ISSN: 0975-766X
Research Article
Available Online through
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FORMULATION AND EVALUATION OF CLOTRIMAZOLE VAGINAL TABLE IN COMBINATION WITH LACTOBACILLUS AND GLYCEROL MONOLAURATE

Harini Vuyyuru[1]*, Prasanth Sai.R.V[1], Pujitha.I[1], Nagu.A[1], Perreddy.K[1].
[1]SRM College of Pharmacy, Srm University, Kattankulathur-603203.Tamilnadu.
Email: prasanthz.ramz@gmail.com

Received on 14-05-2011 *Accepted on 27-05-2011*

Abstract

The objective of this project work is to formulate clotrimazole vaginal tablet to treat vaginal infections, vaginal infections are due to changes in the pH. Here clotrimazole is an antifungal agent and glycerol monolaurate is used as a permeation enhancer also acts as anti -microbial agent to get better dispersability and good bioavailability. Along with this lacto bacillus is used to re-establish healthy gut flora and maintains the vaginal pH. The effervescence can be brought by using sodium bicarbonate and adipic acid by that dispersabilty will be increased. Six formulations of clotrimazole vaginal tablets are prepared using different concentrations of glycerol monolaurate (1-12mg) by wet granulation method to figure out the optimized formulation. Formulation F6 containing 12mg of glycerol monolaurate show rapid disintegration when compared to other formulations F1 to F6. The in-vitro dissolution profile of F6 formulation also confirms this by its better dissolution profile of 98 .9% within 60 minutes and was found to have equivalent percentage drug release with that of innovator product. Hence the formulation F6 is found to be promising and can be considered as the best formulation.

Key words: Clotrimazole, glycerol monolaurate, Dispersibility.

Introduction

The wide spread use of tablets has been achieved as a result of this convenience and also the diversabilty of the tablet types. They have been in wide spread use since the latter part of the 19th

and their popularity continues. The term compressed tablet is believed to have been first used by "JOHN WYETH ". During the same period molded tablets were introduced to be used as Hypodermic tablets for injections[1]Tablets are classified according to their route of administration or function .[2]

Vaginal tablets [3]:

These are ovoid shaped tablets that are inserted into the vagina (using special inserter) following insertion , retention and slow dissolution of the tablet occur , releasing the therapeutic agent to provide the local pharmacological effect. (e.g.: for the treatment of bacterial or fungal infection) the vaginal tablets are also used to provide the systemic absorption of the therapeutic agents . These tablets are widely used as antibacterial , antiseptic and astringent to treat vaginal infections. The vaginal route is commonly used for the administration of locally acting drugs such as antimicrobials, labour inducing agents, spermicidal agents, prostaglandins and steroid. The vagina offers a relatively large surface area (approximately 60cm^2) for drug absorption. However, it is much smaller than that offered by the nasal (150 cm3), rectal (200-400 m2), pulmonary (75-700 m2) and intestinal (200 m2) routes. The highly vascular surface of the vaginal mucosa ensures relatively rapid absorption and onset of action, as well as the maintenance of sink conditions. The metabolic activity of the vagina towards peptides and proteins is less than that of the GI tract, making this route an attractive alternative to the oral delivery of these moieties . Reduced first - pass effects after vaginal application of estrogens, progestogens and prostaglandins have all been reported in a number of studies[4].

The choice of excipients in tablet formulations depends on the API, the type of tablet, the desired characteristics, and the manufacturing process used. Several types of tablets are available in the market. These include prompt release, from which the drug dissolves in a very short time (sublingual or buccal tablets), and immediate release and modified release, which includes most of the oral administered tablets that are swallowed . Other types include effervescent, belayed, chewable, multiple compressed and topical tablets , and tablets for solution[5.]

Materials and Instruments

Table: 1 Materials used:

Materials	Suppliers
Clotrimazole I.P	Halcyon labs pvt.ltd
Lactose I.P	Cee pharma ,Mumbai
Glycerol monolaurate	Pcognis, Denmark.
Starch I.P	Akin laboratories, Hyderabad
Polyvinyl pyrollidine k30	Akin laboratories, Hyderabad
Colloidal silica	Degussa
Magnesium state	Akin laboratories, Hyderabad
Methyl paraben	Salicylates & chemical ltd, Mumbai
Carbopol	Akin laboratories, Hyderabad
Lacto bacillus acidophilus	Unisankyo ltd, Hyderabad
Talc	Akin laboratories, Hyderabad
Sodium starch glycolate	Akin laboratories, Hyderabad
Adipic acid	E.merk ltd, Mumbai
Sodium bicarbonate	E.merk ltd, Mumbai

Table-2: Equipments used.

SNo	Equipments	Manufacturer
1	UV-Visible spectrophotometer	Schimadzu, Japan
2	Vernier Calipers	Mitutoyo, Japan
3	Laboratory hot air oven	Kilburn, Mumbai
4	Electronic balance	Oreintal,Switzerland
5	Friabilator	Campbell, Mumbai
6	Rotary compression machine	Cadmach machine, Germany
7	Stability chamber	Cadmach machine, Germany

8	pH meter	Susima Technologies (p) Ltd
9	Planetary mixer	Harrison machine, Calcutta
10	Dissolution apparatus	Electrolab TDT8 dissolution tester USP.
11	Hardness tester	Pfizer hardness tester, serve well instruments and equipments pvt.ltd, Bangalore
12	Glass ware	Borosil
13	Bulk density apparatus	Electrolab, Malaysia
14.	Disintegration test apparatus	Electrolab, Japan
15.	Moisture analysis	Sartorious, Mumbai

Wet granulation method:

Preparation of clotrimazole effervescent vaginal tablet:

1st stage

The method of preparation of the vaginal tablet is by wet granulation method . Weigh 100mg of the drug and add excipients like lactose and dried starch , and then sifiting is done through 60 # for 10 minutes .

2 nd stage :

Prepare 9. 7 gms of poly vinyl pyrolidine solution using water and then prepare starch solution of 33 g ms using 0 . 64gms, 0 . 16gms o f methyl paraben and propyl paraben sodium then add PVPK mixture to the below mixture . Add the paste to the dry mixed powder and mix it for 10 minutes until the damp mass is formed . Pass the mass through the 14 # and dry at a temperature of 50 to 60^0c and finally pass through 20 # to complete drying .

3rd stage :

Then pass all the lubricants through 60 and 30 # one by one and mix to the above mixture . Add dried granules and lubricants and effervescent the blend and mix it for 10 min and compress the tablet at an average wt of 850 mg per tablet .

Table-3: Formulation of Clotrimazole vaginal tablet.

		FORMULATIONS(mg)					
Sno	**Ingredients**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	Clotrimazole I.P	100	100	100	100	100	100
2	Lactobacillus	30	30	30	30	30	30
3	Glycerol monolaurate	1	2	5	8	10	12
4	Lactose	371	370	367	364	362	360
5	Polyvinylpyrollidine k30	9.7	9.7	9.7	9.7	9.7	9.7
6	Starch	33	33	33	33	33	33
7	Carbopol	7	7	7	7	7	7
8	Methyl paraben	0.648	0.648	0.648	0.648	0.648	0.648
9	Propyl paraben sodium	0.10	0.10	0.10	0.10	0.10	0.10
10	Sodium starch glycolate	34	34	34	34	34	34
11	Talc	8	8	8	8	8	8
12	Magnesium stearate	3.2	3.2	3.2	3.2	3.2	3.2
13	Aerosil	1.6	1.6	1.6	1.6	1.6	1.6
14	Adipic acid	56.66	56.66	56.66	56.66	56.66.	56.66
15	Sodium bicarbonate	43.7	43.7	43.7	43.7	43.7	43.7
16	Dried starch	150.392	150.392	150.392	150.392	150.392	150.392
17.	TOTAL	850	850	850	850	850	850

Table no: 4 Raw material analysis of clotrimazole.

S.No	**Analysis Items**	**Specifications**	**Results**
1	Macroscopic Characters	White/pale yellow,crystalline powder	White
2	Solubilty	Freely soluble in chloroform, ethanol, methnol, practically insoluble in water	Soluble in methanol

3	Identification	Confirms to IR.	Confirms to IR
4.	Melting Point	143°C	143◦C
5	pH	4.5 – 7.0	7
6	Heavy metals	10 ppm	8 ppm
7	Loss on drying	Not more than 0.5% per 1.0 gm	0.35%
8	Sulphated ash	Not more than 0.1% per 1.0 gm	0.37%
9	Assay	98.0% to 99.8.%	99.8%

COMPATIBILITY STUDY:

Compatibility studies performed using IR spectro photometer. The spectrums of all formulations are shown in fig 1-6 .

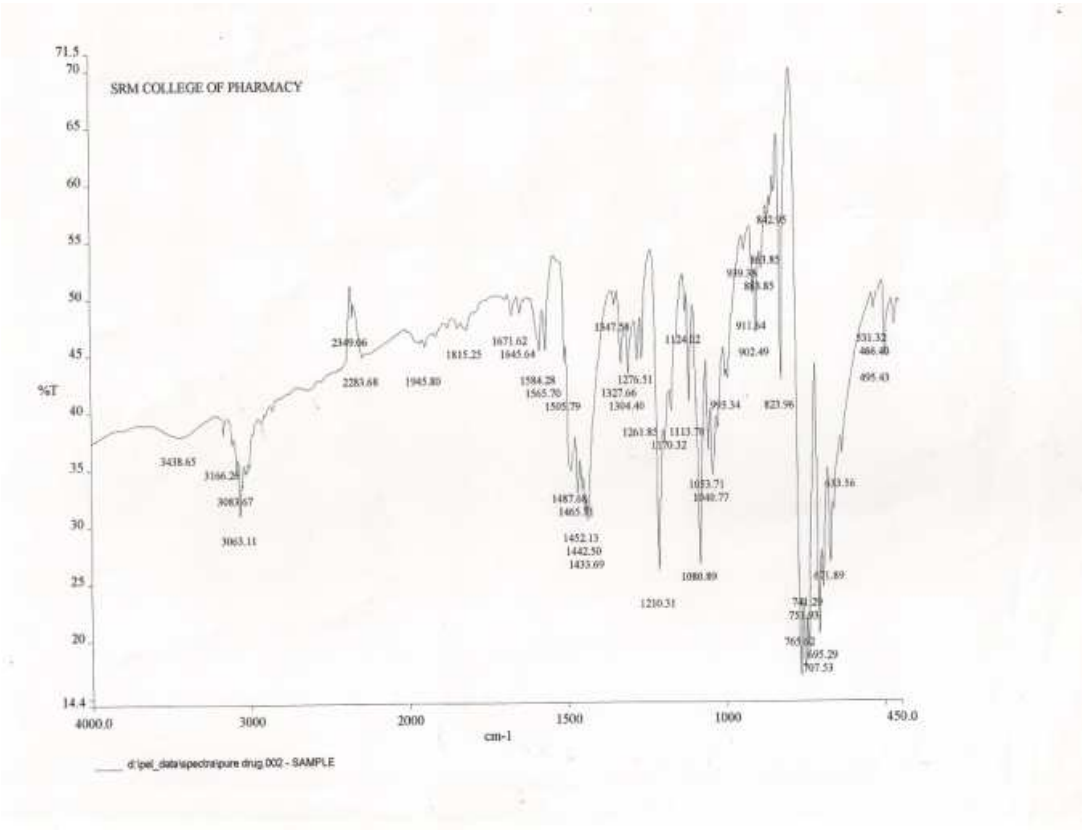


Fig: 1 IR Spectrum of Clotrimazole.

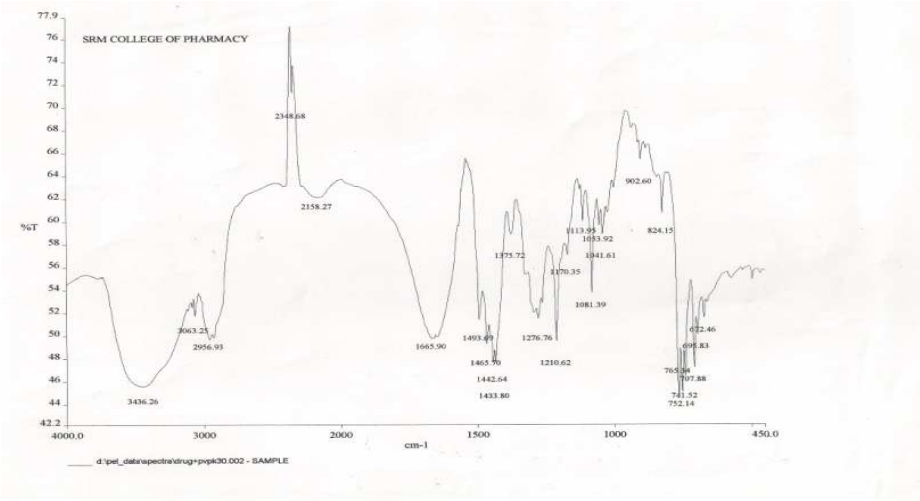


Fig: 2 IR Spectrum of Clotrimazole with PVPK 30

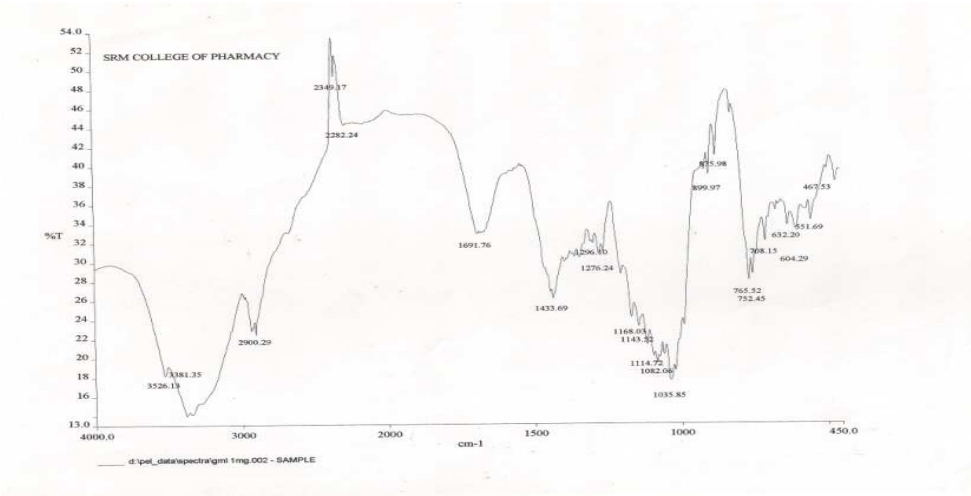


Fig: 3 IR Spectrum of Clotrimazole with Glycerol Monolaurate

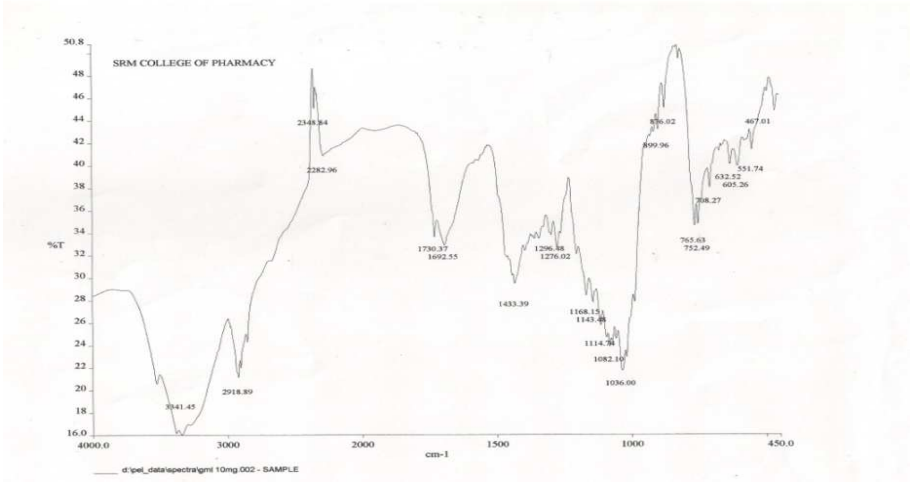


Fig: 4 IR Spectrum of Clotrimazole formulation

Table -5: Assay of Clotrimazole.

SNO	FORMULATION CODE	PERCENTAGE OF DRUG
1	F1	98.1
2	F2	99.7
3	F3	98.7
4	F4	99.7
5	F5	98.9
6	F6	99.8

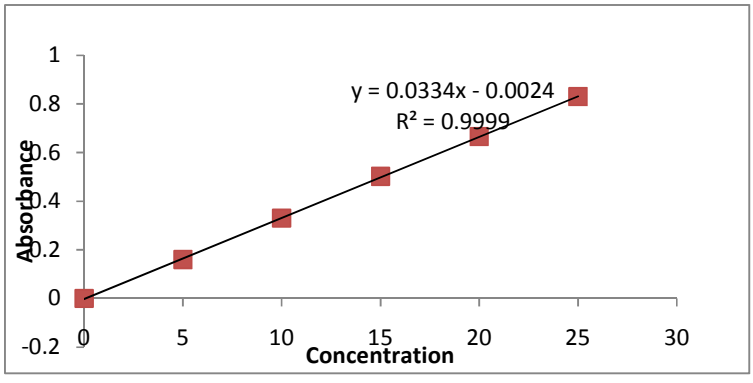
Table No.6: Standard Graph Values of Clotrimazole.

Concentration (µg/ml)	Absorbance
0	0
5	0.160
10	0.330
15	0.502
20	0 .665
25	0.830

Standard graph of clotrimazole:

Standard graph of clotrimazole was plotted by taking absorbance on X -axis and concentration (µg/ml) on Y-axis, the plotted graph is shown in fig no.6.

Fig no-5: Standard calibration graph for clotrimazole



PRE FORMULATION STUDIES:

Table No 7: Bulk density and Tapped density[6, 7]

S.NO	Formulation	Bulk density(gm/cc)	Tapped density(gm/cc)	Compressibility index (%)	Hausner's Ratio	Angle of repose
1	F1	0.625	0.704	12.64	1.12	26º.96´
2	F2	0.611	0.709	14.80	1.16	25º.43´
3	F3	0.574	0.714	19.60	1.24	24º.65´
4	F4	0.588	0.724	18.78	1.23	25º.74´
5	F5	0.602	0.694	13.25	1.15	24º.89´
6	F6	0.614	0.675	9.03	1.09	25º.46´

Table No-8: Moisture Content.

SNO	FORMULATION CODE	PERCENTAGE OF MOISTURE
1	F_1	0.66
2	F_2	0.71
3	F_3	0.82
4	F_4	0.65
5	F_5	0.83
6	F_6	0.76

Table No: 9. Seive Analyses of Clotrimazole Granules.

SNO	SEIVE NO	RESULTS OF ANALYSED GRANULES					
		F1	F2	F3	F4	F5	F6
1	60	18.27	19.2	17.2	18.6	20.2	16.9
2	100	43.85	43.7	39.7	44.1	43.7	43.8
3	120	66.1	65.9	61.2	66	64.6	64.3
4	140	78.7	79.8	75.8	78.6	78.5	78.2

5	200	90.01	89.1	85.43	89.8	89.7	89.8
6	COLLECTOR	99.98	99.0	95.03	99.7	99.6	99.7

Table No.10: Evaluation Parameters for tablet[8]

S.NO	Formulation	Thickness(mm)	Average Hardness (kg/cm^2)	Percentage of weight loss (%)	% Deviation	Disintegration (min)
1.	F1	5.22	5	0.69	1.24 ±0.91	6.2
2	F2	5.24	6	0.24	1.37 ±0.58	5.8
3	F3	5.26	6	0.34	1.42 ±0.24	5.6
4	F4	5.21	7	0.57	1.39± 0.36	5.5
5	F5	5.32	7	0.68	0.94 ±0.56	5.5
6.	F6	5.24	8	0.9	0.93 ± 0.88	5.0

h) In-vitro drug release:

Table No: 11 In - vitro dissolution profile of clotrimazole F1

F1	F2	F3	F4	F5	F6
%CDR	%CDR	%CDR	%CDR	%CDR	%CDR
27	27.54	27.2	27.9	29.16	29.97
32.15	34.44	33.90	34.9	35.80	37.51
40.65	43.36	41.46	42.2	43.11	44.17
49.60	51.79	53.92	55.1	56.21	57.31
55.92	54.5	55.92	57.58	58.95	60.33
60.81	56.5	60.2	61.39	62.78	63.9
71.14	62.49	63.58	64.52	66.19	67.84
80.68	72.1	73.82	74.69	75.54	77.10
83.19	82.84	83.42	84.90	81	87.71
86.52	86.2	87.18	90.96	92.7	92.5
95.07	91.74	92.50	94.85	95.2	97.2
95.07	96.3	97	98.32	96.2	98.9

Table No-12: In- vitro dissolution profile of Innovator.

S.no	Time(Mins)	%CDR	Log % of CDR
1	5	29.8	1.47
2	10	37.9	1.57
3	15	44	1.64
4	20	56.6	1.75
5	25	59.7	1.77
6	30	63.4	1.80
7	35	66.9	1.82
8	40	77.2	1.88
9	45	86.5	1.93
10	50	92.1	1.96
11	55	96.6	1.98
12	60	98.6	1.99

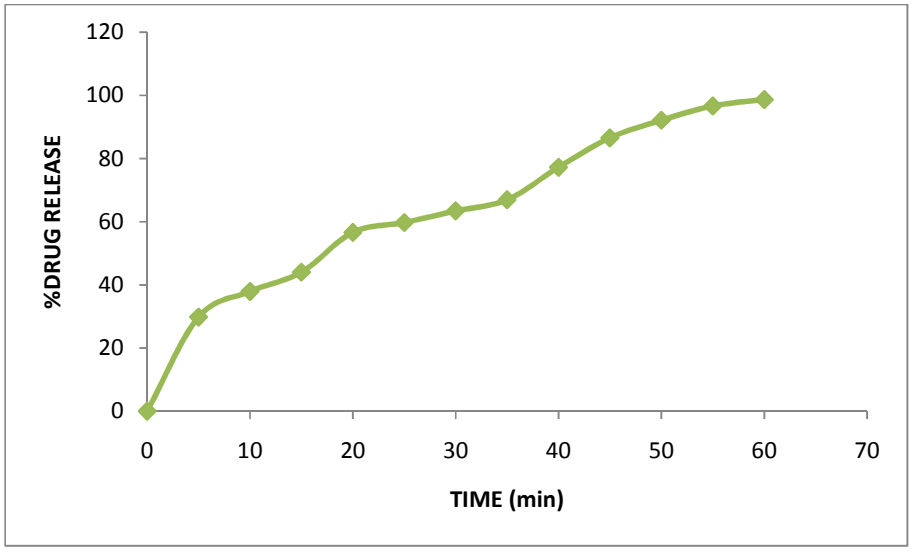


Fig no-6: In - vitro dissolution profile of Innovator

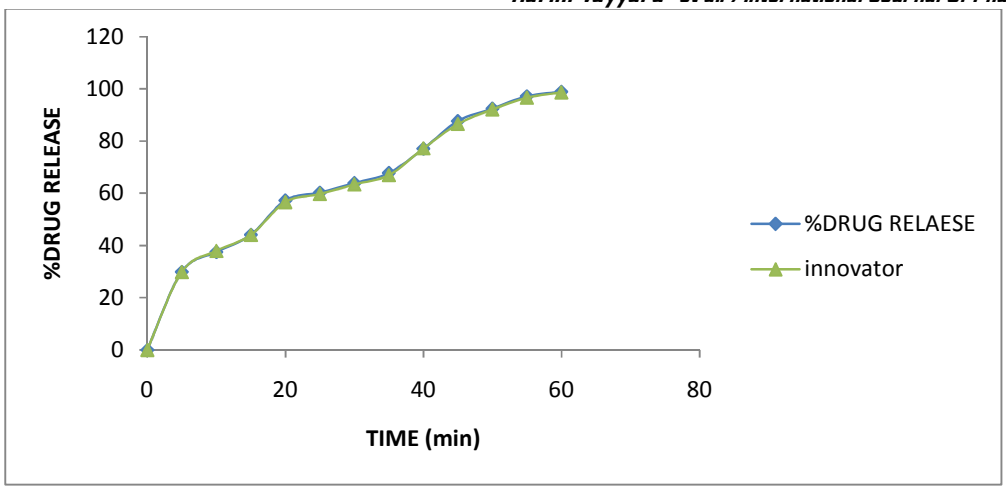


Fig no: 7 In - vitro dissolution profile of formulation (F6) and Innovator.

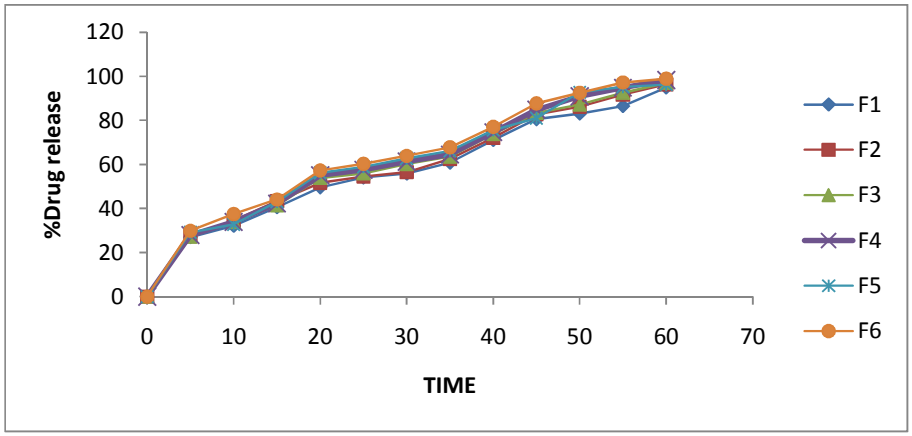


Fig no-8: Comparison graph of F1 , F2 , F3 , F4 , F5 , F6 formulations.

Table No: 13 Stability data:

a) Physical and chemical parameters of clotrimazole vaginal tablets of F6 after one month at 40 ° c / 75 % RH

Parameter	Initial	After 1 month
Description	White to white oval shaped tablets	White to white oval shaped tablets
Hardness(kp)	8	8
Thickness(mm)	5.24	5.23
Friability (%)	0.9	0.87
Assay	99.8	99.3

Table No: 14

b) Physical and chemical parameters of clotrimazole vaginal tablets of F6 after one month at 25 ° c / 60 % RH

Parameter	Initial	After 1 month
Description	White to white oval shaped tablets	White to white oval shaped tablets
Hardness(kp)	8	7.8
Thickness(mm)	5.24	5.21
Friability (%)	0.9	0.9
Assay	99.8	98.9

Table No: 15

Dissolution profiles of clotrimazole vaginal tablet of F6 after one month at 40 ° c/ 75 % RH

Time interval (min)	In - vitro drug release (%)	
	Initial	After 1 month
0	0	0
5	29.9	29.2
10	37.5	36.9
15	44.1	43.8
20	57.3	56.9
25	60.3	59.7
30	63.9	63.1
35	67.8	67.2
40	77.1	76.8
45	87.7	87.0
50	92.5	92.1
55	97.2	96.7

60	98.9	98.1

Table No: 16

Dissolution profiles of clotrimazole vaginal tablet of F6 after one month at 25 ° c / 60 % RH

Time interval (min)	In-vitro drug release (%)	
	Initial	After 1 month
0	0	0
5	29.9	29.1
10	37.5	36.3
15	44.1	43.1
20	57.3	56.6
25	60.3	59.5
30	63.9	62.8
35	67.8	66.6
40	77.1	76.3
45	87.7	86.8
50	92.5	91.6
55	97.2	96.9
60	98.9	97.7

Discussion

Vaginal tablets of clotrimazole were formulated by wet granulation method using glycerol monolaurate as polymer and were summarized in table 3.

Compatibility studies were performed using IR Spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied . The characteristics absorption peaks of clotrimazole were obtained at wave number 2349.06, 2283 . 68, 1945.80, 1815.25, 1671. 62 and 1645.64.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum . This is indicates that the drug is compatible with formulation components .

The blends were analyzed for the parameters such as bulk density , tapped density , compressibility index , hausners ratio , angle of repose and sieve analysis .

Bulk density and tapped density values range between 0 . 574 – 0. 625, 0 . 675 – 0. 709 are tabulated in table no 7 and the values are found to be within limits .

Compressibility index has been proposed as an indirect measure of bulk density , size , shape , surface area and cohesiveness of materials .

Compressibility index values ranges between 12.64-9.03 for F1 - F6 formulation and the values are formulated in Table No: 7.

Hausner's ratio (the quotient of bulk density and TD) express the relative mechanical compression of granules . With the help of HR attempts can be made at predicting both extents of compression and flow problems .

Hausners ratio values ranges between 1.12 -1. 09 were summarized in Table No : 7

Moisture content for all clotrimazole granules were found from F1 to F6 formulations and the values ranges from 0.66-0.76 and they were summarized in Table no : 8

Sieve analysis is to determine the size of the clotrimazole particles with series of standard sieves stacked one above the other . Seive analysis values for F1to F6 range from 16. 9, 43.8, 64.3 , 78.2 , 89.8 , and 99.7 and were tabulated in Table No : 9

Visually examined tablets in each formulation showed oval , uncoated tablets on both sides .

Tablets mean thicknesses was almost uniform in all formulations and are found to be in the range of 5 .22 to 5.24 mm. The values are tabulated in table no.10

Hardness of each formulation was analyzed. The formulations F1 to F6 found to have good hardness so they were taken for further studies to measure hardness of tablets of each batch range between 5 to 8 kg /cm^3 the values are tabulated in table no 10.

Friability values are found to be less than 1 % in all cases and considered to be satisfactory and the values 0 .69 to 0.9 are summarized in the table 10

The total weight of each formulation was maintained constant however the weight variation of the tablet was within the limits of 5 % and the values were summarized in table 10 .

The prepared tablets were checked for assay as per USP specifications and all the formulations passed the test and the percentage of active ingredient ranges from 98 to 99 . 8 %.

However all the tablets passed the pharmacoepial specifications for the disintegration of uncoated tablet within 15min and the values 6.2, 5.8, 5.6, 5.5, 5.5 and 5 were summarized in table no. 10. In case of tablets prepared with different concentrations of glycerol monolaurate it was observed that the formulation containing 12mg concentration of glycerol monolaurate (F6) shows rapid disintegration of 5.5 mts when compared with other formulations .

In - vitro dissolution studies of formulations F1 - F6 were carried out in 0.5 w / v sodium lauryl sulphate buffer for 60 mins and percentage of drug release values range from 95.7 to 98.9 % and were summarized below from table no 11 . And the innovator were summarized in table no 12 . It was found that above formulations meet the standard limits (85 % drug release in 60 mins)

Among all the formulations , the formulation F6 containing 12mg Glycerol monolaurate shows faster disintegration and better dissolution profile with the percentage drug release of 98.9%

Stability studies were performed for about 1 month in 40 ° c / 75 % RH and 25 ° c / 60 % RH for the best formulation (F6) and compared the physical and chemical parameters with that of initial and final conditions .

And the results are summarized in from Table No : 13 to16 .

Summary & Conclusion

Clotrimazole tablets were formulated by using (all ingredients) glycerol monolaurate as permeation enhancer in combination with lactobacillus in maintaining vaginal pH

The compatibility studies were carried out by using IR spectrophotometer and the drug was found to be compatible with all the excipient used in the different formulations .

The granules shows good flow property from the preformulation studies and has been suitably compressed into tablets and were analysed for the parameters such as average weight , friability , hardness , thickness , weight variation , moisture content , bio adhesion , insoluble content , assay , disintegration time , in - vitro dissolution and stability studies . The results shows all the parameters are within the limits .

Formulation F6 containing 12mg of glycerol monolaurate show rapid disintegration when compared to other formulations F1 to F6 .

The in - vitro dissolution profile of F6 formulation also confirms this by its better dissolution profile of 98 . 9 % within 60 minutes and was found to have equivalent percentage drug release with that of innovator product . Hence the formulation F6 is found to be promising and can be considered as the best formulation and further studies can be carried out with this .

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Corresponding Author:
Prasanth sai.R.V*,
Email: *prasanthz.ramz@gmail.com*