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FORMULATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE TABLETS OF ITRACONOZOLE BY USING NATURAL AND SYNTHETIC POLYMERS

Munija Panchenddula[1], Deverkonda Nikitha[2], Afra Fathima[3], M. Nithya Yashasvi[4], Lakkakula Prashanthi[*]

[1]Vice Principal, Vision College of Pharmaceutical Sciences and Research, Boduppal, Hyderabad, India.

[2,3,4]Students, Pharm D 4th year, Vision College of Pharmaceutical Sciences and Research, India.

[*]Assistant Professor, Department of Pharmaceutics, Vision College of Pharmaceutical Sciences and Research, Boduppal, Hyderabad, India.

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***Corresponding Author: Lakkakula Prashanthi**
Assistant Professor, Department of Pharmaceutics, Vision College of Pharmaceutical Sciences and Research, Boduppal, Hyderabad, India.
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ABSTRACT

Itraconazole is an antifungal medication used to treat a number of fungal infections and has half-life 21 h. Sustained release. The main objective of the present study was to develop sustained release formulation using Natural and synthetic polymers i.e., Sodium alginate, Chitosan and HPMC K 15 M respectively. Drug Excipient Compatibility studies revealed that there was no considerable change. Direct compression technique was used to prepare tablets which were evaluated for pre compression and post compression parameters. Nine formulations were prepared in which F1-F3 were prepared using Sodium alginate, F4-F6 by Chitosan and F7-F9 using HPMC K 15 M polymers at 1:1, 1:2 and 1:3 to the drug and polymer ratios respectively. F7 was selected as the best formulation which sustained the drug release up to 99.71 % in 12 h out of nine formulations (F1-F9). Release model of sample was found to follow zero order kinetics with high linearity. The best formulation was found to be stable during stability studies for 3 months.

KEYWORDS: Chitosan, compatibility, *direct compression, Hpmc K 15 m, Sodium alginate, Sustained release.*

1. INTRODUCTION

Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended period of time 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.[1,2,3]

If the active compound has a long half-life, it is sustained on its own, If the pharmacological activity of the active is not directly related to its blood levels, Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[4,5,6]

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ.[7,8]

- Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulation.[9]
- If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose.
- The above factors need serious review prior to design.[10]
- Itraconazole is used to treat serious fungal or yeast infections. Itraconazole oral solution is only used to treat oropharyngeal or esophageal candidiasis (thrush, oral thrush). Itraconazole capsule is used to treat fungal infections, such as aspergillosis (fungal infection in the lungs), blastomycosis (Gilchrist's disease), or histoplasmosis (Darling's disease). Sporanox® capsule is also used to treat onychomycosis (fungal infection in the fingernails or toenails). Itraconazole tablet is only used to treat onychomycosis of the toenails. This medicine works by killing the fungus or yeast and preventing its growth.[11,12,13]

2. MATERIAL'S

Itraconazole, sodium alginate, chitosan, HPMC K15M, PVP K 30, MCC, Megnisium sterate, Talc.

3. METHODOLOGY

3.1 Formulation development of Tablets

All the formulations were compress by direct compression. The compositions of different formulations are given in Table 2.1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Itraconazole. Total weight of the tablet was considered as 250mg.

Procedure

1. Itraconazole and all other ingredients were individually passed through sieve no ¹ 60.
2. All the ingredients were mixed thoroughly by triturating up to 15 min.
3. The powder mixture was lubricated with talc.

4. The tablets were prepared by using direct compression method.

Table 1: Formulation composition for tablets.

INGREDIENTS (MG)	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Itraconazole	100	100	100	100	100	100	100	100	100
Sodium alginate	30	60	90	-	-	-	-	-	-
Chitosan	-	-	-	30	60	90	-	-	-
HPMC K 15 M	-	-	-	-	-	-	30	60	90
PVP K 30	5	5	5	5	5	5	5	5	5
MCC	108	72	48	108	72	48	108	72	48
Magnesium sterate	4	4	4	4	4	4	4	4	4
Talc	3	3	3	3	3	3	3	3	3
Total weight	250	250	250	250	250	250	250	250	250

3.2 Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content uniformity, assay, disintegration time and in vitro drug release, disintegration testing was performed using modified method.

3.3 Drug – excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm-1 to 400cm-1.

3.5 Differential scanning calorimetry (dsc)

The possibility of any interaction between the drug and the polymer during preparation of tablets was assessed by carrying out thermal analysis of drug and polymer alone as well as physical mixture. DSC analysis was performed using Hitachi DSC 7020, on 5 to 15 mg samples. Samples were heated in sealed aluminum pan at a rate of 10°C/min conducted over a temperature range of 30 to 350°C under a nitrogen flow of 50 mL/min.

3.6 Stability Studies

For the determination of stability of prepared optimized formulation, accelerated stability studies were carried out on optimized formulation. Tablets were stored according to ICH guidelines at 40±2oC/75±5% RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber. After completion of required duration time, sample was withdrawn and tested for different tests such as hardness, drug content and in- vitro drug release.

4. RESULTS AND DISCUSSION

The present study was aimed to developing sustained release tablets of Itraconazole using various polymers. All the formulations were evaluated for physicochemical properties and in vitro drug release study.

4.1 Analytical Method

Graphs of Itraconazole were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 262 nm and 265 nm respectively.

Table 2: Observations for graph of Itraconazole in 0.1N HCL.

Concentration (µg/ml)	Absorbance
0	0
2	0.139
4	0.254
6	0.361
8	0.482
10	0.584

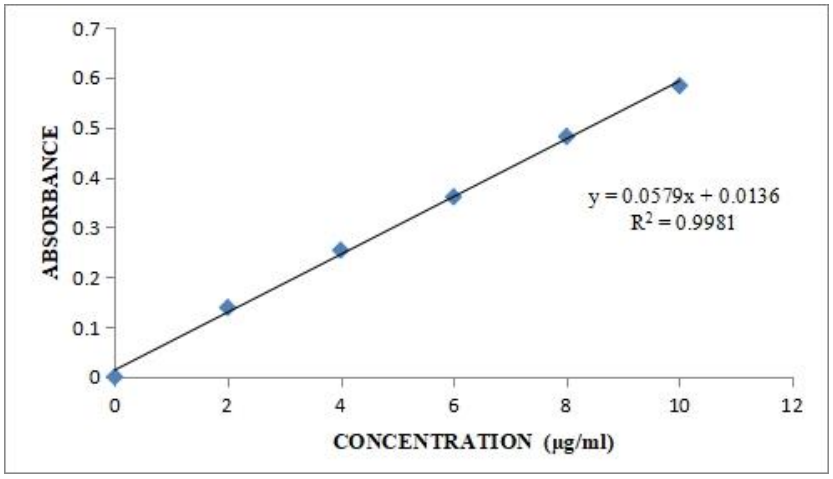

Fig. 1: Standard curve of Itraconazole.

Table 3: Standard graph values of Itraconazole at 265 nm in pH 6.8 phosphate buffer.

Concentration (µg/ml)	Absorbance
0	0
2	0.135
4	0.262
6	0.381
8	0.498
10	0.631

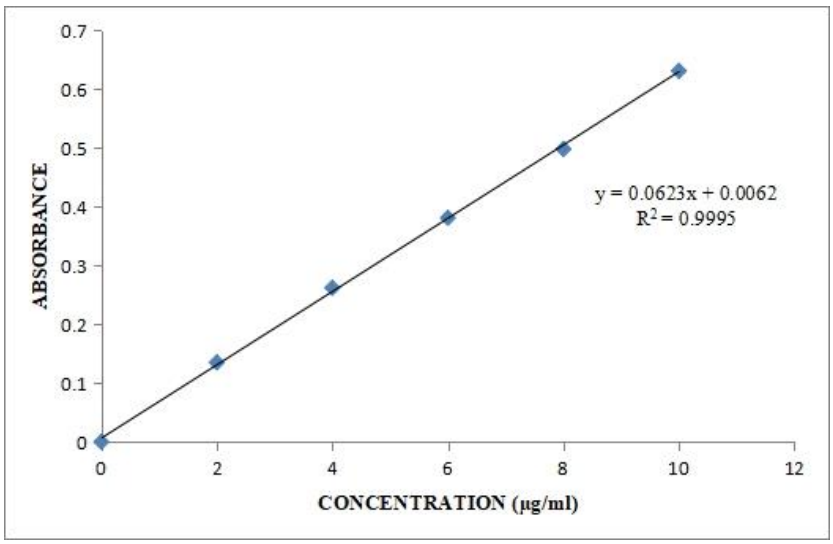

Fig. 2: Standard curve of Itraconazole.

4.2 Preformulation parameters of powder blend

Table 4: Pre-formulation parameters of Core blend.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.33±0.48	0.58±0.01	0.69±0.05	15.94±0.01	1.18±0.04
F2	25.24±0.52	0.48±0.09	0.57±0.05	15.78±0.05	1.18±0.06
F3	28.12±0.35	0.54±0.02	0.65±0.04	16.92±0.04	1.2±0.07
F4	27.08±0.47	0.54±0.05	0.64±0.04	15.62±0.05	1.18±0.08
F5	25.12±0.51	0.53±0.02	0.65±0.05	18.46±0.09	1.22±0.07
F6	26.45±0.65	0.56±0.03	0.66±0.02	15.15±0.02	1.17±0.05
F7	25.01±0.21	0.49±0.05	0.57±0.06	14.03±0.01	1.16±0.02
F8	26.8±0.35	0.56±0.04	0.67±0.08	16.41±0.00	1.19±0.05
F9	27.7±0.42	0.52±0.09	0.64±0.02	18.75±0.09	1.23±0.06

All the values represent n=3

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties. The tapped density of all the formulations powders has good flow properties. The compressibility index of all the formulations was found to be 14.03±0.01 to 18.75±0.09 which show that the powder has good flow properties. All the formulations have shown the Hauser ratio 1.2 to 1.23 indicating the powder has good flow properties.

4.3 Quality Control Parameters for tablets

Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the compression tablet.

Table 5: Quality control parameters for tablets.

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	248.36	4.6	0.32	3.14	98.58
F2	249.82	4.1	0.14	3.56	96.16
F3	247.21	5.6	0.89	3.42	99.38
F4	245.52	4.9	0.14	3.59	98.86
F5	250.01	5.1	0.51	3.62	99.43
F6	249.82	4.5	0.23	3.11	97.50
F7	249.57	4.7	0.56	3.83	99.31
F8	246.98	5.0	0.86	3.24	98.72
F9	249.18	4.0	0.49	3.46	96.61

All the parameters such as weight variation (245.52 to 250.01mg), friability (<1%), hardness (4.0 to 5.6kg/cm2), thickness (3.11 to 3.83mm) and drug content (95.37-99.43%) were found to be within the IP limits.

***4.4 IN VITRO* DRUG RELEASE STUDIES**

Table 6: Dissolution Data of Itraconazole tablets F1-F9.

Time (H)	% Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	16.19	21.5	14.62	12.41	16.76	10.20	7.14	12.31	11.55
1	22.95	28.5	19.86	18.66	20.89	15.89	15.12	18.49	17.47
2	31.78	36.28	21.35	28.59	29.24	20.64	20.32	26.62	21.62

3	43.81	41.90	29.45	31.84	35.32	25.11	27.16	30.87	28.47
4	56.76	46.27	39.8	40.35	42.75	28.96	33.47	34.75	32.12
5	59.21	52.86	46.25	45.78	48.09	38.30	42.62	47.15	42.85
6	65.42	60.25	55.73	52.60	56.16	40.56	51.45	50.91	48.41
7	71.56	67.83	62.26	60.71	61.36	45.31	63.63	56.75	53.65
8	84.39	73.40	73.24	68.54	67.12	53.78	67.74	69.01	59.12
9	96.12	82.34	77.59	72.28	73.78	57.41	78.85	72.50	63.56
10		90.27	81.70	76.12	78.79	62.02	82.70	78.96	67.37
11		97.52	89.62	85.36	82.31	66.46	87.09	83.49	74.80
12			98.10	96.85	89.45	72.39	99.71	86.75	78.24

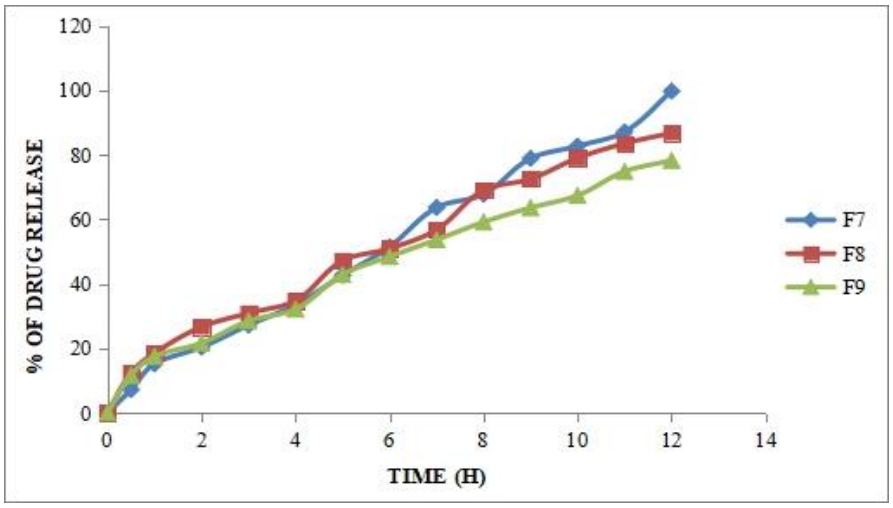

Fig 3: Dissolution profile of Itraconazole (F7, F8, F9 formulations).

Different formulations (F1-F9) were prepared using different polymers like Sodium alginate, Chitosan and HPMC K 15 M alone at different ratios. Formulations F1-F3 were prepared using Sodium alginate at the ratio of 1:1, 1:2 and 1:3 which showed the drug release about 96.12 %, 97.52 % and 98.10 %.Formulations F4-F6 were prepared using Chitosan at the ratio of 1:1 , 1:2 and 1:3 with the drug release of 96.85 %, 89.45 % and 72.39 % and the formulations F7-F9 were prepared by using HPMC K 15 M polymer at the ratio of 1:1, 1:2 and 1:3. showed the drug release of 99.71 %, 86.75 % and 78.24 % at the end of 12 h. Among all these formulations F7 was selected as the best ideal formulation which exhibited 99.71 % of drug release in 12 h. Finally Concluded that F7 formulation was considered as optimized formulation.

Table 7: Release kinetics.

Cumulative (%) Release Q	Time (T)	ROOT (T)	LOG (%) Release	LOG (T)	LOG (%) Remain	Release Rate (Cumulative % Release / t)	1/CUM % Release	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
7.14	0.5	0.707	0.854	-0.301	1.968	14.280	0.1401	-1.146	92.86	4.642	4.528	0.113
15.12	1	1.000	1.180	0.000	1.929	15.120	0.0661	-0.820	84.88	4.642	4.395	0.247
20.32	2	1.414	1.308	0.301	1.901	10.160	0.0492	-0.692	79.68	4.642	4.303	0.338
27.16	3	1.732	1.434	0.477	1.862	9.053	0.0368	-0.566	72.84	4.642	4.176	0.465
33.47	4	2.000	1.525	0.602	1.823	8.368	0.0299	-0.475	66.53	4.642	4.052	0.590
42.62	5	2.236	1.630	0.699	1.759	8.524	0.0235	-0.370	57.38	4.642	3.857	0.785
51.45	6	2.449	1.711	0.778	1.686	8.575	0.0194	-0.289	48.55	4.642	3.648	0.994
63.63	7	2.646	1.804	0.845	1.561	9.090	0.0157	-0.196	36.37	4.642	3.313	1.328
67.74	8	2.828	1.831	0.903	1.509	8.468	0.0148	-0.169	32.26	4.642	3.183	1.458
78.85	9	3.000	1.897	0.954	1.325	8.761	0.0127	-0.103	21.15	4.642	2.765	1.876
82.7	10	3.162	1.918	1.000	1.238	8.270	0.0121	-0.082	17.3	4.642	2.586	2.055
87.09	11	3.317	1.940	1.041	1.111	7.917	0.0115	-0.060	12.91	4.642	2.346	2.296
99.71	12	3.464	1.999	1.079	-0.538	8.309	0.0100	-0.001	0.29	4.642	0.662	3.980

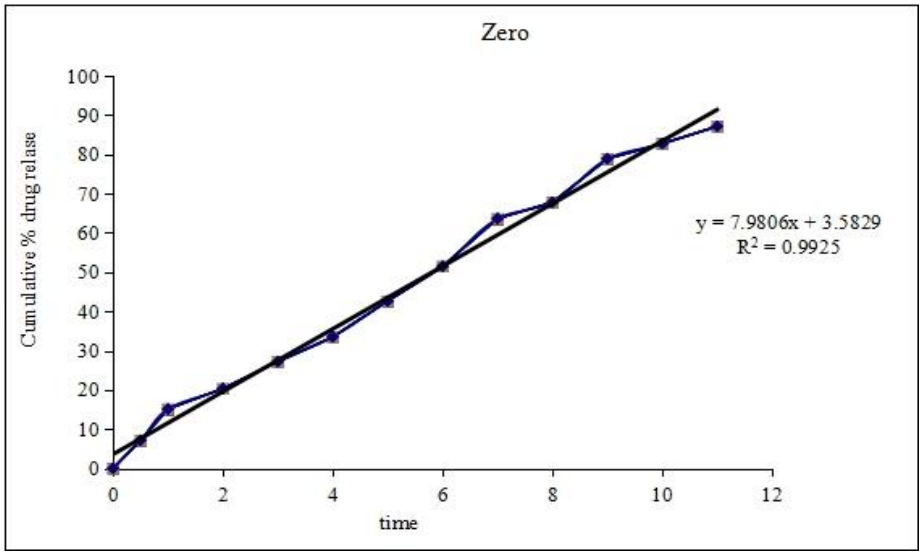

Figure 4: Zero order release kinetics graph.

To study the release rate kinetics and the release mechanism of the drug from the tablet formulations, the Optimized in vitro drug release data were treated with the mathematical equation such as first order kinetics equation, zero-order kinetics equation, Higuchi's equation, and Korsemeyer's equation. The data obtained are represented in Table. When data were treated with Zero order equation to learn about the mechanism of drug release, it was observed that the values did not give a good fit for the Zero order equation. None of the Kinetics followed the good fits, which was confirmed by the poor correlation coefficient values and equations. And the values are

$$y = 7.980x + 3.582$$

$$R^2 = 0.992$$

From the above graphs it was evident that the formulation F7 was followed Zero order release mechanism.

Table 8: Kinetics Correlation coefficient values.

Release Kinetics	Correlation coefficient values
Zero order release kinetics	$R^2 = 0.992$
Higuchi release kinetics	$R^2 = 0.943$
Peppas release kinetics	$R^2 = 0.987$
First order release kinetics	$R^2 = 0.951$

Drug – Excipient compatibility studies

Figure 10.11: FT-IR Spectrum of Optimized Formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Itraconazole and excipients used in the preparation of different Itraconazole Sustained release formulations. Therefore, the drug and excipients are compatible to form stable formulations under study. The FTIR spectra of Itraconazole and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence, they were compatible.

4.5 DSC

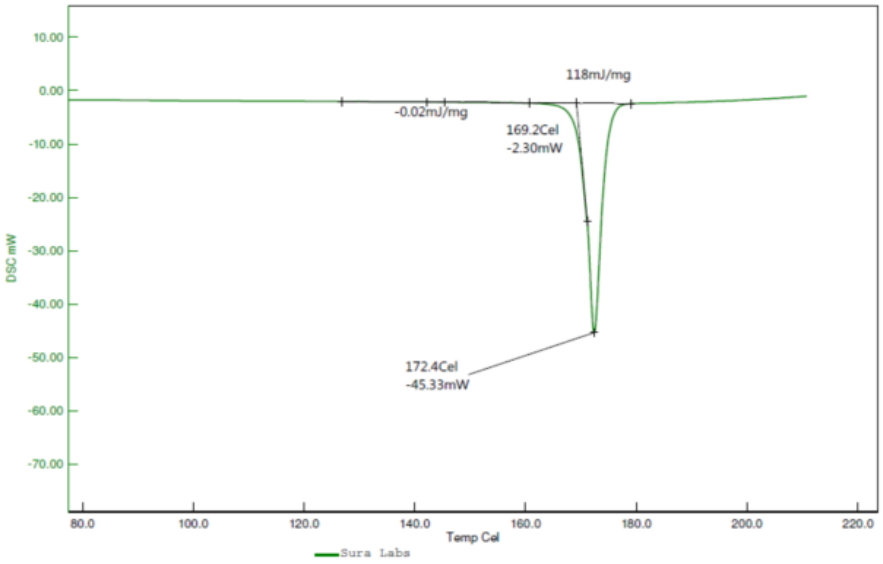

Figure 5: DSC of Itraconazole pure formulation.

4.6 ACCELERATED STABILITY STUDIES

The stability study of the optimized tablets was carried out according to ICH guidelines at 40±2oC/75±5% RH for three months by storing the samples in (Lab-care, Mumbai) stability chamber. The results from stability studies are shown in table.

Table 10.8: Stability dissolution profile of F7 for 1st, 2nd & 3rd months

Dissolution Profile

Table 9: Stability dissolution profile of F7 for 1st, 2nd and 3rd months.

S. No.	Time (Hours)	F7 (1st Month)	F7 (2nd Month)	F7 (3rd Month)
1	0	0	0	0
2	0.5	7.16	7.58	7.31
3	1	15.35	14.20	11.43
4	2	20.47	20.64	20.98
5	3	27.61	27.14	26.62
6	4	33.86	32.82	33.12
7	5	42.14	42.52	42.75
8	6	51.24	51.40	50.83
9	7	63.30	63.56	63.54
10	8	67.76	66.91	67.61
11	9	78.19	78.11	78.28
12	10	82.31	81.36	81.51
13	11	87.47	87.72	87.26
14	12	99.26	99.12	99.06

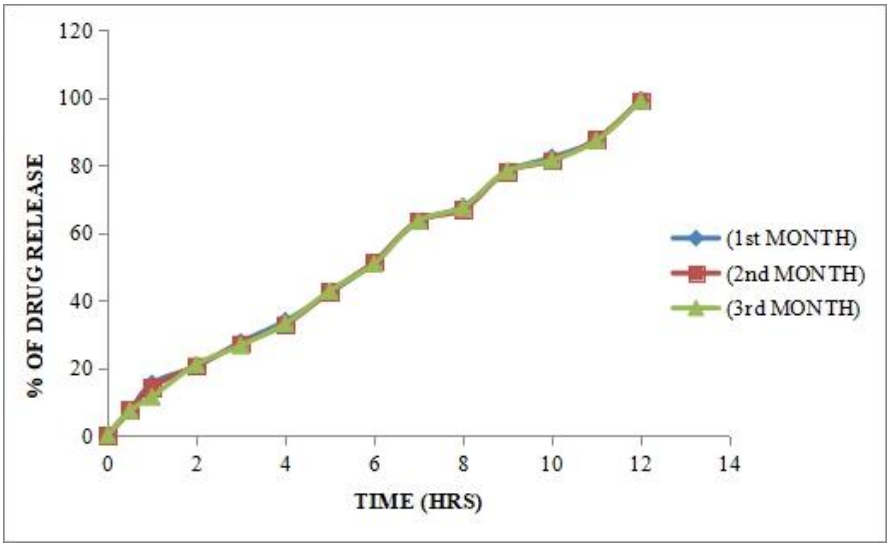

Figure 6: Drug release profile of formulation F7 during stability.

Table 10: Physicochemical parameters of most satisfactory formulation during stability studies for optimized formulation.

Time Period (Month)	Hardness(kg/cm2)	Drug Content (%)
1	4.6	99.30
2	4.5	99.28
3	4.4	99.20

There was no major change in the various physicochemical parameters evaluated like hardness, drug content, in vitro dissolution pattern at the various sampling points. There was no statistically significant difference between the initial values and the results obtained during stability studies.

5. CONCLUSION AND FUTURE SCOPE

The aim of the present study was to formulate and evaluate the sustained release tablets of Itraconazole by using Natural and synthetic polymers to achieve prolonged therapeutic effect by continuously releasing the medication over an extended period of time after administration of single dose. The basic goal of therapy is to achieve steady state blood levels that is therapeutically effective and non-toxic for a prolonged period of time. The design of proper dosage regimen is an important element in accomplishing this goal. A fixed dose of 100 mg of Itraconazole was used in the formulation. Various formulations like Sodium alginate, Chitosan and HPMC K 15 M were used as release retardants to study the effect on drug release. The total weight of the tablet was 250 mg. All the formulations (F1-F9) passed the evaluation parameters and were found to be in limits. Among all the formulations F7 with 100mg polymer content (30mg HPMC K 15 M) showed the drug release of 99.71 % in 12 h and was selected as the ideal formulation. When the stability results of best formulation were studied at 40 ± 2°C / 75 ± 5% RH for 3 months were compared with their initial results it was found that there was no significant difference in hardness, drug content and drug release of optimized formulation.

6. FUTURE SCOPE

This work shall be helpful for patients struggling during ingestion of solid unit forms, having natural and synthetic polymers, these are very reliable to the consumers. Now this present investigation has been extended using newer natural and synthetic polymers along with other manufacturing methods for future scope.

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