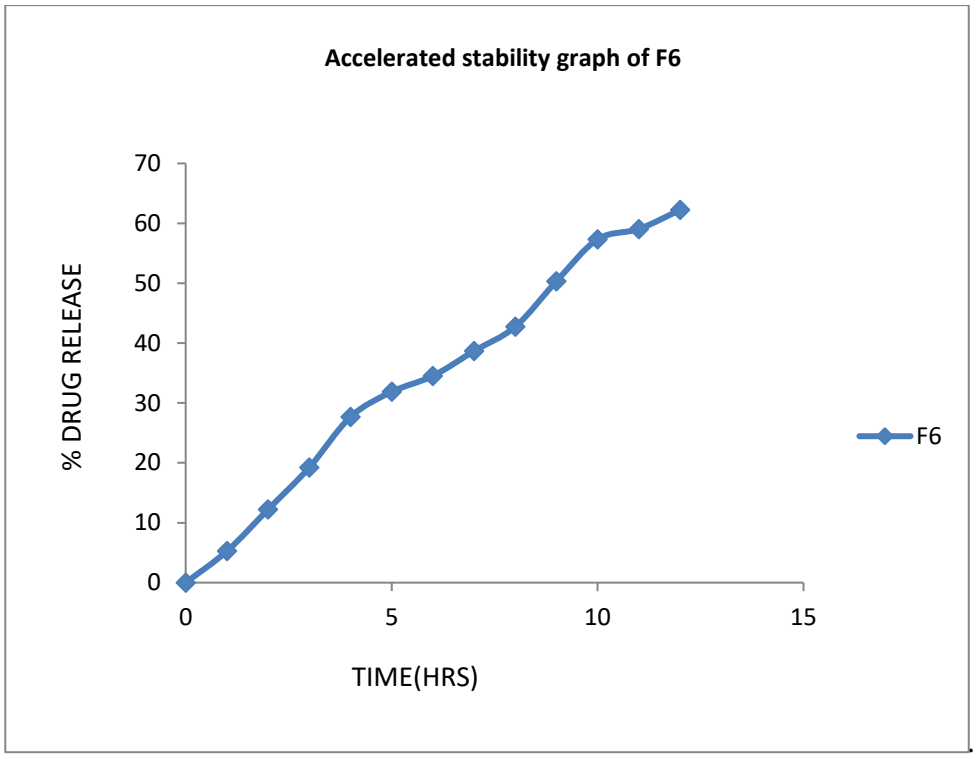

Figure 34: Accelerated stability graph of F6

Inference

The controlled stability samples showed comparable dissolution profile with the initial release. And also there was no change in the physical characteristics**.** Hence we may conclude that Model drug extended release formulation had good stability's formulation had good stability.