buffer pH 6.8 and SVF pH 4.2. The finding indicate that the presence of IPEC along with chitosan and carbopol 971P in F9 formulation exhibit uniform pH independent swelling degree.

3.7 Mucoadhesive study[8]

In vitro Mucoadhesive testing for dosage form was evaluated by detachment force measurement.

Mucoadhesive strength of formulation F1-F10 are summarized in table 13 and represented in figure 21. Formulation F9 and F10 containing IPEC along with chitosan and carbopol971P exhibited highest mucoadhesive strength which may be due to presence of free carboxylic and amine group which are available to form bond with mucous layer.

3.8 *In- vitro* dissolution studies[9]

The dissolution were carried out in USP type II dissolution apparatus using phosphate buffer pH 6.8 and simulate vaginal fluid pH 4.2 as dissolution medium respectively. All the formulation from F3-F10 were tested for their release pattern for the period of 8 h and result obtained are summarized in table 16 and table 14 respectively.

F8 formulation containing the higher concentration of carbopol 971P was able to retard the drug release till 8h and also was able to oppose the disintegration action of chitosan due to strong gel network around the layer. Last two formulation (F9, F10) containing chitosan, carbopol 971P along with IPEC of chitosan and carbopol971P possess the gradual drug release pattern, above 98% drug release was observed till the end of 8h. Optimized formulation F9 was able to release 98.84 and 98.74% of miconazole nitrate in phosphate buffer pH 6.8 and SVF pH 4.2 at the end of 8h and thus able to give pH independent drug release.

3.9 *In-vitro* Diffusion Studies[10]

The percentage cumulative drug diffusion studies for optimized formulation F9 was done in Franz- diffusion cell using sheep buccal mucosa as the model mucous membrane and using (i.e. phosphate buffer pH 6.8, SVF pH 4.2) as the diffusion medium. It was evident from the studies that 96.46 % and 97.95 % of drug was diffused at the end of 8 h when phosphate buffer pH 6.8 and SVF ph 4.2 was used as diffusion medium respectively. This is because of its adhesive properties, good release and diffusion behavior F9 was selected for the stability studies.

Diffusion profile of F9 formulation were given in table 18, table 19 and figure 31, figure 32 respectively.

3.10 *In-vivo* X-ray studies[11]

The mucoadhesion and retention property was evaluated in albino female rabbit and the X-ray photographic images were taken. Optimized formulation F-9, developed by using barium sulphate (replacing 50mg of miconazole nitrate) and was administered to rabbit. The duration of tablet in rabbit buccal and vaginal mucosa was monitored by radiograms. It was evident from the pictures that the tablet showed swelling properties and remained intact and adhered to buccal and vaginal mucosa for 8h.

3.11 Stability studies[12]

Stability studies were carried out for the most satisfactory formulation F9, at 30±2ºC, 65±55%RH for two months. At the time interval of 30days and 60 days, sample was evaluated. These was no major change in the various physiochemical like hardness, drug content and in-vitro drug dissolution studies at various sampling points. Thus there was no significant difference between the initial values and the result obtained during stability studies, thus indicating stability of prepared formulation.

3.12 Preformulation study

Table 2: Solubility of Miconazole nitrate

Solvents	Solubility
Methanol	Freely soluble
Ethanol and Chloroform	Slightly soluble
Water and Ether	Very slightly soluble

3.13Melting point Determination

The melting point of miconazole nitrate was determined by using Chemline CL-725 (melting point apparatus) and melting point was found to be in range of 177-182°C.

Differential scanning calorimetry (DSC) studies

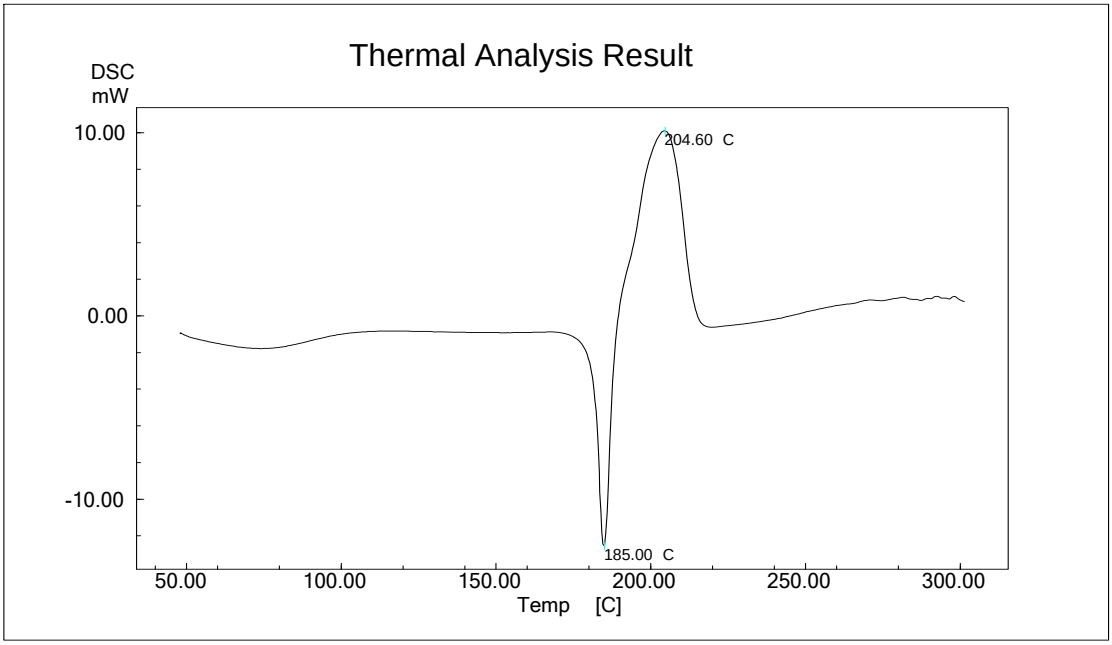

Figure 1: DSC Thermogram of Miconazole nitrate

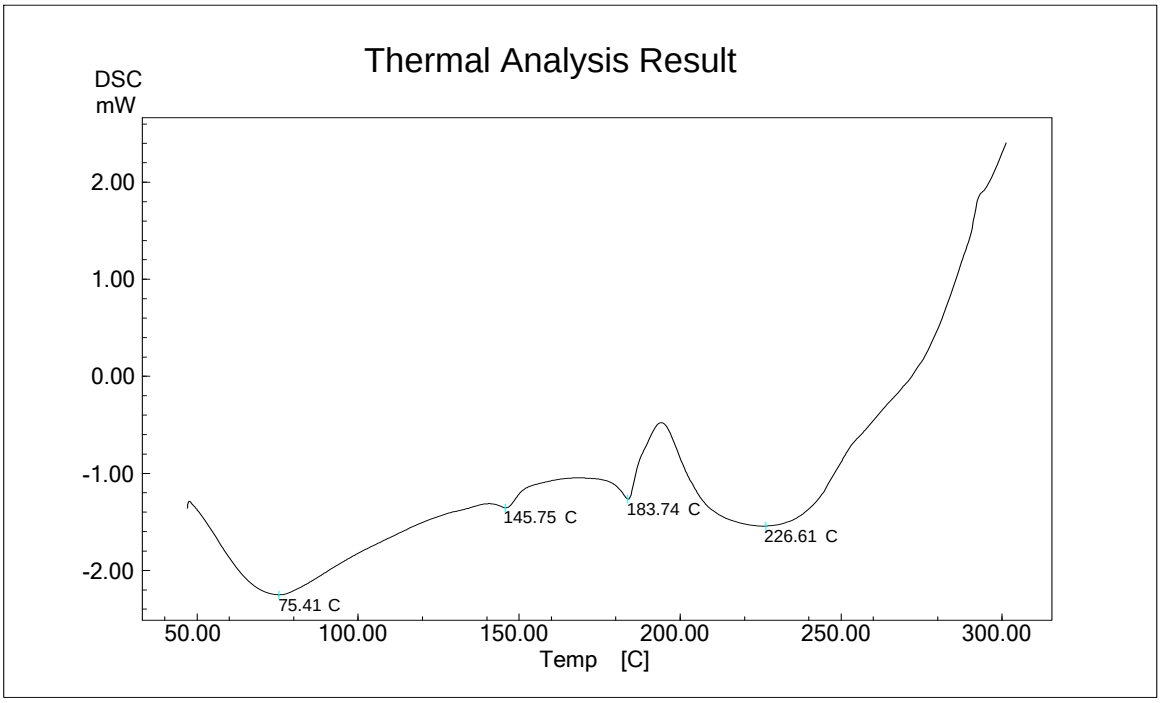

Figure 2: DSC Thermogram of Miconazole nitrate + Polymer

3.14 IR -SPECTROSCOPY

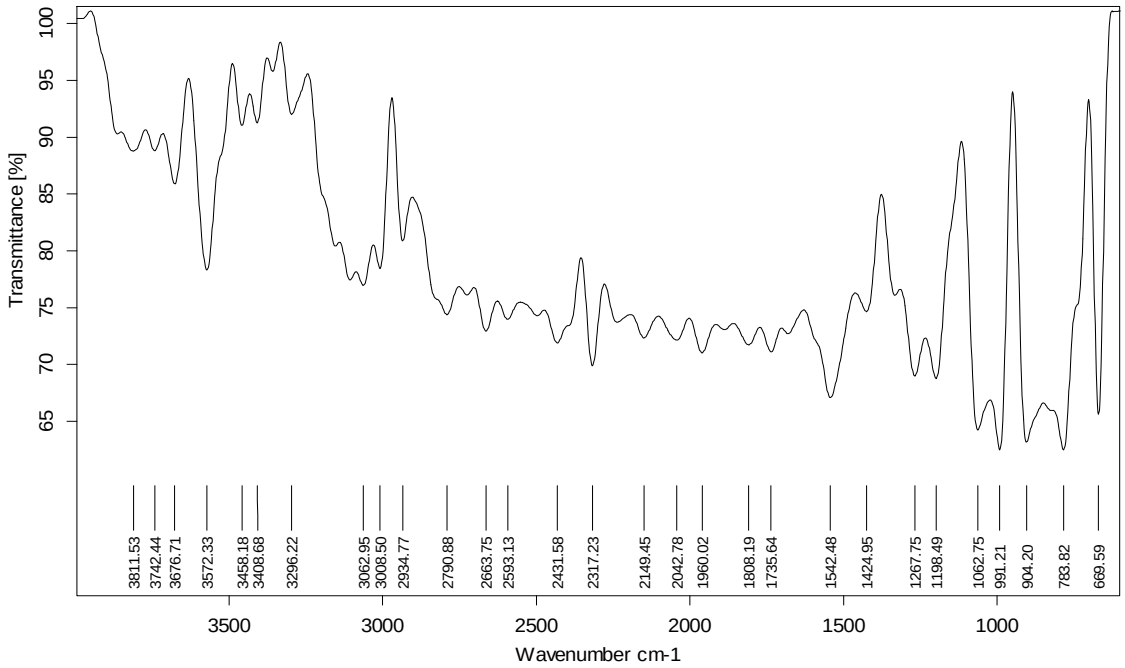

Figure 3: FTIR spectra of miconazole nitrate

Table 3: FTIR interpretation of miconazole nitrate

S.NO	Functional group	Wave number cm^{-1}
1	CH=CH	3062
2	C-H	2934
3	C-O-C	1267
4	C=N	1424
5	C-Cl	745

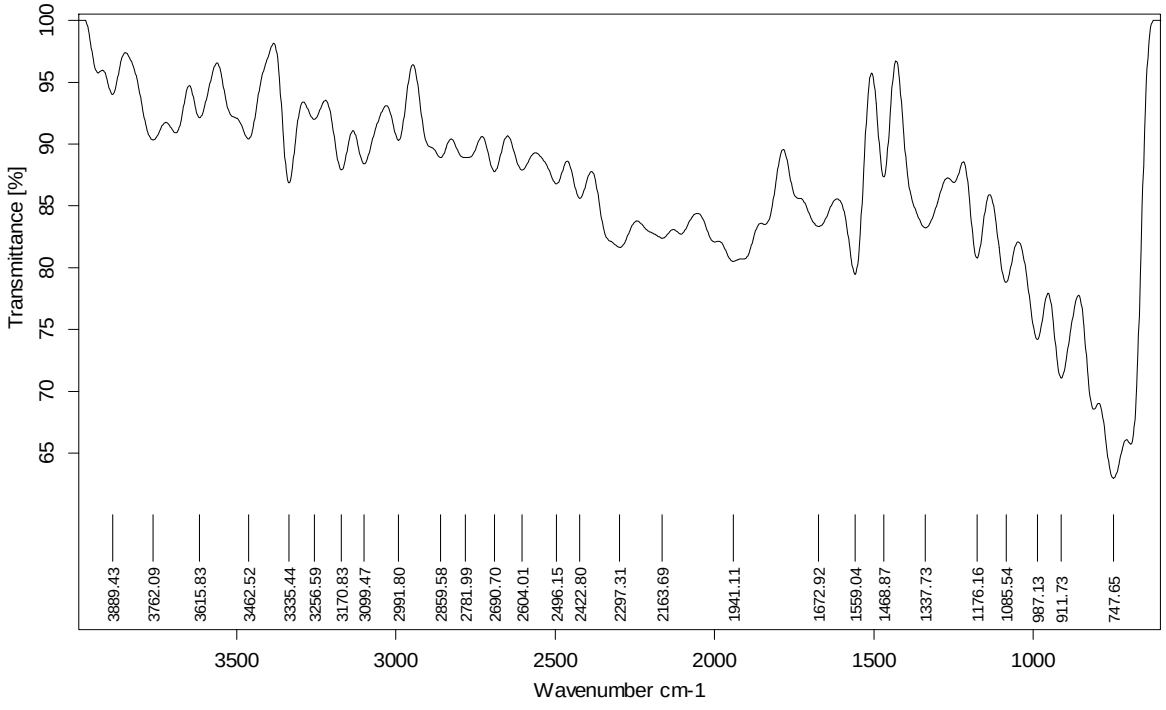

Figure 4: FTIR spectra of MN+ carbopol 971P

Table 4: FTIR interpretation of MN + carbopol 971P

S.NO	Functional group	Wavenumber (cm^{-1})
1	CH=CH	3099
2	C-H	2991
3	C-O-C	1176
4	C=N	1468
5	C-Cl	747

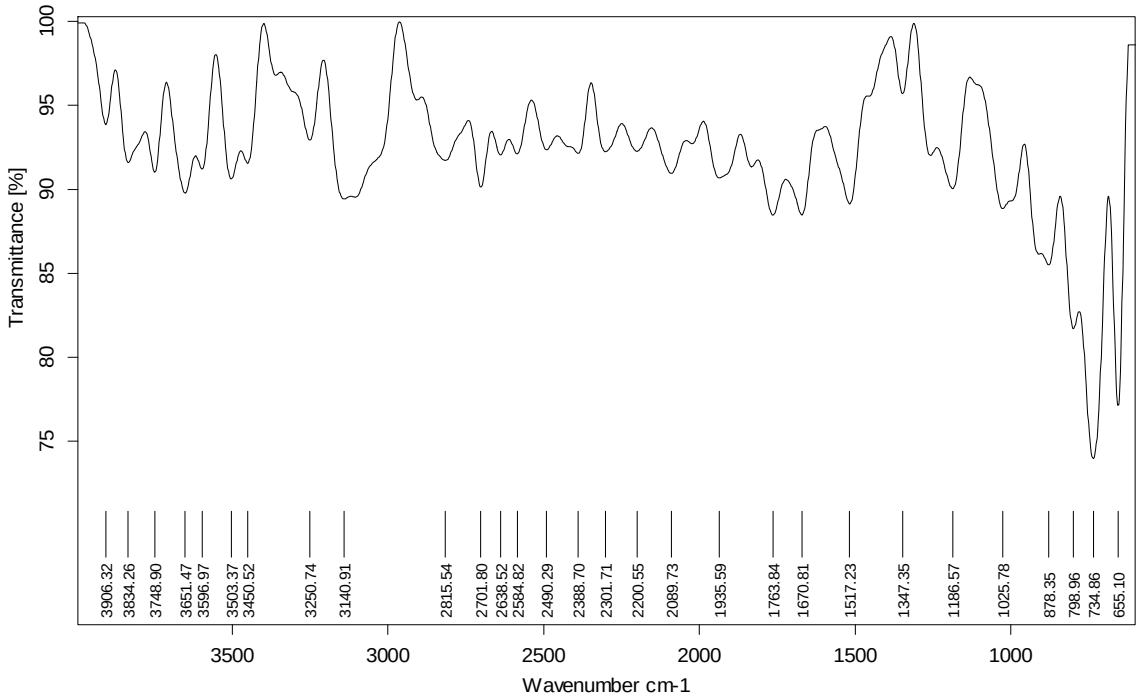

Figure 5: FTIR spectra of MN+ Polycarbophil

Table 5: FTIR interpretation of MN+ Polycarbophil

S.NO	Functional group	Wavenumber(cm-1)
1	CH=CH	3067
2	C-H	2927
3	C-O-C	1255
4	C=N	1474
5	C-Cl	745

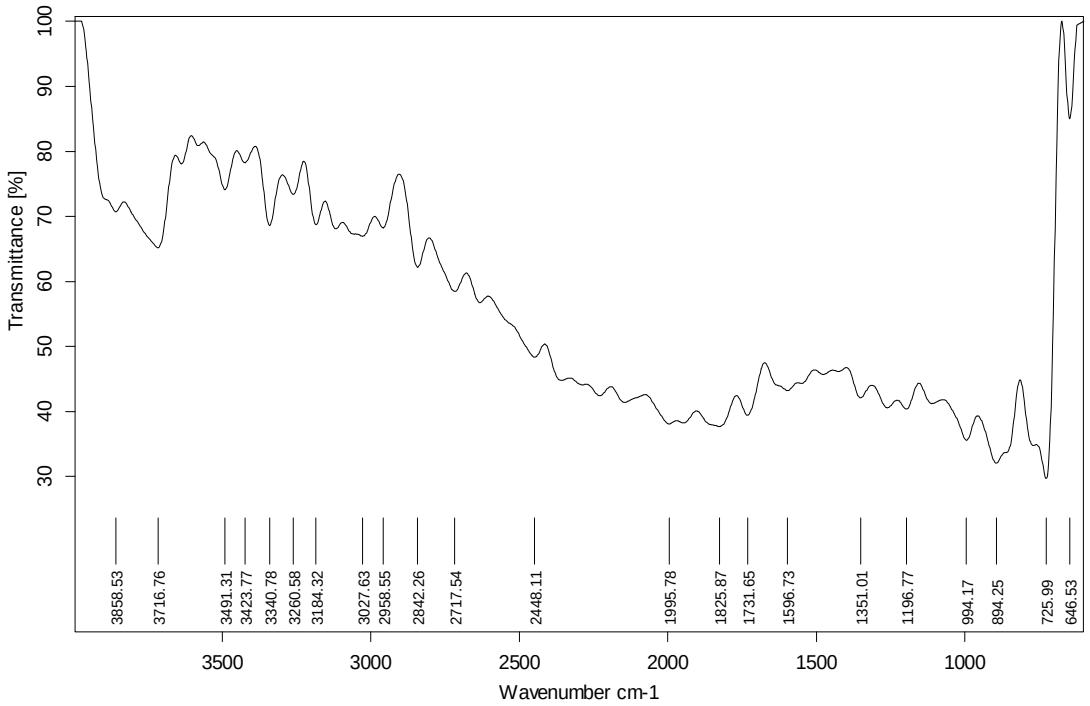

Figure 6: FTIR spectra of MN + Chitosan-Carbopol971P IPEC

Table 6: FTIR interpretation of MN+ Chitosan-carbopol971P IPEC

S.NO	Functional group	Wavenumber (cm^{-1})
1	O-H	3491
2	N-H	3340
3	C=O	1731
4	C-O	1196
5	C-H	2958

Characterization of IPEC by FTIR

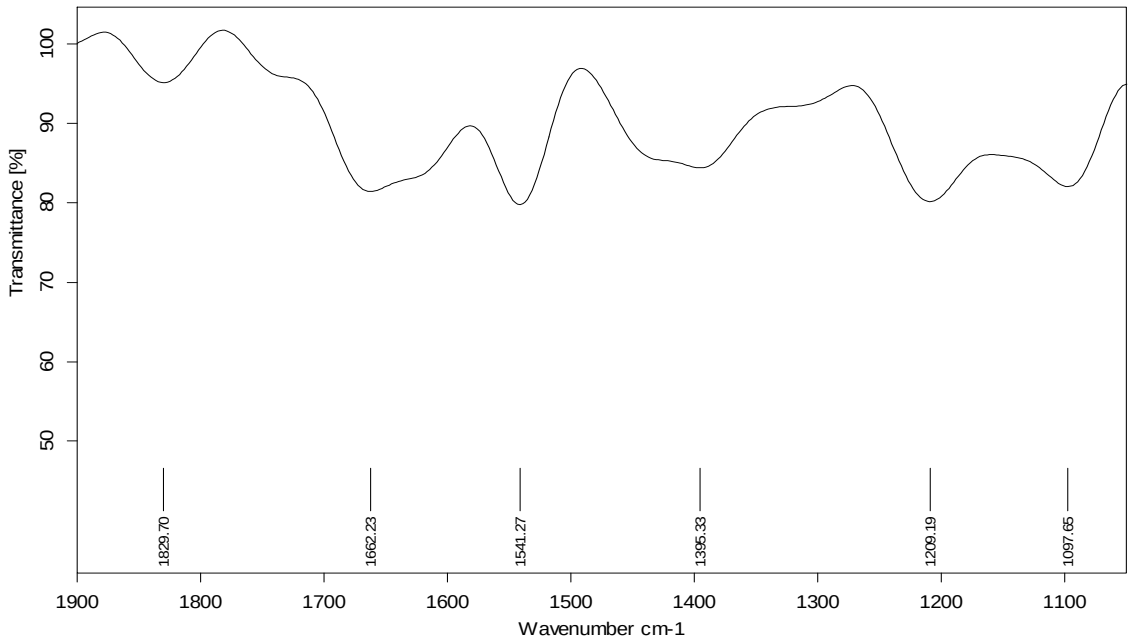

Figure 7: FTIR spectra of chitosan in Wavenumber 2000-1000 cm^{-1}

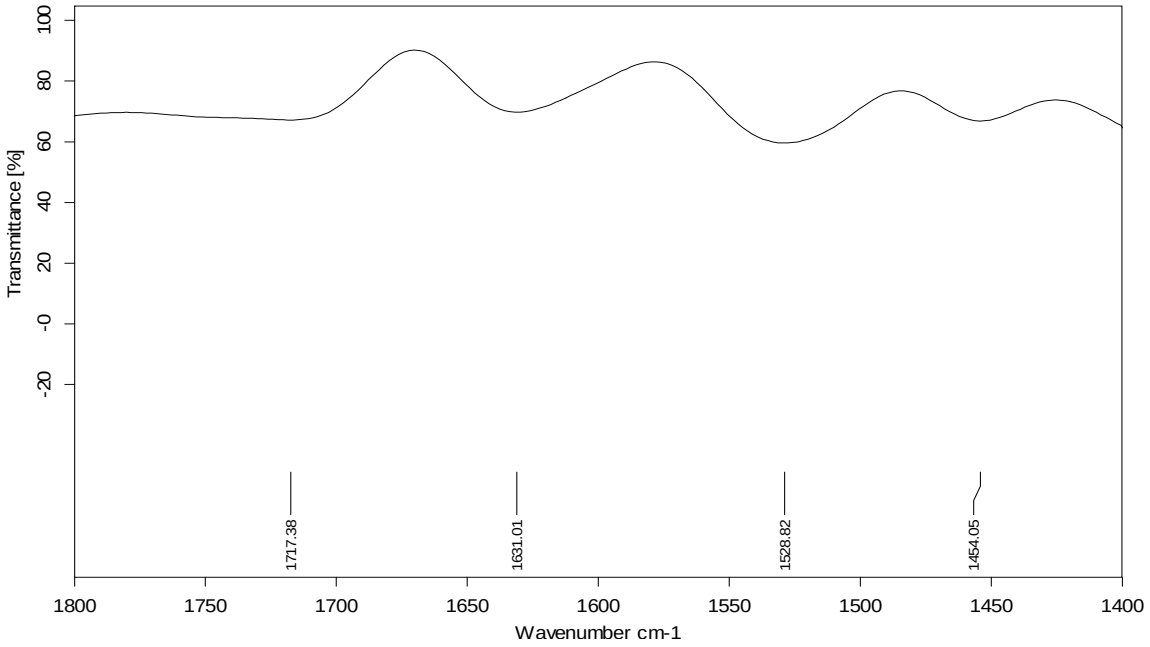

Figure 8: FTIR spectra of chitosan in Wavenumber 1800 – 1400^{-1}cm

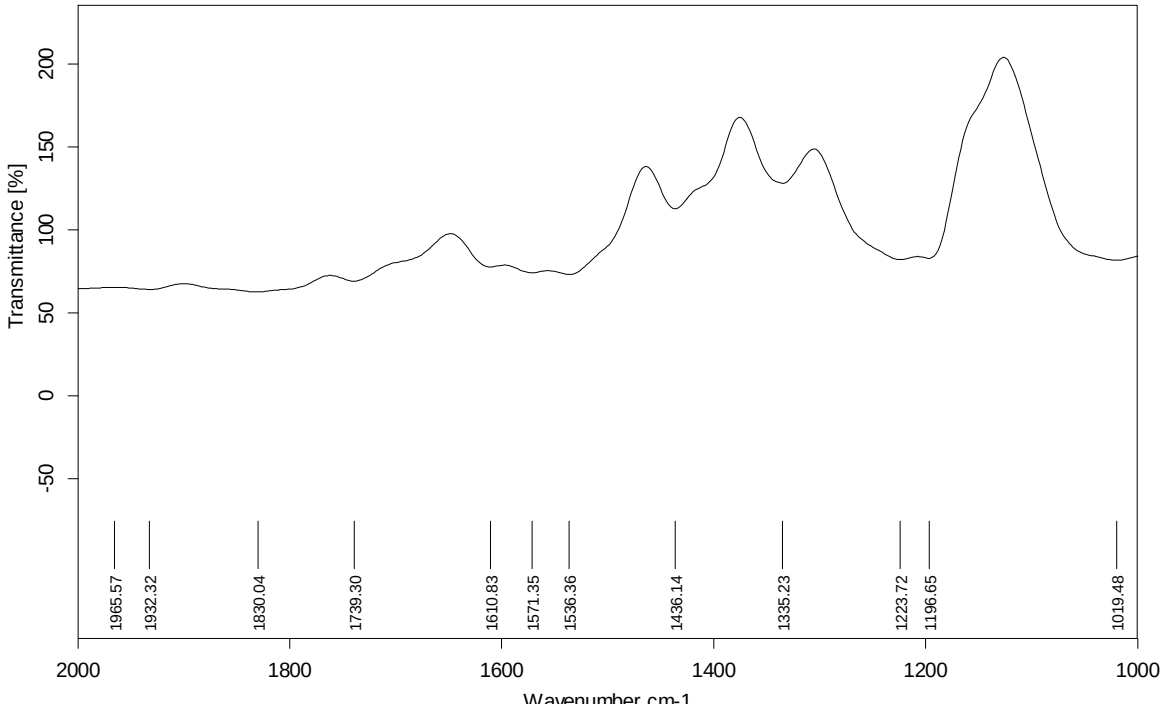

Figure 9: FTIR spectra of carbopol971P in Wavenumber 2000- 1000 cm^{-1}

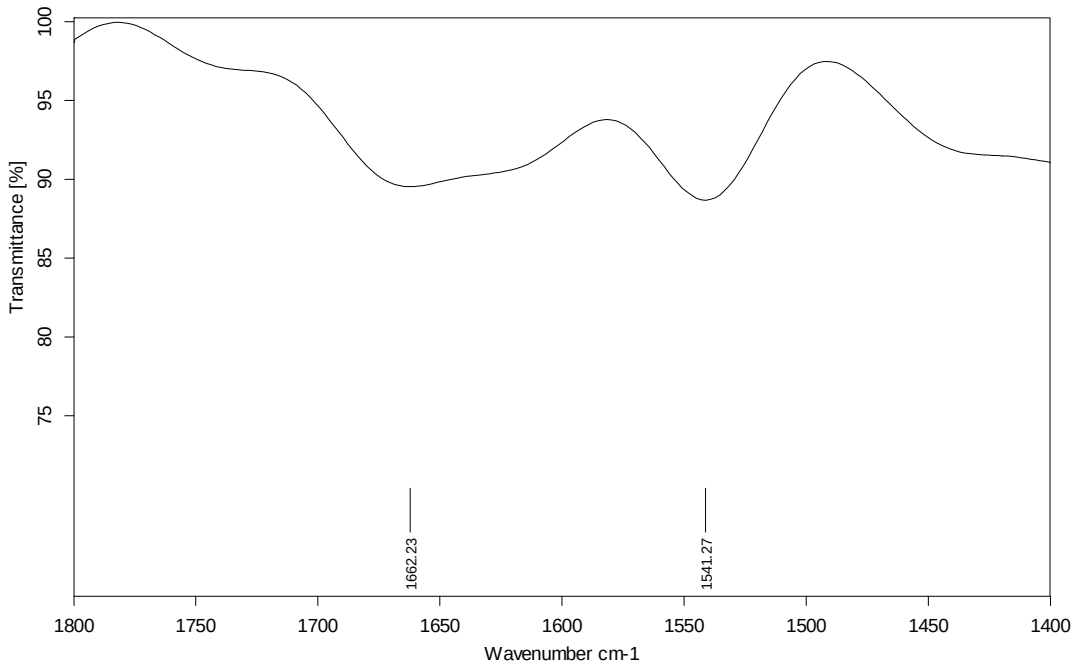

Figure 10: FTIR spectra of carbopol971P in Wavenumber 1800-1400 cm^{-1}

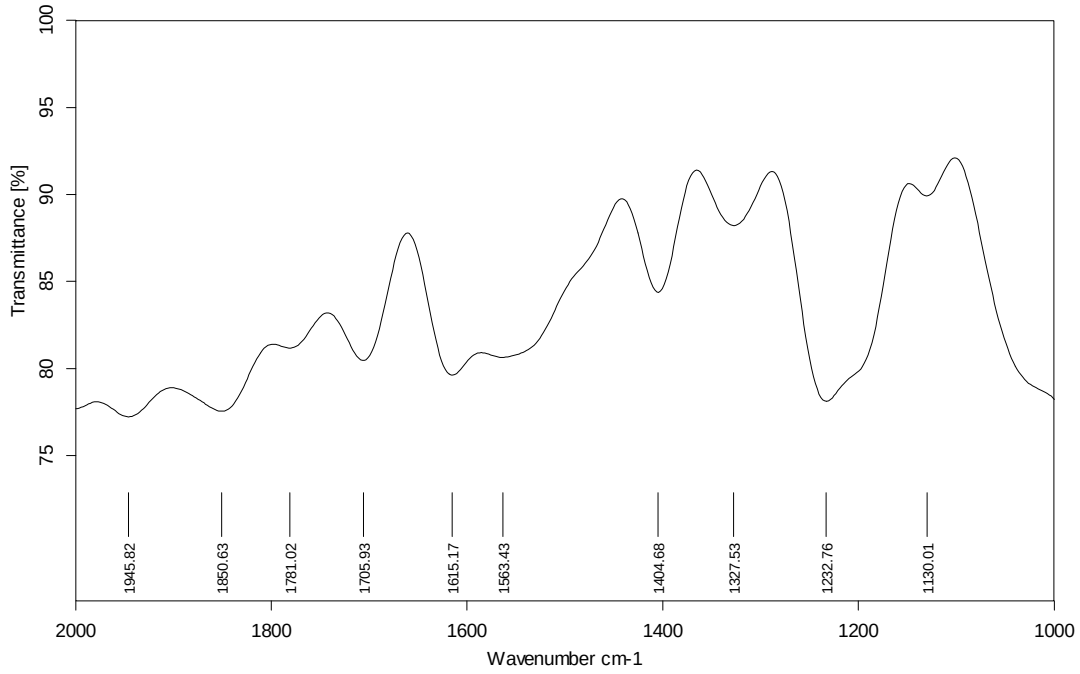

Figure 11: FTIR spectra of IPEC in Wavenumber 2000-1000 cm^{-1}

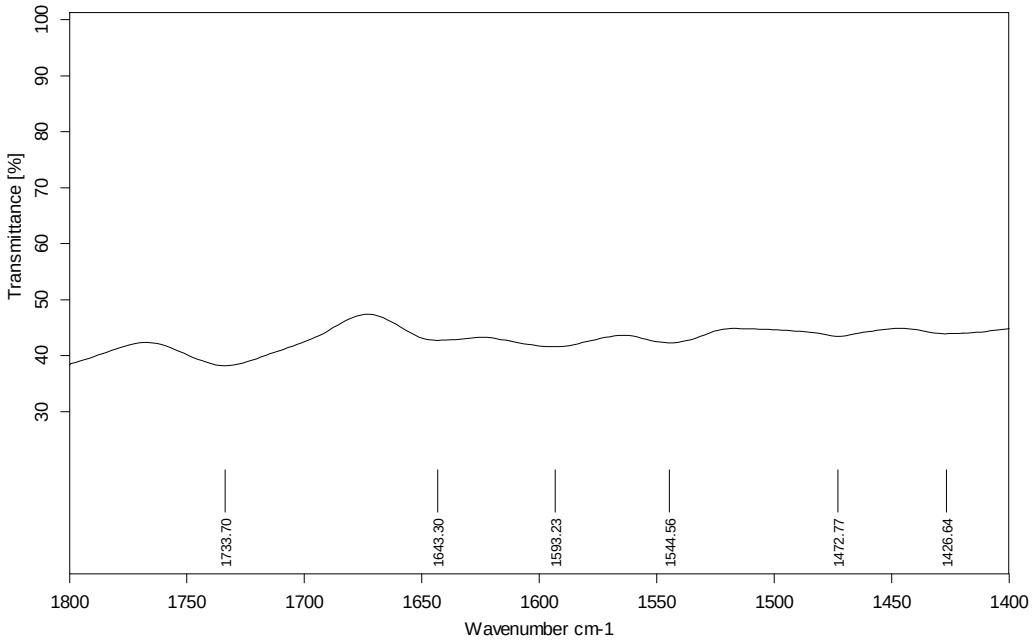

Figure 12: FTIR spectra of IPEC in Wavenumber 1800-1400cm^{-1}

Standard curve of miconazole nitrate

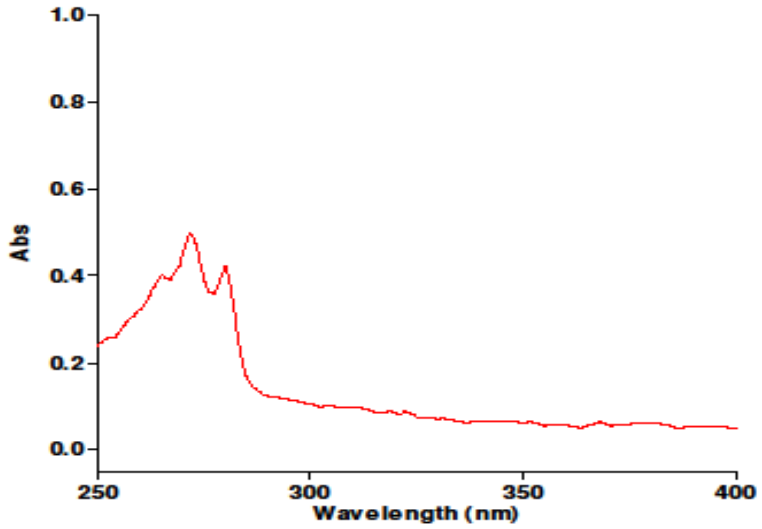

Figure 13: Absorption maxima of miconazole nitrate in phosphate buffer pH 6.8.

Table 7: Standard calibration data for miconazole nitrate

Sl. NO.	Concentration(µg/ml)	Absorbance *
1	10	0.139±0.018
2	20	0.317±0.015
3	30	0.436±0.023
4	40	0.567±0.011
5	50	0.677±0.022

* All values are mean of three readings ± S.D

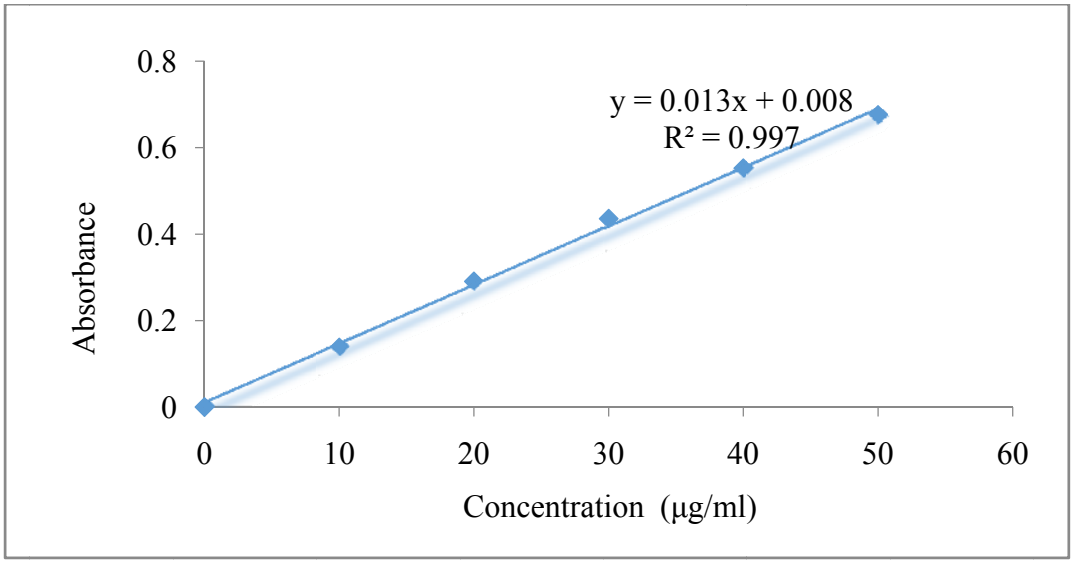

Figure 14: Calibration curve of miconazole nitrate in phosphate buffer pH 6.8

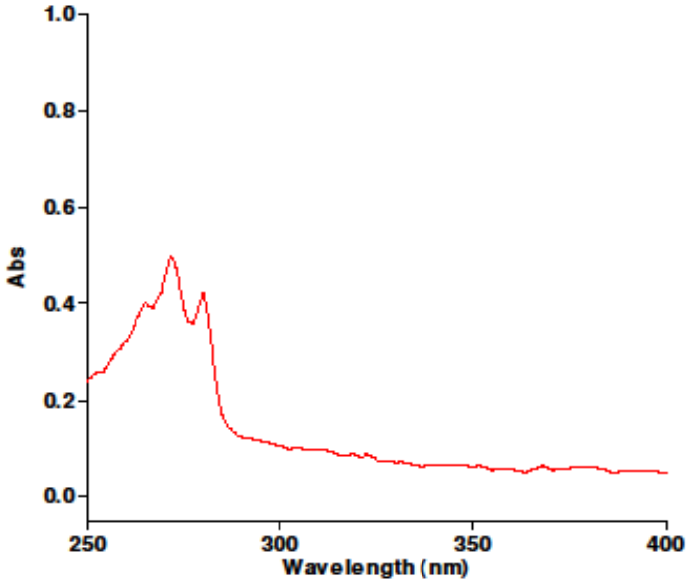

Figure 15: Absorption maxima of miconazole nitrate in SVF pH 4.2.

Table 8: Calibration curve data of miconazole nitrate in SVF pH4.2.

S.NO	Concentration(µg/ml)	Absorbance *
1	25	0.113±0.013
2	50	0.227±0.015
3	75	0.322±0.012
4	100	0.446±0.016
5	125	0.549±0.018

* All values are mean of three readings ± S.D

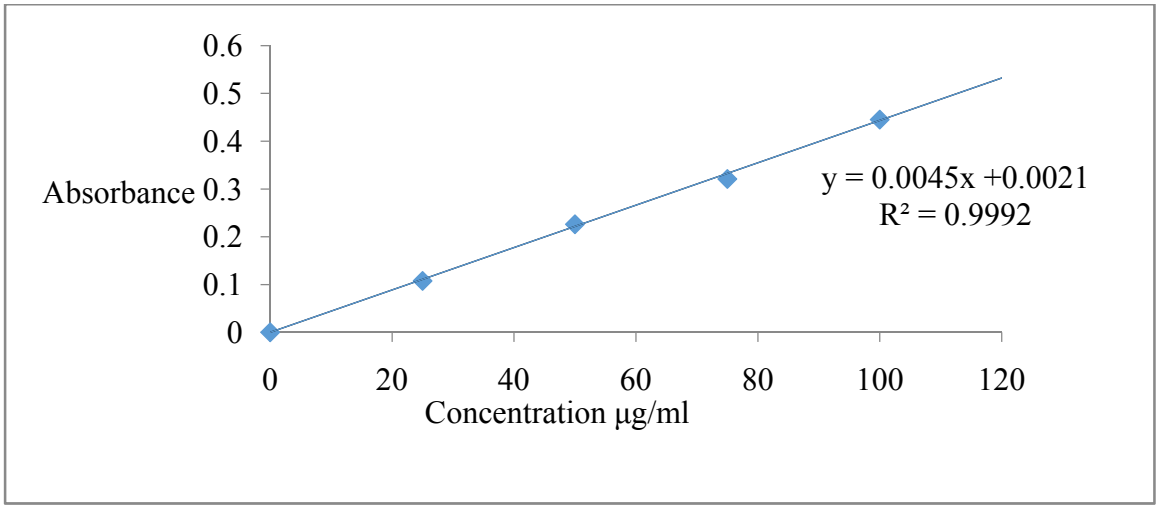

Figure 16: Calibration curve of miconazole nitrate in SVF pH 4.2.

3.14 Precompressional parameters

Micromeretic properties of F1-F10

Table 9: Preformulation studies of F1-F10

Formulation	Angle of repose (°) Mean ± SD	Bulk density (gm/ml) Mean ± SD	Tapped density(gm/ml) Mean ± SD	Carr's index (%) Mean± SD	Hausner's ratio Mean± SD
F1	33.63±0.80	0.351±0.003	0.398±0.01	11.80±0.63	1.13±0.01
F2	31.32±1.07	0.354±0.001	0.388±0.02	8.76±0.47	0.78±0.05
F3	32.06±0.25	0.356±0.003	0.392±0.06	9.18±0.48	1.10±0.09
F4	33.21±0.35	0.328±0.001	0.369±0.05	11.11±0.83	1.09±0.05
F5	34.34±0.51	0.368±0.005	0.398±0.02	7.53±0.68	1.08±0.02
F6	29.83±0.27	0.343±0.006	0.391±0.04	12.27±0.42	1.13±0.02
F7	30.19±0.15	0.328±0.004	0.372±0.01	11.82±0.56	1.13±0.02
F8	29.78±0.15	0.353±0.005	0.385±0.02	8.31±0.66	1.09±0.02
F9	27.37±0.16	0.319±0.005	0.466±0.01	9.33±0.56	1.13±0.02
F10	29.21±0.35	0.327±0.001	0.508±0.01	12.2±0.45	1.12±0.02

3.15 Post-compression evaluation data

Table 10: Post compression evaluation data of F1-F10

Formulation Code	Weight(mg)* n= 20	Thickness(mm)* n= 10	Hardness(kg/cm)^{2*} n= 10	Friability n= 20	% Drug content*
F1	149.2±0.53	4.2±0.03	5.5±0.22	0.67	93.6±0.12
F2	150.0±0.78	4.3±0.02	5.8±0.42	0.54	92.4 ±0.25
F3	149.5±0.55	4.1±0.01	5.4±0.34	0.62	95.9 ±0.18
F4	149.1±0.57	4.3±0.05	5.3±0.23	0.54	96.4±0.15
F5	149.3±0.42	4.0±0.04	5.2±0.32	0.51	97.2±0.12
F6	150.2±0.86	4.1±0.02	6.0±0.31	0.15	97.8±0.15
F7	149.2±0.26	4.3±0.02	6.3±0.52	0.11	93.7±0.14
F8	149.6±0.42	4.2±0.03	6.2±0.61	0.15	94.3±0.12
F9	150.0±0.82	4.0±0.01	6.5±0.53	0.11	98.6 ±0.11
F10	149.5±0.55	4.1±0.02	5.3±2	0.12	98.4 ±0.15

* All values are mean of three readings ± SD

3.16 Swelling studies Data

All values are mean of three readings ± SD

Table 11: Swelling index data of F1-F10 in phosphate buffer pH 6.8.

Formulation	1h	2hr	3h	4h	5h	6h	7h	8h
F1	20±0.35	35±0.54	70±0.65					
F2	19±0.42	41±0.49	76±0.55					
F3	180±0.43	232±0.57	341±0.33	411±0.58	453±0.37	485±0.53	518±0.63	523±0.35
F4	204±0.34	277±0.56	389±0.65	449±0.57	498±0.33	532±0.24	543±0.76	551±0.35
F5	372±0.57	421±0.33	453±0.36	523±0.25	571±0.18			
F6	312±0.45	394±0.26	435±0.27	486±0.79	532±0.27	527±0.67	593±0.78	611±0.34
F7	94±0.67	102±0.23	125±0.65	177±0.67	234±0.78	297±0.57	310±0.67	352±0.67
F8	99±0.35	142±0.56	162±0.78	213±0.38	289±0.67	334±0.28	364±0.34	382±0.73
F9	96±0.76	201±0.47	372±0.34	487±0.79	638±0.45	723±0.87	863±0.56	946±0.47
F10	78±0.65	188±0.43	275±0.84	398±0.37	538±0.37	699±0.37	738±0.37	814±0.25

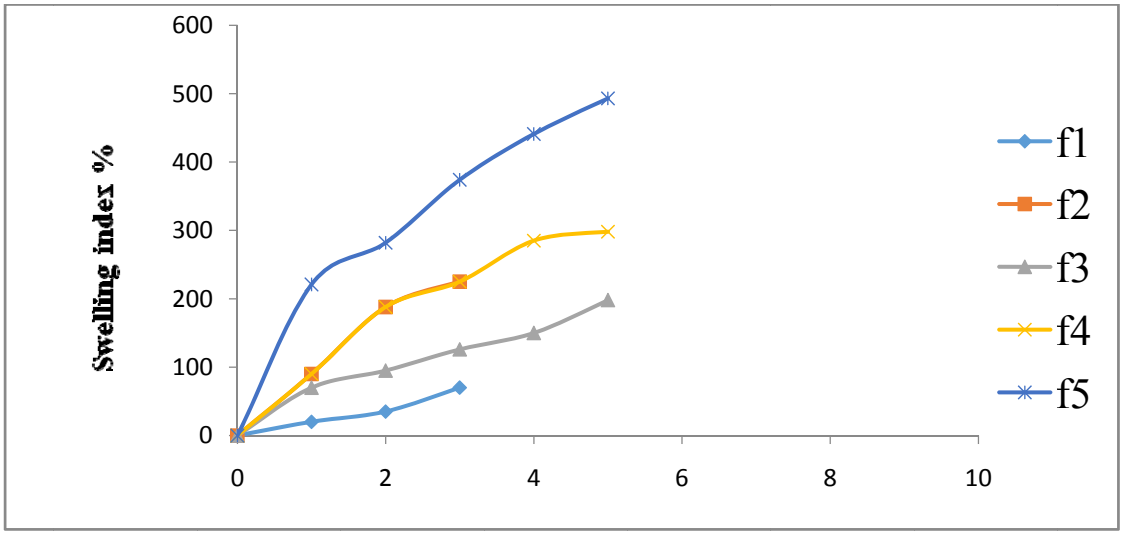

Figure 17: Swelling index graph of F1-F5 in Phosphate buffer pH 6.8

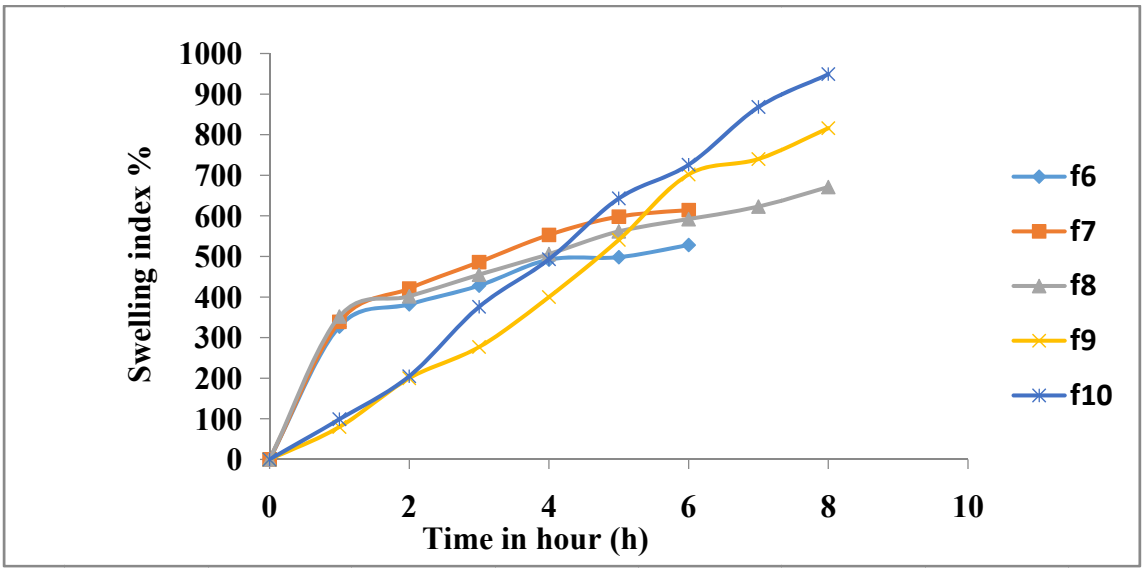

Figure 18: Swelling index graph of F6-F10 in phosphate buffer pH 6.8.

Table 12: Swelling index data of F1-F10 in SVF pH 4.2

Formulation code	1h	2h	3h	4h	5h	6h	7h	8h
F1	75±0.34	95±0.24	126±0.27	150±0.21				
F2	90±0.41	188±0.56	225±0.52	287±0.53				
F3	221±0.35	282±0.43	374±0.54	441±0.67	498±0.26			
F4	327±0.52	382±0.34	428±0.56	492±0.58	498±0.36	528±0.54		
F5	338±0.35	423±0.56	487±0.34	554±0.58	598±0.45	614±0.34		
F6	352±0.54	402±0.65	455±0.35	506±0.36	562±0.37	592±0.27	623±0.32	671±0.39
F7	94±0.17	112±0.34	129±0.26	181±0.45	234±0.45	277±0.45	310±0.25	352±0.23
F8	102±0.36	134±0.27	164±0.35	227±0.28	280±0.27	334±0.34	365±0.45	396±0.56
F9	98±0.13	205±0.28	375±0.57	489±0.37	641±0.34	726±0.27	865±0.53	948±0.43
F10	79±0.18	189±0.38	278±0.27	398±0.26	537±0.29	698±o.46	738±0.62	816±0.67

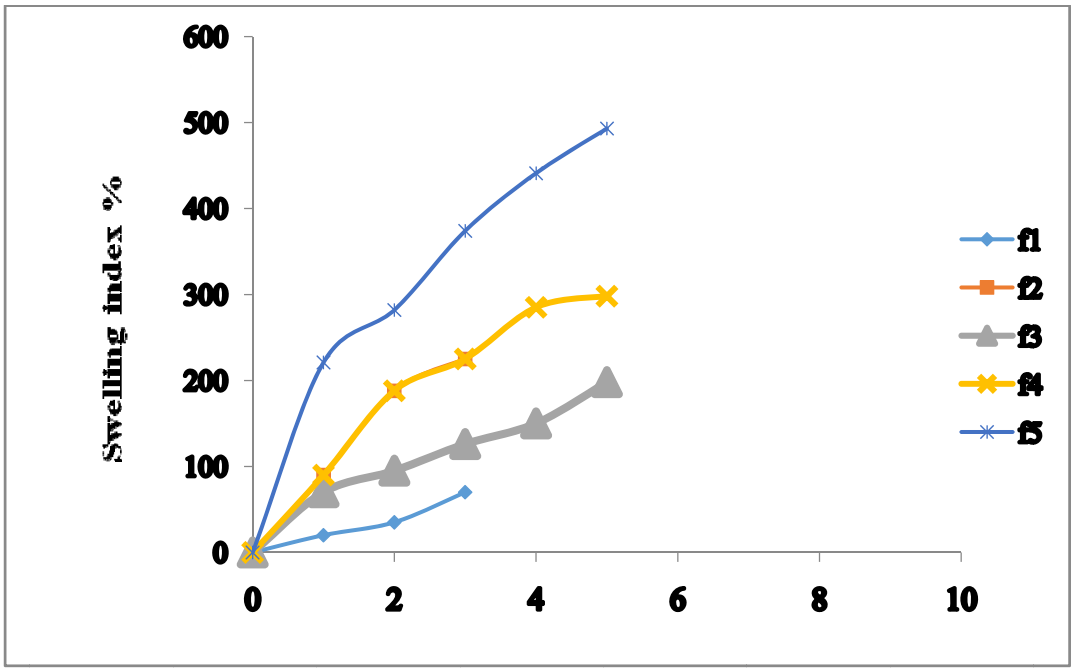

Figure 19: Swelling index graph of F1-F10 in SVF pH 4.2.

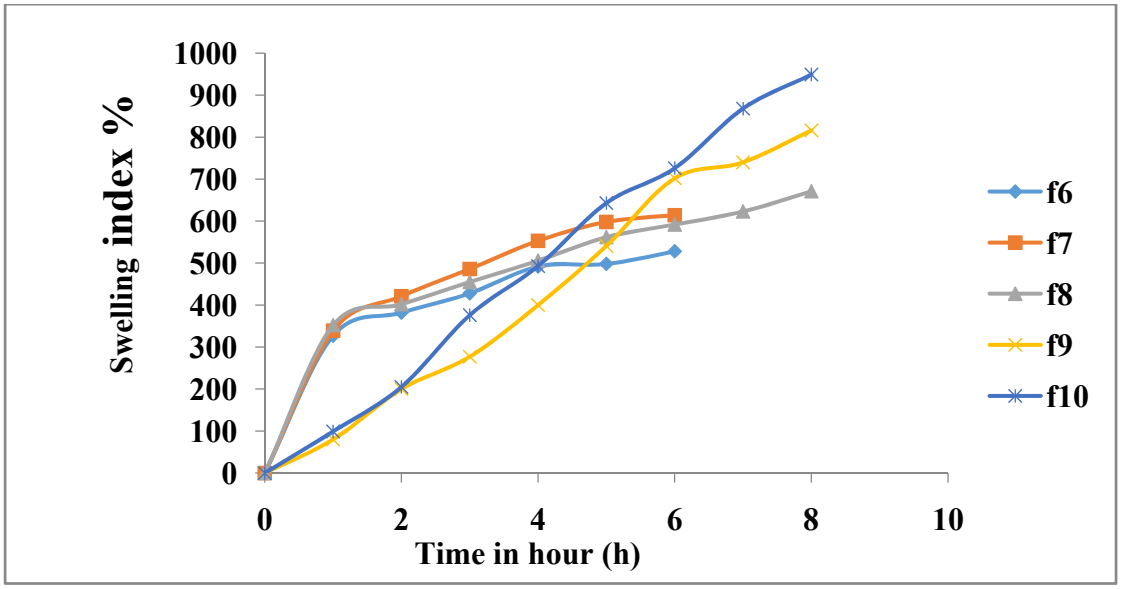

Figure 20: Swelling index graph of F6-F10 in SVF pH 4.2.

3.17*In-vitro* mucoadhesive strength

Table 13: Mucoadhesive strength of F1-F10

Formulation code	Mucoadhesive strength(Gm) (Mean±SD)
F1	25±0.01
F2	37±0.02
F3	42±0.03
F4	45±0.01
F5	52±0.03
F6	58±0.03
F7	63±0.04
F8	59±0.03
F9	68±0.01
F10	64±0.01

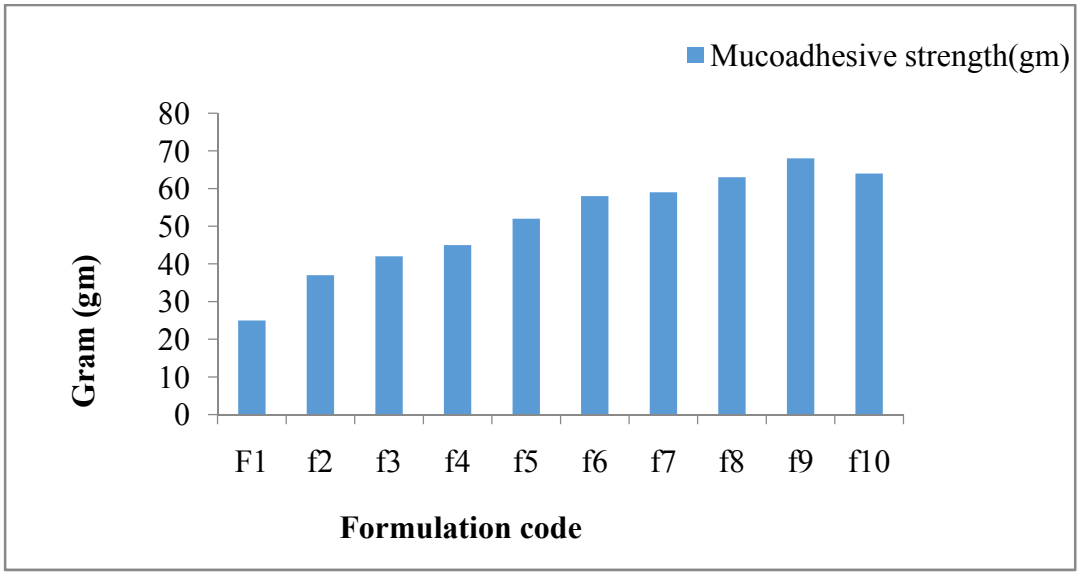

Figure 21: Mucoadhesive strength graph of F1-F10.

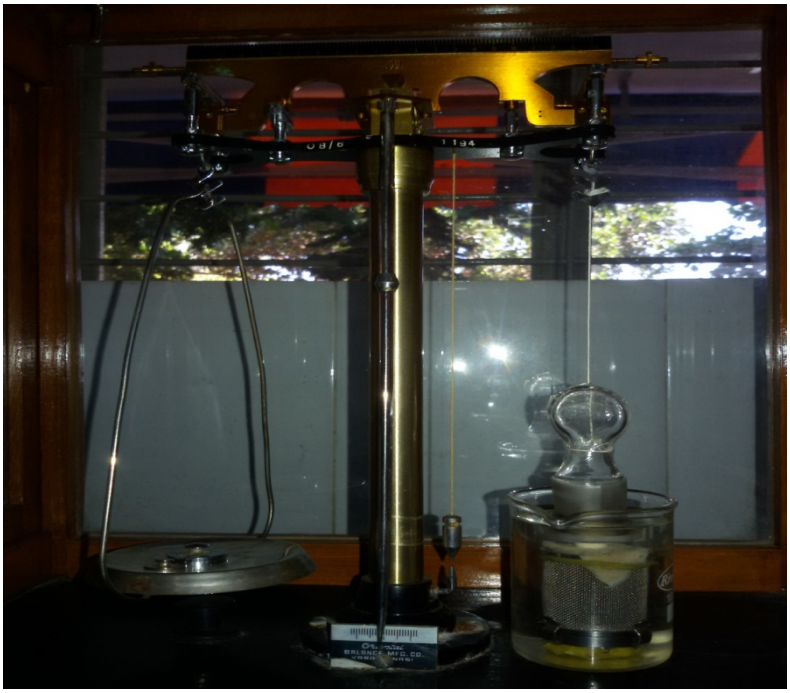

Figure 22: Modified weight balance apparatus

3.18*In- vitro* dissolution studies

Table 14: In-vitro dissolution studies of F3-F10 in phosphate buffer pH 6.8

Time (h)	F3% Mean±SD	F4% Mean±SD	F5% Mean±SD	F6% Mean±SD	F7% Mean±SD	F8% Mean±SD	F9% Mean±SD	F10% Mean±SD
1	28.55±0.69	28.45±0.97	27.99±0.34	19.42±0.26	38.44±0.57	20.92±0.75	10.68±0.75	15.26
2	35.05±0.82	54.05±0.28	33.54±0.71	26.41±0.33	52.09±1.48	36.43±0.61	20.84	27.20
3	62.98±0.25	70.25±0.29	49.86±0.29	41.56±0.44	67.19±0.16	44.72±0.82	33.12	36.36
4	78.26±0.32	90.26±0.90	69.13±0.13	58.19±0.40	83.59±0.44	53.54±0.60	47.81	57.7
5	84.59±0.27	93.58±0.32	85.94±0.54	67.59±1.40	89.37±0.27	67.76±0.93	60.37	66.49
6	----	----	89.18±0.18	82.22±1.70	94.63±0.58	78.83±0.34	78.78	81.18
7	----	----	90.39±0.33	91.82±0.26	95.95±0.17	84.69±0.38	87.34	90.36
8	----	----	----	---	---	97.71±0.14	98.74	96.80

Table 15: kinetic modelling for drug dissolution profiles of F3-F10 in phosphate buffer pH 6.8

KINETIC MODEL	PARAMETER	F3	F4	F5	F6	F7	F8	F9	F10
ZERO ORDER	REGRESSION	0.965	0.957	0.947	0.973	0.898	0.994	**0.995**	0.988
FIRST ORDER	REGRESSION	0.966	0.967	0.949	0.918	0.985	0.800	**0.772**	0.900
HIGUCHI	REGRESSION	0.945	0.982	0.948	0.973	0.969	0.984	**0.973**	0.981
KORSMEYER – PEPPAS	SLOPE	0.741	0.760	0.691	0.845	0.505	0.726	**0.952**	0.929
	REGRESSION	0.931	0.982	0.947	0.977	0.983	0.994	**0.997**	0.991

Table 16: *In- vitro* dissolution studies in of F3-F10 in Simulated vaginal fluid pH 4.2

Time (h)	F3% Mean±SD*	F4% Mean±SD*	F5% Mean±SD*	F6% Mean±SD*	F7% Mean±SD*	F8% Mean±SD*	F9% Mean±SD*	F10% Mean±SD
1	28.55±0.69	28.45±0.97	27.99±0.34	19.42±0.26	38.44±0.57	20.92±0.75	10.68	15.26
2	35.05±0.82	54.05±0.28	33.54±0.71	26.41±0.33	52.09±1.48	36.43±0.61	20.84	27.20
3	62.98±0.25	70.25±0.29	49.86±0.29	41.56±0.44	67.19±0.16	44.72±0.82	33.12	36.36
4	78.26±0.32	90.26±0.90	69.13±0.13	58.19±0.40	83.59±0.44	53.54±0.60	47.81	57.7
5	84.59±0.27	93.58±0.32	85.94±0.54	67.59±1.40	89.37±0.27	67.76±0.93	60.37	66.49
6	----	----	89.18±0.18	82.22±1.70	94.63±0.58	78.83±0.34	78.78	81.18
7	----	----	90.39±0.33	91.82±0.26	95.95±0.17	84.69±0.38	87.34	90.36
8	----	----	----	---	---	97.71±0.14	98.74	96.80

*All values are mean of three reading ± SD

Table 17: Kinetic modelling of drug release profile from F3-F10 in Simulated vaginal fluid pH 4.2

KINETIC MODEL	PARAMETER	F3	F4	F5	F6	F7	F8	F9	F10
ZERO ORDER	REGRESSION	0.965	0.957	0.947	0.973	0.898	0.994	**0.995**	0.988
FIRST ORDER	REGRESSION	0.966	0.967	0.949	0.918	0.985	0.800	**0.772**	0.900
HIGUCHI	REGRESSION	0.945	0.982	0.948	0.973	0.969	0.984	**0.973**	0.981
KORSMEYER – PEPPAS	SLOPE	0.931	0.760	0.691	0.845	0.504	0.726	**0.985**	0.927
	REGRESSION	0.931	0.982	0.947	0.977	0.981	0.994	**0.997**	0.991

3.19*In-vitro* diffusion studies

Table 18: *In-vitro* diffusion data of F9 in phosphate buffer pH 6.8

Time(h)	Drug release (Mean ±SD)
1	16.3±0.56
2	32.9±0.63
3	50.44±0.75
4	65.16±0.47
5	78.38±0.56
6	85.70±0.38
7	91.88±0.28
8	96.46±0.29

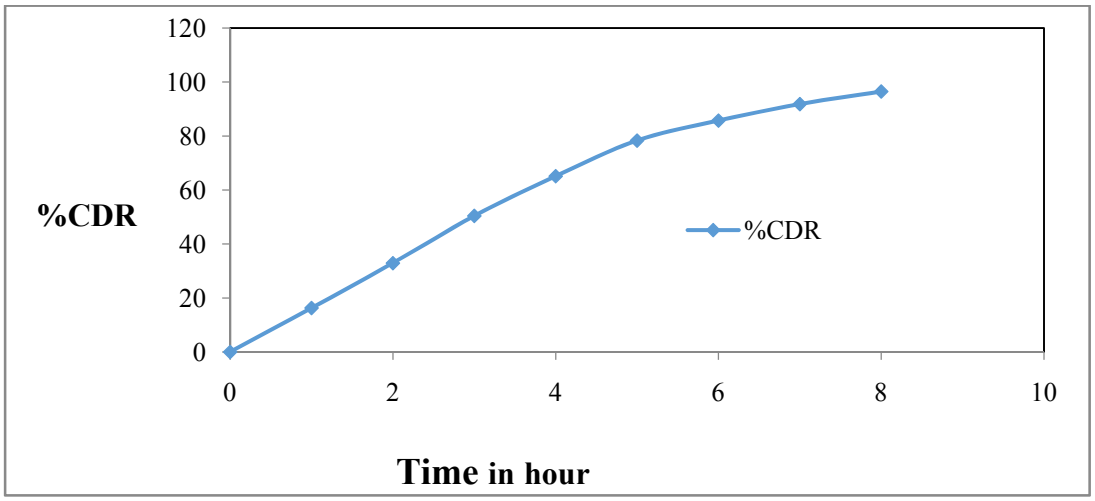

Figure 31: Diffusion data of F9 in Phosphate buffer pH 6.8

Table 19: In-vitro diffusion data of f9 in simulated vaginal fluid pH 4.2

Time(h)	Drug release (Mean ±SD)
1	12.35±0.58
2	23.84±0.68
3	37.35±0.78
4	53.28±0.49
5	69.68±0.58
6	86.92±0.35
7	90.97±0.32
8	97.95±0.33

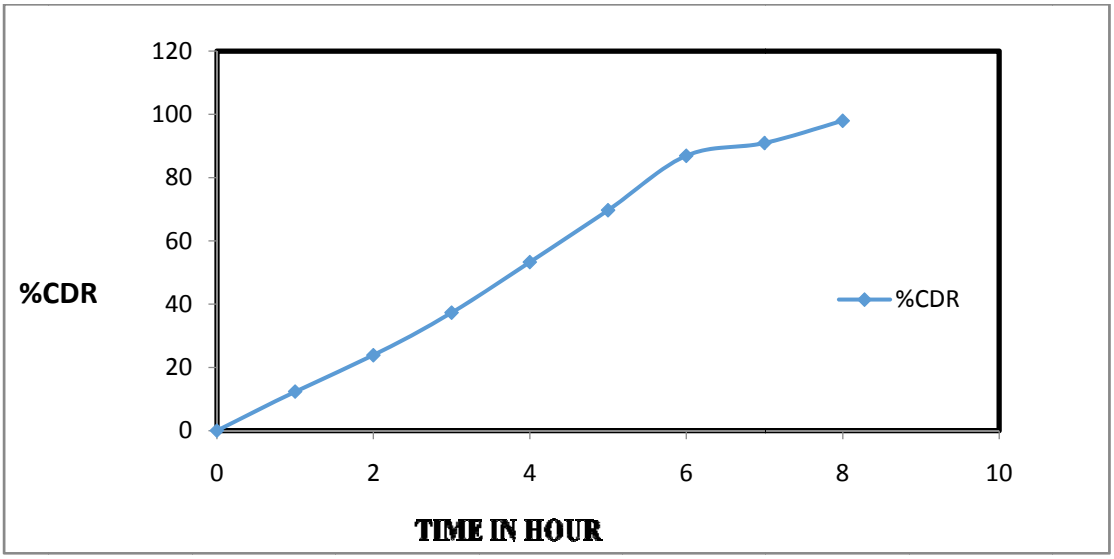

Figure 32: Diffusion pattern of F9 in SVF pH 4.2.

3.20 Stability studies

Table 20: Physiochemical parameters of F9 after 2 months stability studies

Time(Days)	Stability condition	Hardness(kg/cm2)*	Drug content%*
0	30±2ºC,65±5%RH	6.5±0.331	98.6±0.112
30	30±2ºC,65±5%RH	6.3±0.262	98.0±0.183
60	30±2ºC,65±5%RH	6.1±0.283	97.7C0.146

*All values are mean of three readings ± SD

Table 21: Drug release studies of Formulation-9 after 2 months of stability studies

Time (h)	%CDR After 30 days*	%CDR After 60 days*
1	9.5±0.590	9.2±0.481
2	18.6±0.484	17.4±0.362
3	30.74±0.632	28.34±0.674
4	38.32±0.532	39.16±0.431
5	48.9±0.438	45.3±0.236
6	68.9±0.215	67.2±0.362
7	85.4±0.312	83.4±0.153
8	95.3±0.632	94.2±0.578

* All values are mean of three readings ± SD

4. CONCLUSION

There is strong prophylactic and clinical need to develop new solid dosage form for candidacies with desired characteristics such as better therapeutic efficacy, retention for intended interval, patient flexibility with cost effective medication. The mucoadhesive hybrid drug delivery system developed viz., Interpolyelectrolyte complexes have demonstrated their superiority and suitability for buccal and vaginal route for candidacies. Thus the study shows that the developed system has a great appeal for the convenient treatment of candidacies that may be explored in improving the limitations of existing drug delivery system.

5. AKNOWLEDGEMENT

Authors specially acknowledge to Yarrow chem., Mumbai for providing gift sample of miconazole nitrate. Author thanks to Professor Mr. G S Shanta Kumar for his continuous assistance for his guidance and support towards this research work.

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