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Formulation and Evaluation of Metronidazole Mucoadhesive Vaginal Tablets

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Abstract:- Vaginitis is a very common gynecological problem in women of all age groups. There are three types of infectious vaginitis: candidiasis, trichomoniasis, and bacterial vaginosis. Vaginitis can be caused by single or mixed vaginal infections. Approximately 30% of women suffering from vaginitis problem. The present study is to formulate and evaluate mucoadhesive tablet, this will increase the residence time at the site of the absorption also it associate with the self-cleansing action of vaginal tract. These results indicate that metronidazole containing vaginal mucoadhesive systems can be further developed for safe, convenient, and effective treatment of vaginal candidiasis with required dose frequency. A new emerging system is proposed for improving the sustained release of formulation and their combination using different polymers, such as, HPMC K-100M, Polyethylene oxide WSR-303, Xanthum gum and Grantrez. All polymer and their combination with different concentration blends with drug were with poor flow properties and compressibility. Hence, wet granulation method with PVP K 30 as binder was used for further tableting were tried in order to get desired sustained release of drug over of 8 hrs. All the formulations were evaluated % drug content, *in vitro* drug release, % water uptake study, IR spectrum and mucoadhesive strength. The tablets with 10% w/w of polymer showed a good sustained release over a period of 8h. It was found that, as the polymer concentration was increased, the drug release decreased. The drug release from HPMC K-100: Polyox WSR-303(1:1) tablet (F15) was found to be 90.93±0.23% after 8 hrs of dissolution using USP (XXIII) dissolution apparatus II (DT 60, Veego Instruments).

Keywords:- *Mucoadhesive, Metronidazole, HPMC K-100 M, Polyethylene oxide WSR-303, Xanthum gum, Grantrez.*

I. INTRODUCTION

Now a days the compressed tablet is most popular dosage form in sustained drug delivery. The vaginal route is commonly used for the administration of locally acting drugs such as antimicrobials, labor-inducing agents, spermicidal agents, prostoglandins and steroids. Moreover, the administration of drugs for systemic effects via the vagina is also feasible In comparison to all other mucosal membranes, the vaginal mucosa offers the advantage that drug delivery systems can remain for the longest time period at the site of application. Moreover; vaginal rings can remain on the vaginal mucosa even for months, which renders this route of non-invasive administration unique and provides promising opportunity for more efficient and convenient therapies. Metronidazole is use as antiinfective activity and its half life is 8 hr. The present study is to formulate and evaluate the vaginal mucoadhesive tablet, this will increase the residence time at the site of the absorption are associated with the self-cleansing action of vaginal tract. The mucoadhesive polymers can hold mucosa and increase patient compliance compare to other dosage from. These results indicate that metronidazole containing vaginal mucoadhesive systems can be further developed for safe, convenient, and effective treatment of vaginal candidiasis with required dose frequency.

II. MATERIAL

Metronidazole (Gift sample of M/s. Hindustan Antibiotics Ltd., Pimpri-Chinchawad) 2018, HPMCK100M (Colorcon Asia, Goa), Gantrez (alpha), Xanthum Gum (Kopran, Mumbai.), Polyox WSR-303 (Colorcon Asia, Goa), Magnesium sterate (Research Lab. Mumbai), MCC (Research Lab. Mumbai), Talc (Research Lab. Mumbai), Polyvinyl pyrrolidone (Research Lab. Mumbai), Methanol (Research Lab. Mumbai), Isopropyl alcohol (Loba Chem., Mumbai).all the reagent were used of analytical grade.

➢ *Pre- Formulation Studies*

The powder blend were determined by the angle of repose, compressibility index, bulk density, Tapped Density and hausner ratio. But the flow of powder shows poor compressibility hense, the powder blends prepared by wet granulation method using wetting agent. Drug exicipient compatibility studies done by FT-IR Spectroscopy. The IR spectra of previously dried samples of polymers were recorded by potassium bromide dispersion technique. The base line correction was made using dried potassium bromide (KBr). 2-3 mg of sample of polymers were mixed with previously dried potassium bromide and kept in sample cell, the cell was then fitted on sample holder and IR spectra was recorded using FTIR spectrometer (FTIR-8400s) with diffused reflectance and major functional groups were identified.

➢ *Standard Curve*

A standard curve was prepared by dissolving 10 mg of Metronidazole in 10ml of distilled water. It was further diluted with distilled water respectively. The sample solutions were prepared by the various dilution of concentration range of 1 to 10 µg/ml. The absorbances of these solutions were determined spectrophotometrically at 400-200nm respectively. The absorbance values obtained using absorbance-concentration data, Lambert and Beer's graphs were plotted.

➢ *Formulation*

The powder blend were prepared by taking required quantities of drug & using various polymers at different concentration level and mixed thoroughly. After that microcrystalline cellulose (MCC) was added as binder. All the components mixed for at least 15 min, then passed through 60-mesh sieve, then add 70% ethanol was used as wetting agent to prepare the damp mass, the granules were prepared by passing through 18 mesh sieve and dried at 55°C. The dried granules were mixed with lubricants, glindant and compressed using single punch tableting. These powder blends with different polymer concentrations i.e. 10% (w/w), 20% (w/w), 30% (w/w) and 40% (w/w) formed & subjected to various evaluation tests. Formulae for the preparation of powder blends using various polymers is given in **(Table 1).**

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
Metronidazole	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250	250
HPMCK100M (mg)	50	100	150	200	-	-	-	-	-	-	-	25	50	75	25	50	75	100
PEO-WSR 303 (mg)	-	-	-	-	50	100	150	200	-	-	-	25	50	75	-	-	-	-
Xanthum Gum	-	-	-	-	-	-	-	-	100	150	200	-	-	-	-	-	-	-
Gantrez	-	-	-	-	-	-	-	-	-	-	-	-	-	-	25	50	75	100
MCC	190	140	90	40	190	140	90	40	140	90	40	190	140	90	190	140	90	40
Total (mg)	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500

Table 1:- Formulae of Metronidazole MDDS Prepared With Hpmck100m, Polyox-Wsr 303, Xanthum Gum and Gantrez

[**Note:-**Each formulation contains 1% (w/w) Magnesium Stearate & 1%(w/w) Talc as lubricant & glidant respectively.]

➢ *Preparation of Tablets:*

The tablets with different polymer concentrations (10%, 20%, 30% and 40%) were prepared by wet granulation and compressed using single punch tableting machine (Rimek Mini Press MT-II). The powder was weighed and individually filled in the die cavity (12mm diameter) and a constant pressure was applied. The formulae for typical tablet preparation is given in **(Table1).**

➢ *Evaluation:*

The evaluation of tablets are performed various quality control tests such as thickness of tablet, Hardness, Friability, uniformity of weight and content uniformity of drug and other specific valuation tests for MDDS like adhesive strength, swelling index, and drug release rate.

➢ *Tablet thickness*

Thickness of tablets was determined using Vernier calliper. Ten tablets from each batch were used, and average values were calculated.

➢ *Hardness*

Hardness of 3 matrix tablets from each formulation type was determined using Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then the constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2.

➢ *Friability*

The friability of the tablets was determined using Roche friabilator. 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 min. after 4 min the tablets were weighted again. The friability was then calculated using the formula,

$$\text{Friability (\%)} = \frac{\text{Initial Weight- Final Weight}}{\text{Initial Weight}} \times 100$$

➢ *Uniformity of Weight:*

The uniformity of weight of each tablet is done by sampling and weighing 10 tablets at random and average weight is calculated. Not more than two of the individual weight deviate from the average weight by more than the percentage as mentioned in IP.

➢ *Percent drug content:*

Three tablets from each formulation were triturated in morter and pestle. Powder equivalent to dose of drug was weighed and dispersed in to 100ml of distilled water and sonicated using ultrasonicator for 20mins. The resultant solution was then filtered through whatman filter paper no.41 and further diluted with distilled water. Drug content was spectrophotometrically determined at 319.5nm (Model-UV 1700 Shimadzu, Japan). The mean of three determinations was calculated.

➢ *Drug release studies:*

Drug release studies of prepared tablets were performed using USP XXIII, the tablets were stick on a glass slide by soaking it with some water to drug release. It was used with 900 ml of citrate phosphate buffer pH-5.2 as dissolution medium at 37±0.5^{0}C. The speed of the paddle was adjusted to 50 rpm. An aliquot of 1 ml sample was collected at an interval of 1hr and analyzed for the content of Metronidazole by UV-spectrophotometer at 319.5 nm after appropriate dilution. An equivalent volume (1 ml) of fresh dissolution medium was added to compensate for the loss due to sampling and results of drug release study were reported.

➢ *Water uptake studies:*

Tablets were weighed (W1) and placed separately in Petri dishes containing 5 ml of Citrate phosphate buffer pH-5.2. The dishes were stored at room temperature. After 0.5, 1, 2, 3, 4, 5, 6, 7, 8 & 12hrs, the tablets were removed and the excess water on their surface was carefully removed using filter paper. The swollen tablets were reweighed (W2) and the % water uptake was calculated by the following formula:

$$\%\,\text{Water uptake} = \frac{W2 - W1}{W1} \times 100$$

➢ *In-vitro mucoadhesion strength*

Adhesive properties of Metronidazole tablet formulations were carried out using a texture analyser with a 10gm load cell. Texture analysis is a useful tool and has been used as a valid methodology for mechanical characterization of pharmaceutical mucoadhesive dosage forms. Goat vaginal Mucosa was used as the vaginal mucosal surface. Goat vaginal Mucosa was collected immediately after slaughter of the animals and were rapidly frozen (−20^{0}C) and stored in citrate phosphate-buffered saline pH 5.2. Before testing, a Goat vaginal mucosal membrane was defrosted at room temperature. The goat vaginal mucosa was then placed on the base of the texture analyser with the vaginal membrane facing upward. A tablet to be tested was attached to the base of an aluminium probe (using double sided adhesive tape) fixed to the mobile arm of the texture analyser. The area of contact on the mucosa was moistened with solution. The tablet was lowered at a rate of 0.1mms^{-1} until contact with the goat tissue was made. A contact force of 10gm was maintained for 10secs., after which the probe was withdrawn from the vaginal membrane at a rate of 5mms^{-1}. The peak Force of Adhesion (N) and the Mucoadhesive Force (gms) was recorded.

III. RESULT AND DISCUSSION

➢ *Pre-Formulation Parameters:*

The preformulation studies were performed. The polymer blends were prepared with polymer concentration of 10%, 20%, 30%, 40% and evaluated for low bulk density, tapped bulk density, carr's compressibility index, Hausner ratio and angle of repose. The Bulk density varied from 0.350±0.04 to 0.667±0.10, Tapped density varied from 0.296±0.13 to 0.905±0.54, Hausner ratio varied from 1.35±0.16 to 1.78±0.46, Carr's Compressibility varied from 35.44±0.37 to 73.02±0.51, the angle of repose was found in range from 29.78±0.33 to 69.32±0.73. **(Table 2)** from this data it is concluded that, the powder blends of drug and polymer are not compressible.

Formulation	Bulk Density (gm/cm^3)	Tapped Bulk Density (gm/cm^3)	Hausner ratio	Carr's Compressibility Index (%)	Angle of Repose (Degrees)
F1	0.350±0.04	0.780±0.05	1.51±0.13	35.44±0.37	35.23±0.76
F2	0.444±0.05	0.573±0.10	1.45±0.14	43.45±0.41	46.70±0.60
F3	0.557±0.08	0.488±0.12	1.43±0.15	35.46±0.47	37.88±0.88
F4	0.451±0.04	0.392±0.17	1.55±0.34	56.67±0.38	48.23±0.73

F5	0.562±0.06	0.581±0.17	1.35±0.16	45.53±0.39	59.33±0.70
F6	0.364±0.07	0.308±0.14	1.56±0.17	36.76±0.40	30.21±0.55
F7	0.570±0.08	0.804±0.34	1.53±0.18	38.44±0.48	31.11±0.69
F8	0.667±0.10	0.905±0.54	1.57±0.19	39.68±0.43	29.78±0.33
F9	0.556±0.09	0.345±0.23	1.60±0.20	40.77± 0.54	38.20±0.51
F10	0.462±0.011	0.296±0.13	1.48±0.34	46.66±0.42	46.25±0.39
F11	0.388±0.03	0.525±0.15	1.40±0.56	48.79±0.37	51.22±0.50
F12	0.388±0.06	0.326±0.03	1.45±0.22	55.61±0.58	40.02±0.47
F13	0.453±0.11	0.484±0.02	1.60±0.23	52.74±0.33	33.75±0.54
F14	0.548±0.15	0.576±0.04	1.61±0.24	40.41±0.46	45.11±0.69
F15	0.470±0.17	0.617±0.02	1.64±0.21	60.75±0.44	43.65±0.41
F16	0.384±0.38	0.736±0.07	1.68±0.35	73.02±0.51	58.77±0.71
F17	0.358±0.27	0.477±0.04	1.78±0.46	72.5±0.54	69.32±0.73
F18	0.453±0.17	0.371±0.03	1.65±0.52	71.93±0.35	48.35±0.67

Table 2:- Pre-Formulation Parameters before Granulation

It was found that, all polymer blends with drug did not good flow properties and good compressibility **(Table 3).** Then after adding binder mixed all the components, then passed through 60-mesh sieve, then add 70% ethanol was used as wetting agent to prepare the damp mass, the granules were prepared by passing through 18 mesh sieve and dried at 55°C. after the granulation The Bulk density varied from 0.244±0.05 to 0.288±0.06, Tapped density varied from 0.271±0.03to 0.336±0.07, Hausner ratio varied from 1.0±0.06 to 1.17±0.05, Carr's Compressibility varied from 5.61±0.58 to 14.77±0.40, the angle of repose was found in range from 15.23±0.66 to 39.32±0.73. From above data it is concluded that, the granules are compressible on single punch compression machine.

Formulation	**Loose Bulk Density (gm/cm^3)**	**Tapped Bulk Density (gm/cm^3)**	**Hausner ratio**	**Carr's Compressibility Index (%)**	**Angle of Repose (Degrees)**
F1	0.250±0.03	0.280±0.05	1.15±0.02	10.17±0.37	15.23±0.66
F2	0.244±0.05	0.273±0.04	1.11±0.04	11.11±0.41	16.70±0.70
F3	0.257±0.08	0.288±0.07	1.12±0.03	11.07±0.47	17.88±0.68
F4	0.251±0.08	0.292±0.07	1.16±0.02	14.13±0.38	18.23±0.63
F5	0.262±0.07	0.281±0.03	1.07±0.06	6.95±0.39	19.33±0.70
F6	0.264±0.06	0.308±0.05	1.15±0.03	14.77±0.40	20.21±0.55
F7	0.270±0.04	0.304±0.08	1.11±0.09	10.0±0.48	21.11±0.69
F8	0.267±0.03	0.300±0.03	1.15±0.04	13.33±0.43	19.78±0.73
F9	0.256±0.03	0.285±0.06	1.12±0.05	12.56± 0.54	18.20±0.51
F10	0.262±0.04	0.292±0.03	1.11±0.04	11.14±0.42	16.25±0.49
F11	0.288±0.03	0.325±0.07	1.14±0.05	11.56±0.37	21.22±0.70
F12	0.288±0.06	0.326±0.03	1.13±0.02	5.61±0.58	22.02±0.47

F13	0.253±0.09	0.284±0.02	1.12±0.03	12.74±0.33	23.75±0.54
F14	0.248±0.05	0.276±0.04	1.12±0.04	10.41±0.46	25.11±0.69
F15	0.270±0.07	0.317±0.02	1.14±0.01	10.75±0.44	33.65±0.41
F16	0.284±0.08	0.336±0.07	1.17±0.05	7.02±0.51	38.77±0.71
F17	0.258±0.07	0.277±0.04	1.0±0.06	7.5±0.54	39.32±0.73
F18	0.253±0.07	0.271±0.03	1.08±0.02	7.93±0.35	38.35±0.67

Table 3:- Pre-Formulation Parameters after Granulation

➢ *FTIR spectral analysis :*

The FTIR graph of the pure drug and combination polymer showing the compatibility. The FTIR spectra of Metronidazole, HPMC K-100M, PEO-303, Xanthum gum, Gantrez, and seleccted formulations (F1, F5, F12, F15) were taken and showed in Fig.1,2,3, 4. Thus, no interactions were observed between the Metronidazole, polymer and other excipients in formulations of matrix tablets.

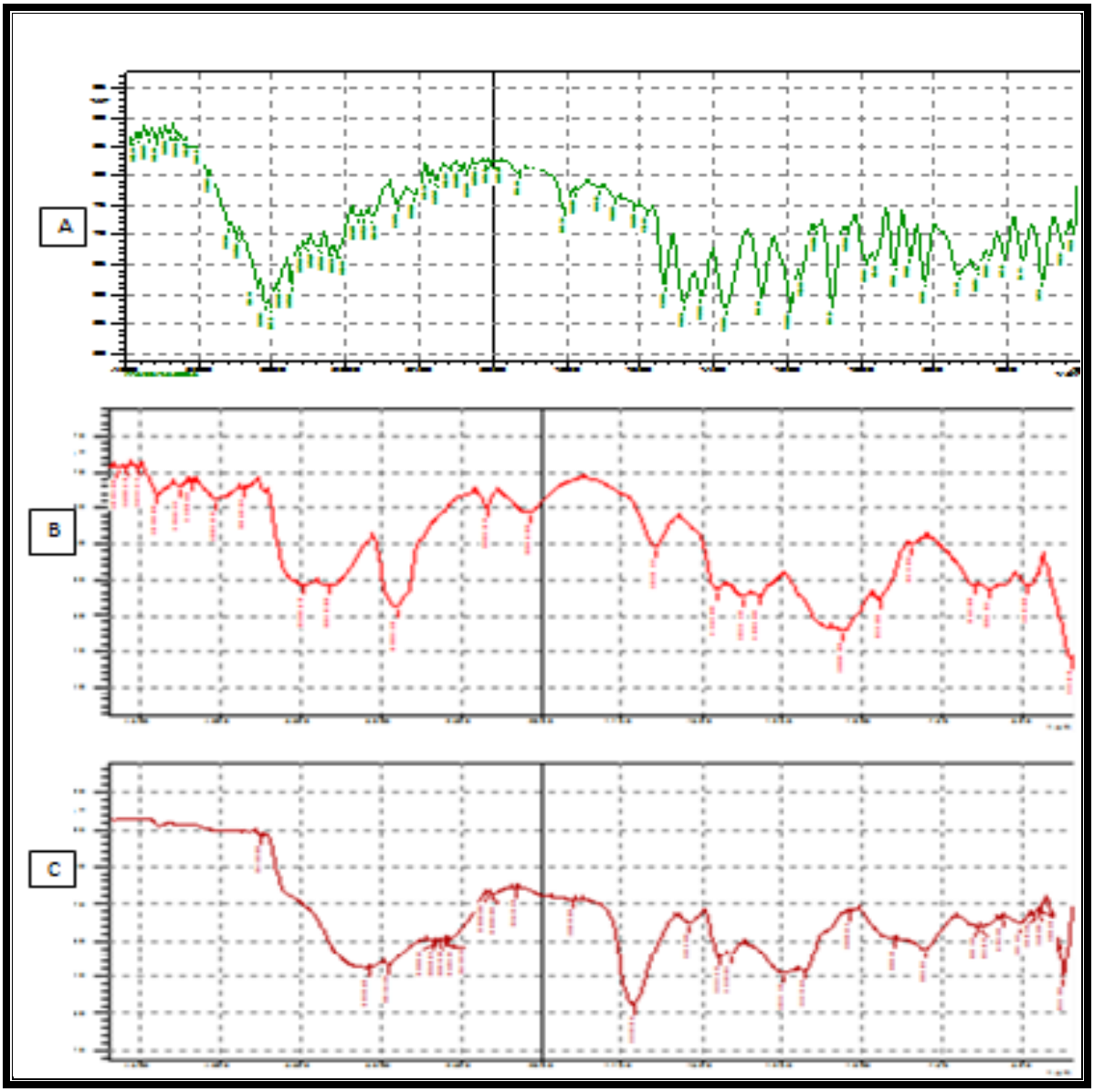

Fig 1:- IR spectrum of A-Pure drug Metronidazole; B-HPMC K-100M; C- Formulation F1

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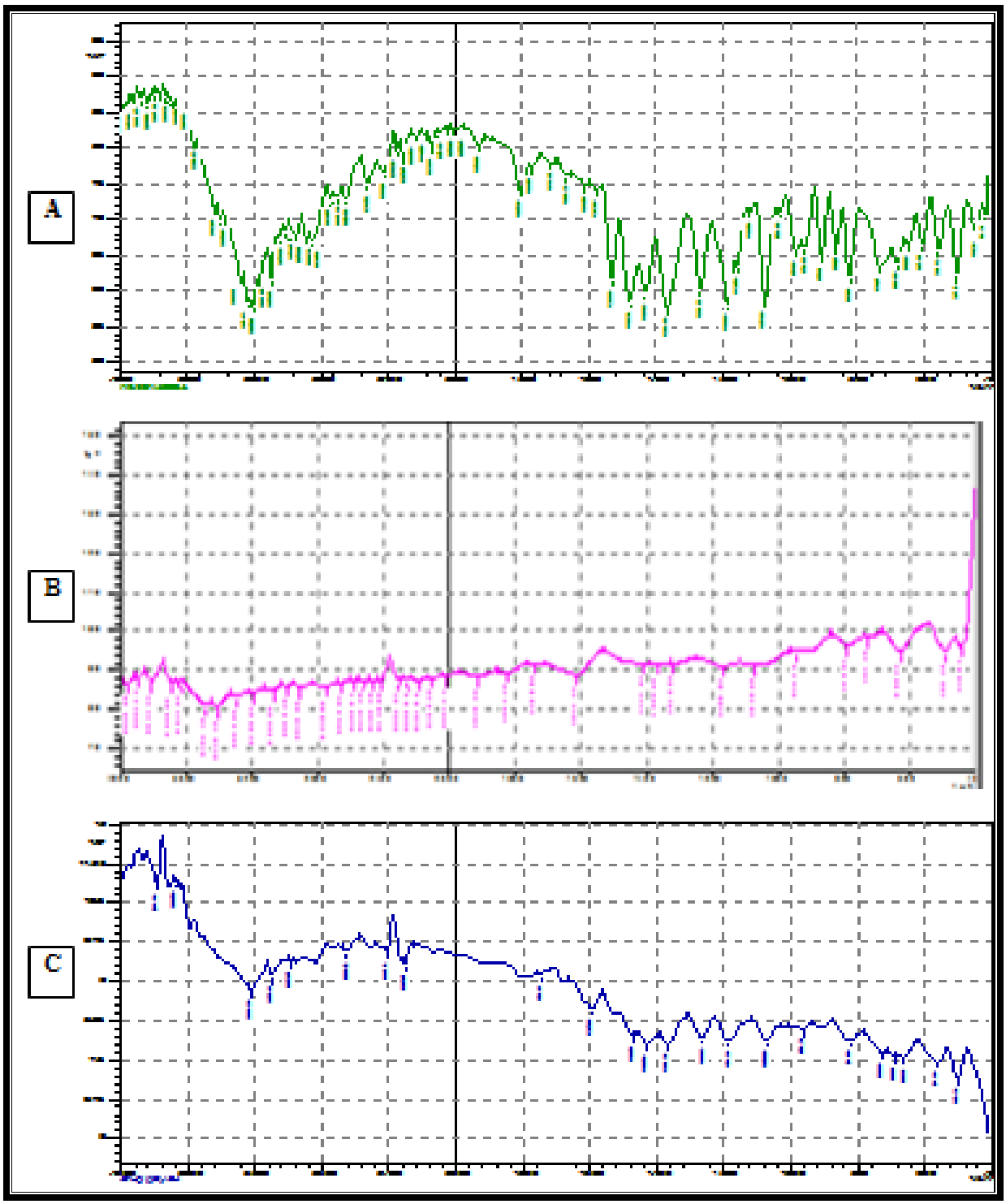

Fig 2:- IR spectrum of A-Pure drug Metronidazole; B-Polyox-303 WSR; C- Formulation F5

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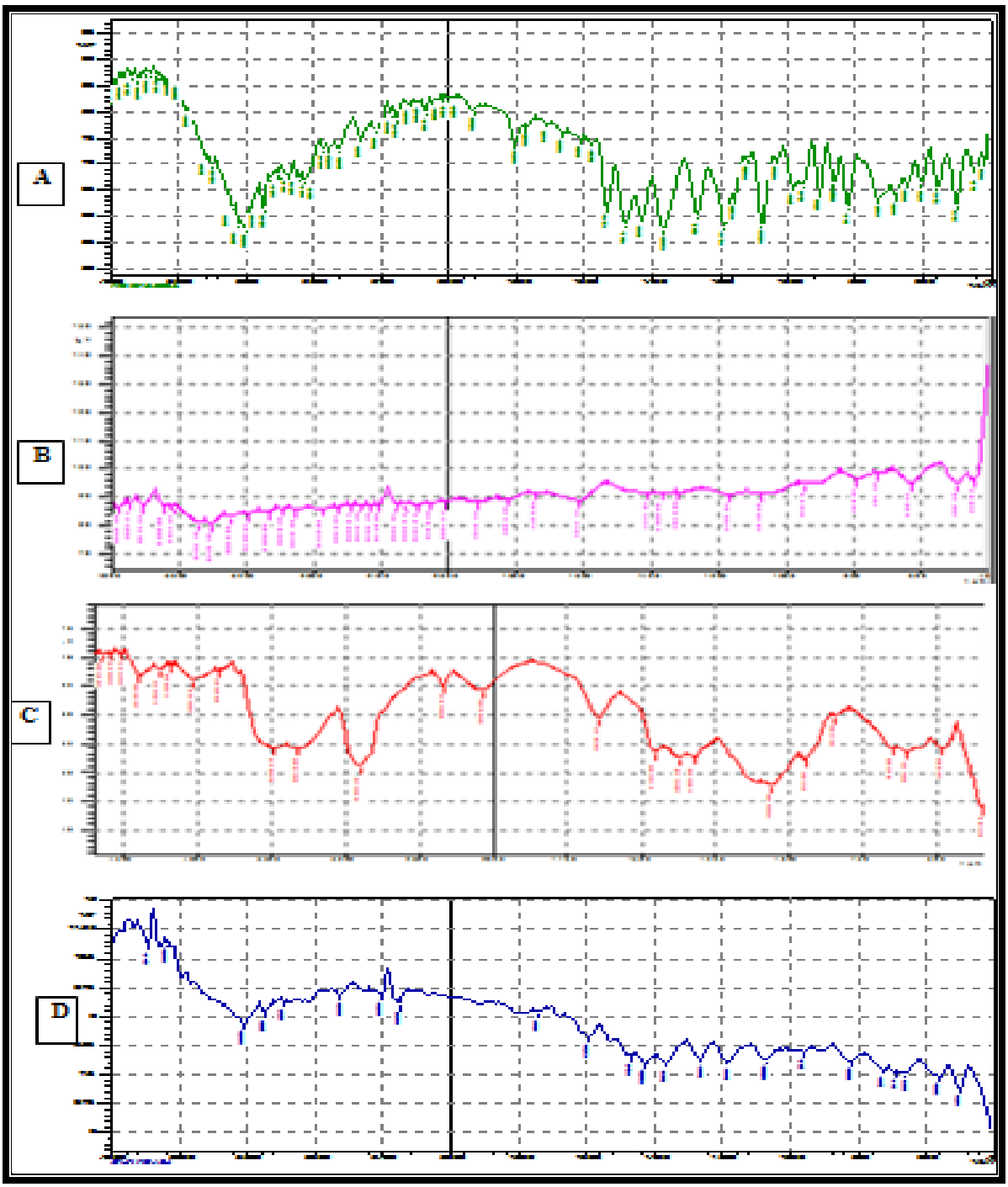

Fig 3:- IR spectrum of A-Pure drug Metronidazole; B-Polyox; C-HPMC K100M; D- Formulation F12

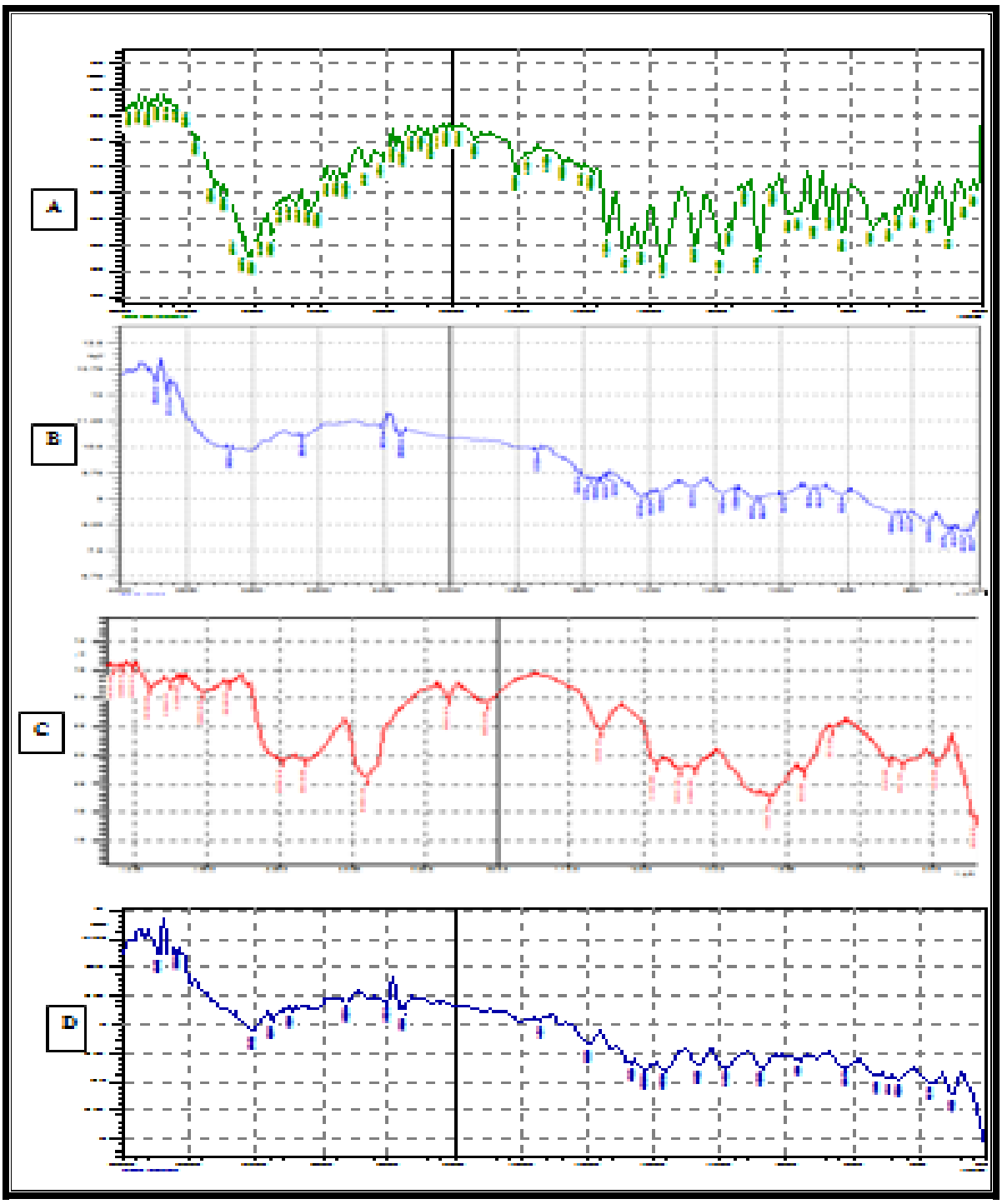

Fig 4:- IR spectrum of A-Pure drug Metronidazole; B-Gantrez; C- HPMC K-100M; D-Formulation F15

➢ *Construction of Standard Graph in Distilled Water:*

The pure drug of metronidazole was accurately weighed 10 mg was mixed with 10 ml of distilled water. The solution producing 1 mg/ml conc. i.e. stock solution. The UV absorbance data at 320.0 nm nm and concentration estimates of Metronidazole at this wavelength showed good linearity (R^2 – 0.9995) over the concentration range of 0-15 µg/ml. Hence, the sample of Metronidazole was found obey Beer- Lmbert`s law over this range.

➢ *Evaluation of Prepared Tablets:*

The tablets with different polymer and different combination concentrations (10%, 20%, 30% and 40% w/w) were prepared by wet granulation method on a single punch tablet compression machine. The powder was weighed and individually filled in the die cavity (12mm diameter) and a constant pressure was applied. The prepared tablets were evaluated for thickness, hardness, average weight, % drug content, *in-vitro* dissolution study, % water uptake, *in-vitro* mucoadhesion study.

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Average Weight of tablet (mg)	Friability (%)	% Drug Content
F1	3.46±0.04	5-6	498±0.27	0.5±0.04	99.50±0.24
F2	3.45±0.07	5-6	498±0.26	0.2±0.07	99.03±0.30
F3	3.44±0.03	5-6	499±0.57	0.7±0.03	99.30±0.34
F4	3.56±0.07	5-6	497±0.22	0.5±0.07	99.76±0.22
F5	3.55±0.05	5-6	497±0.47	0.6±0.05	100±0.37
F6	3.54±0.02	5-6	496±0.16	0.8±0.02	99.98±0.22
F7	3.53±0.07	5-6	500±0.36	0.8±0.07	101.1±0.25
F8	3.55±0.04	5-6	498±0.25	0.6±0.04	99.50±0.37
F9	3.54±0.05	5-6	497±0.54	0.7±0.05	99.05±0.58
F10	3.56±0.03	5-6	496±0.46	0.9±0.03	99.56±0.55
F11	3.58±0.05	5-6	495±0.43	0.7±0.05	99.25±0.63
F12	3.53±0.02	5-6	496±0.37	0.8±0.02	96.48±0.57
F13	3.53±0.01	5-6	496±0.36	0.7±0.01	99.21±0.63
F14	3.54±0.04	5-6	499±0.37	0.4±0.04	96.23±0.57
F15	3.55±0.03	5-6	498±0.35	0.5±0.03	91.33±0.54
F16	3.53±0.05	5-6	497±0.36	0.3±0.05	98.75±0.53
F17	3.56±0.03	5-6	499±0.36	0.6±0.03	98.23±0.58
F18	3.56±0.06	5-6	500±0.35	0.6±0.06	99.23±0.98

Table 4:- Evaluation of Prepared Metronidzole Mucoadhesive Tablet

It is evident from the above plot that, HPMC, Polyox-303 WSR, Xanthan Gum and Gantrez undergoes hydration as soon as it comes in contact with the medium. Swelling index was calculated with respect to time as all the formulation F1 to F18 were in range 515.3±0.24 to 1258.2±0.45. **(Table 5,6,7)** with increase the concentration Polyox in combination increase swelling of polymer. For HPMC, Polyox-303 WSR, Xanthan Gum, Gantrez polymer hydration continued up to 8hours. Visual observation showed that, all polymer appeared swollen almost from the beginning and a viscous gel mass was produced. The HPMC K100M and Polyox-WSR 303 (1:1) matrices showed highest swelling than HPMC K100 M, Gantrez, Xanthan Gum and Polyox-WSR 303. The order of water uptake by various polymers is as follows:

HPMC K100M : Polyox WSR-303 >Polyox WSR-303> HPMC K100M> Xanthan Gum.> Gantrez.

% Water Uptake								
Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	878.5±0.24	778.3± 0.35	669.4± 0.44	638.8± 0.36	510.0±0.45	788.8± 0.34	706.6±0.33	746.6± 0.44
1	888.4±0.27	782.9±0.42	740.9± 0.19	685.5± 0.47	588.7±0.46	868.1± 0.46	855.2±0.35	891.7±0.41
2	897.3±0.43	811.8±0.36	857.2± 0.52	800.9± 0.31	634.1±0.47	894.8± 0.27	902.3±0.42	1038.7±0.37
3	918.8±0.26	813.0±0.47	886.6±0.36	843.2±0.26	691.1±0.48	932.8± 0.18	968.9±0.42	1107.4±0.26
4	956.4±0.43	939.4±0.38	907.3±0.35	927.7±0.42	715.3±0.49	933.5±0.53	981.1±0.37	1130.4±0.35

5	979.4±0.44	972.3±0.35	944.8±0.41	944.4±0.36	766.7±0.54	948.8±0.37	1021.2±0.53	1175.0±0.45
6	998.3±045	998.2±0.21	964.8±0.36	958.8±0.54	810.4±0.55	991.8±0.26	1121.2±0.41	1210.3±0.53
7	1011.0±0.44	1002.0±0.52	983.9±0.25	977.9±0.35	883.9±0.51	1112.0±0.34	1211.3±0.42	1255.0±0.56
8	1110.3±0.45	1050.0±0.42	1012±0.53	998.7±0.33	915.2±0.25	1133.5±0.44	1258.2±0.45	1325.0±0.34

Table 5:- Percent Water Uptake By Single Polymer With Different Concentration.

% Water Uptake					
Time (h)	**F9**	**F10**	**F11**	**F12**	**F13**
0.5	793.6±0.57	574.0±0.39	629.5±0.27	515.3±0.24	725.2± 0.35
1	823.3±0.33	575.6±0.38	662.5±0.23	610.2±0.27	746.0±0.42
2	856.1±0.48	575.6±0.49	697.0±0.35	745.7±0.43	777.0±0.36
3	876.6±0.36	798.0±0.44	714.1±0.24	762.0 ±0.26	797.0±0.47
4	898.3±0.26	825.9±0.28	735.4±0.41	808.0±0.43	805.3±0.38
5	915.7±0.25	836.3±0.36	787.5±0.44	855.7±0.44	817.9±0.35
6	955.7±0.16	860.2±0.31	854.2±0.25	904.2±045	895.9±0.21
7	992.3±0.38	892.9±0.27	888.5±0.38	998.3±0.44	913.8±0.52
8	1010±0.19	915.8±0.43	906.0±0.44	1123.4±0.45	953.2±0.42

Table 6:- Percent Water Uptake by Single & Combination Polymer with Different Concentration

% Water Uptake					
Time (h)	**F14**	**F15**	**F16**	**F17**	**F18**
0.5	745.7± 0.44	695.9± 0.36	668.8±0.45	580.2± 0.34	657.0±0.33
1	830.1± 0.19	733.0± 0.47	687.7±0.46	589.2±0.46	659.3±0.35
2	851.6± 0.52	772.8± 0.31	688.2±0.47	665.9± 0.27	702.2±0.42
3	853.9±0.36	815.0±0.26	708.9±0.48	690.6± 0.18	705.4±0.42
4	882.2±0.35	820.8±0.42	719.3±0.49	715.6±0.53	750.0±0.37
5	898.3±0.41	836.0±0.36	792.2±0.54	729.8±0.37	752.3±0.53
6	1045.3±0.36	881.4±0.54	795.2±0.55	757.5±0.26	866.1±0.41
7	1112.2±0.25	934.5±0.35	815.3±0.51	757.5±0.34	912.2±0.42
8	1155.1±0.53	988.9±0.33	836.2±0.25	815.6±0.44	956.1±0.45

Table 7:- Percent Water Uptake By Single & Combination Polymer With Different Concentration

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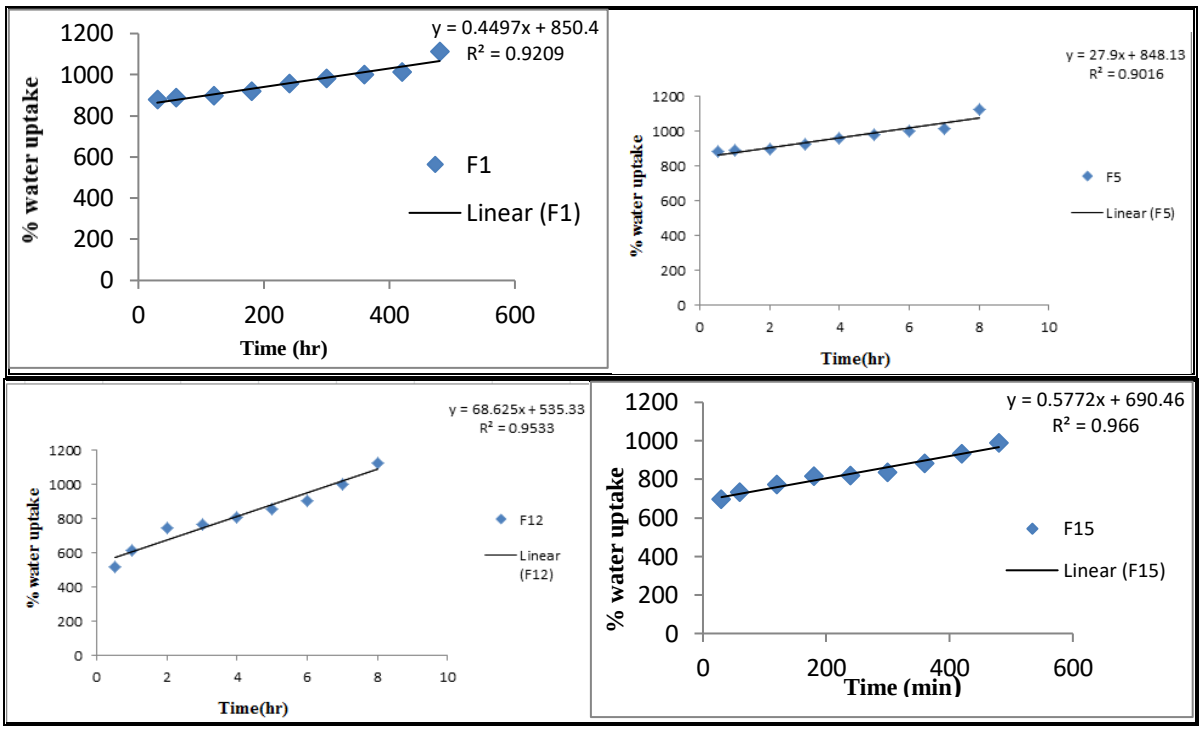

Fig 5:- Plot of log % water uptake vs log time as per the Vergnaud Model

Formulation	Kinetic constant (k)	Swelling exponent (n)	Correlation Coefficient(r^2)
F1	13.30	64.90	0.900
F5	13.37	27.9	0.901
F12	12.35	68.62	0.953
F15	16.57	34.63	0.966

Table 8:- The Characteristics Value Of The Kinetic Model, Calculated By Fitting The Water Uptake Data:

A value of ≤0.5 for n indicates a diffusion controlled mechanism in which the rate of diffusion of the liquid is much less as compared with rate of relaxation of the polymer segment. A value of (n=1) suggests that the stress relaxation process of polymer is very slow as compared with the rate of diffusion of the liquid. This means that the liquid diffuses through the polymer matrix at a constant velocity showing an advancing front making the limit of liquid penetration. Behind this front is swollen gel and ahead of it is the polymer in the glassy state.

From table 8 , it can be inferred that, value of n=0.1 to 0.4 shows change of tablet shape to cylindrical during swelling and the kinetics of water uptake by polymer matrices follow a diffusion controlled mechanism in which the rate of diffusion of the liquid is much less as compared with rate of relaxation of the polymer. Value of "k" represents the hydration rate of polymer which depends on nature of substituents present and the degree of substitution. From the obtained k values, it can be seen that, all polymer matrices exhibited high degree of hydration and water uptake, resulting in to formation of thick gel layer, thus sustaining the release of drug.

➢ *In-vitro dissolution studies*

The release profile obtained after *in-vitro* dissolution study of sustained release tablets of Metronidazole using HPMC K-100M & Polyox-WSR-303 shows that, Cumulative percent drug release at the end of 8 hours, from F1 & F5 was found to be 72.97±0.33% & 87.75±0.66 of drug release. On physical evaluation of tablets during dissolution study, it was found that tablets swell initially and form a strong viscous gel or contact with the dissolution medium. Percent drug release decreased with an increase in concentration of HPMC & Polyox-WSR-303 from 10% w/w to 40% w/w (F1-F8). This may be due to increase in thickness of swollen polymer gel layer, which is acting as a barrier to diffusion of the drug. The release study showed that, lesser quantity of HPMC K100M (10% w/w) was required as compared to HPMC K100M (40% w/w) for sustaining the drug release to adhere the vaginal mucosa for longer period of time. Also it was observed that tablets prepared with Polyox WSR-303 swells slowly in the initial stage of dissolution but later it swells to greater extent to adhere the vaginal mucosa for longer period of time.

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Cumulative % Drug Released								
Time (h)	**F1 HPMC K-100M-10 %**	**F2 HPMC K-100M-20 %**	**F3 HPMC K-100M-30 %**	**F4 HPMC K-100M-40%**	**F5 PEO-303-10%**	**F6 PEO-303-20%**	**F7 PEO-303-30%**	**F8 PEO-303-40%**
0.5	9.078±0.30	7.94±0.37	7.66±0.31	6.52±0.56	4.54±0.23	4.33±0.31	4.18±0.27	3.26±0.24
1	16.59±0.35	16.38±0.52	13.55±0.28	9.8±0.12	8.94±0.24	7.94±0.32	6.95±0.26	6.31±0.58
2	23.48±0.44	17.39±0.41	15.05±0.15	13.34±0.57	17.09±0.54	17.09±0.28	13.34±0.24	11.21±0.56
3	25.99±0.34	20.53±0.25	18.54±0.43	20.37±0.39	30.01±0.24	27.67±0.24	17.39±0.63	16.04±0.25
4	26.73±0.47	23.45±0.26	19.55±0.52	28.33±0.34	34.72±0.25	28.41±0.21	27.68±0.52	23.85±0.24
5	40.08±0.56	38.22±0.25	24.25±0.39	33.25±0.47	41.13±0.48	39.07±0.41	40.89±0.53	33.94±0.41
6	46.07±0.26	49.52±0.26	37.38±0.46	37.46±0.50	69.66±0.25	61.50±0.74	56.10±0.58	49.14±0.58
7	61.78±0.58	57.37±0.32	56.62±0.51	47.35±0.38	77.53±0.56	73.61±0.54	70.75±0.57	61.52±0.74
8	72.97±0.33	70.97±0.43	62.28±0.55	56.83±0.35	87.75±0.66	79.93±0.52	71.33±0.98	69.81±0.91

Table 9:- *In-Vitro* Dissolution Studies of Sustained Release Tablets of Metronidazle Using Hpmc K100m and Polyox-Wsr-303:

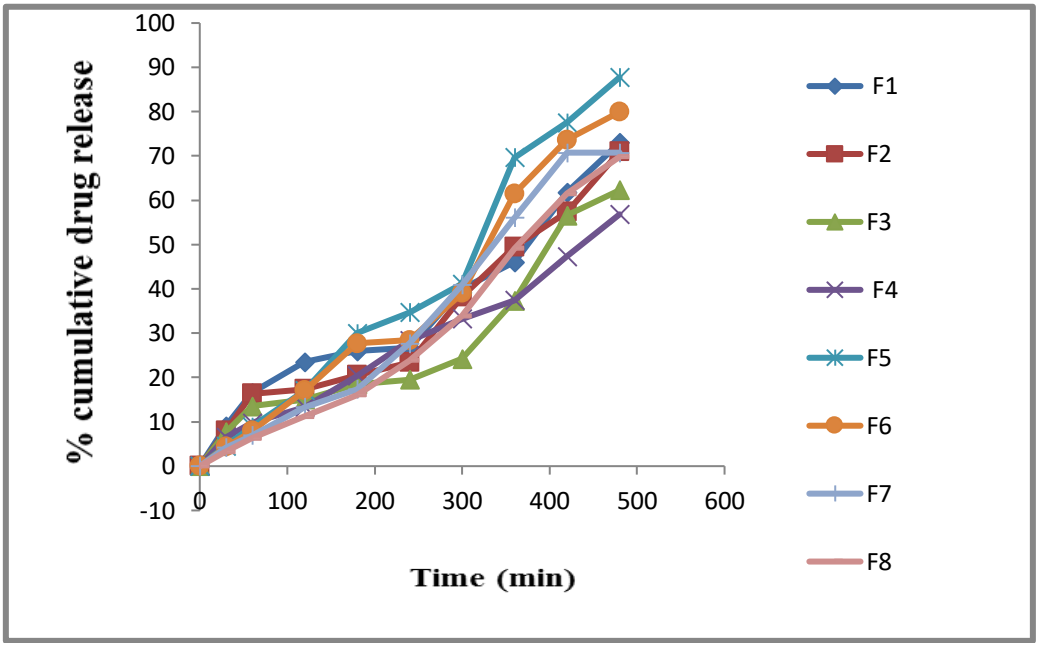

Fig 6:- Release profile of sustained release tablets of Metronidazole using HPMC K-100M & Polyox-WSR-303

Cumulative % Drug Released			
Time (h)	**F9 Xanthan Gum (20%)**	**F10 Xanthan Gum (30%)**	**F11 Xanthan Gum (40%)**
0.5	13.18±0.26	11.48±0.48	10.49±0.35
1	17.16±0.33	13.41±0.48	12.77±0.26
2	22.92±0.25	17.39±0.53	16.96±0.47
3	27.91±0.46	22.44±0.32	20.45±0.44
4	32.40±0.58	29.48±0.47	22.60±0.45
5	37.40±0.37	37.09±0.31	37.43±0.52
6	42.47±0.26	39.97±0.28	38.54±0.46
7	48.54±0.51	48.37±0.54	47.08±0.35
8	56.24±0.49	52.89±0.37	49.33±0.39

Table 10:- *In-Vitro* Dissolution Studies of Sustained Release Tablets of Metronidazle Using Xanthan Gum:

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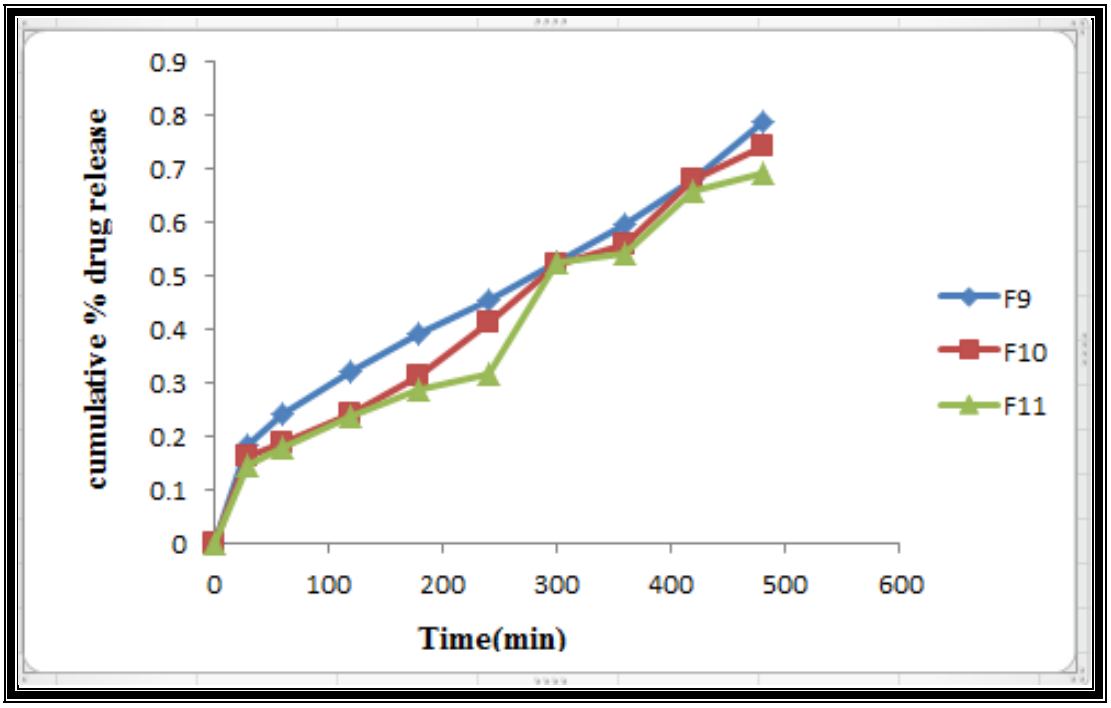

Fig 7:- Release profile of sustained release matrix tablets of Metronidazole using Xanthan Gum

With increase in polymer concentration in the formulation (F5 to F8), overall drug release was also decreased. after 8 hrs of dissolution study F5, F6, F7, & F8 was 87.75±0.66%, 79.93±0.52%, 71.33±0.98% , 69.81±0.91% released drug respectively.

Cumulative % Drug Released							
	F12	**F13**	**F14**	**F15**	**F16**	**F17**	**F18**
Time (h)	**HPMC K-100: Polyox - 303WSR (1:1) 10%**	**HPMC K-100: Polyox-303WSR (1:1) 20%**	**HPMC K-100: Polyox - 303WSR (1:1) 30%**	**HPMC K-100M: Gantrez (1:1) 10 %**	**HPMC K-100M: Gantrez (1:1) 20 %**	**HPMC K-100M: Gantrez (1:1) 30 %**	**HPMC K-100M: Gantrez (1:1) 40%**
0.5	7.80±0.29	6.24±0.25	5.53±0.21	11.77±0.46	9.57±0.55	8.72±0.42	7.80±0.41
1	18.72±0.48	13.69±0.24	9.58±0.25	13.69±0.24	12.27±0.34	10.85±0.36	10.22±0.52
2	30.92±0.27	20.22±0.21	15.75±0.27	17.89±0.35	17.67±0.15	15.75±0.51	15.19±0.23
3	41.30±0.39	23.36±0.20	18.88±0.29	26.98±0.18	23.57±0.44	26.68±0.38	25.55±0.58
4	49.64±0.17	34.08±0.23	31.16±0.25	36.43±0.36	33.09±0.25	30.75±0.27	27.20±0.89
5	54.44±0.34	44.18±0.54	43.88±0.28	55.38±0.52	42.05±0.21	41.20±0.36	29.50±0.25
6	69.09±0.55	56.77±0.53	52.57±0.29	69.76±0.53	56.13±0.35	54.64±0.28	42.15±0.26
7	72.68±0.24	60.52±0.52	55.60±0.27	72.60±0.32	62.71±0.52	58.24±0.54	50.62±0.23
8	90.93±0.45	70.22±0.50	59.07±0.31	86.92±0.43	67.10±0.32	64.25±0.35	60.67±0.21

Table 11:- *In-Vitro* Dissolution Studies Of Sustained Release Tablets Of Metronidazole With Various Polymer Combinations At Concentrations (1:1):

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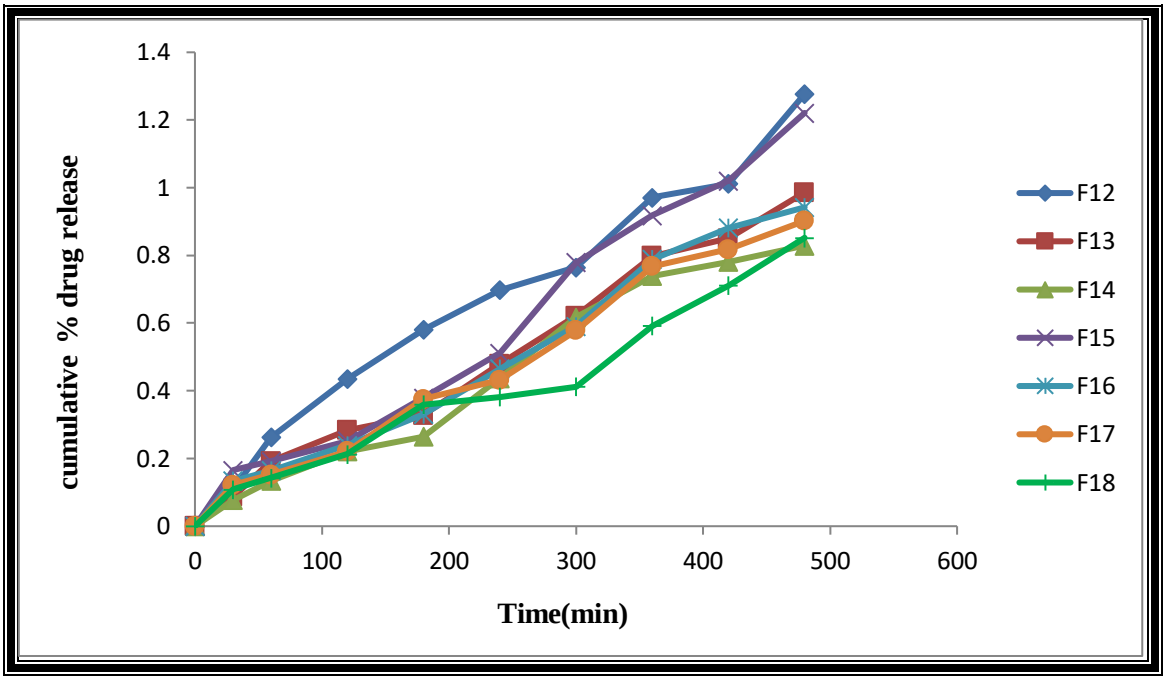

Fig 8:- Release profile of sustained release tablets of metronidazole using combination with various polymer combination at same ratio(1:1) i.e. HPMC K100 & Polyox WSR-303 and Gantrez & HPMC K-100M

With increase in polymer concentration in the formulation (F12 to F18), overall drug release was also decreased. After 8 hrs of dissolution study F12 F13, F14, F15, F16, F17 & F18 released 90.93±0.23%, 70.22±0.21%, 59.07±0.35%, 86.92±0.57%, 67.10±0.32, 64.25±0.34 and 60.67±0.21% drug respectively. The sustained release tablets of Metronidazole with Gantrez : HPMC K-100M (1:1) showed 86.92±0.43% drug release after 8h which may be due to slow hydration of polymers, that results in less swelling of polymer. Visual observation also shows less swelling of tablets prepared with Gantrez and HPMC K100. The tablets prepared with Polyox WSR-303:HPMC K-100M (1:1) showed 90.93±0.35% drug release after 8h, it is due to good swelling of HPMC K-100: Polyox WSR-303(1:1) which lead to faster release of drug than Gantrez : HPMC K-100M (1:1).

IV. KINETIC OF DRUG RELEASE

Formulation Code	Zero order	First order	Matrix Order		Korsmeyer Peppas		Hixon & Crowell
	R^2	R^2	R^2	K	R^2	N	R^2
F1	0.9740	0.9400	0.9247	0.9005	0.9679	0.6756	0.9580
F5	0.9846	0.9161	0.8922	0.1126	0.9944	1.0686	0.9472
F9	0.9387	0.9774	0.9870	2.1577	0.9885	0.5073	0.9694
F12	0.9415	0.9481	0.9941	0.5727	0.9920	0.8143	0.9869
F15	0.9895	0.9376	0.9173	0.6157	0.9584	0.7748	0.9653

Table 12:- Kinetic Values Obtained From Different Formulations of Metronidazole:

The results of release kinetic analysis from the sustained release matrix tablets are shown in table no 12. In general, Fickian diffusion was used to describe the release of the drug from the matrix tablets. However, in the case of swelling polymers, release kinetics of the drug did not follow Fickian diffusion because the polymer swells and changes volume. In order to describe drug release from swelling polymers, Korsmeyer and Peppas equation called the “Power law” was applied. This equation correlates two mechanisms of drug transport that seem independent, Fickian diffusion and a case-II transport, thereby describing the release of a drug from a swelling polymer. When n is 0.45, drug release is diffusion-controlled; when n is 0.89, drug release is swelling-controlled. When n is between 0.45 and 0.89, release can be defined as a combination of both phenomena. Table no.12 shows the values of n and all of the correlation coefficients for each formulation. Almost, all formulations have n values approximate 0.0160 to 1.0686, which indicate drug release is controlled by Fickian diffusion. Only formulation F5 showed n value as 1.0686 indicating nonfickian transport.

➢ *In-vitro mucoadhesion strength*

Formulation code	Mucoadhesive Strength (gms)	Force of adhesion (dyne/cm^2)
F1	101.93±0.24	10.0±0.02
F5	163.09±0.21	16.0±0.05
F9	103.09±0.24	13.0±0.05
F12	203.87±0.17	15.0±0.06
F15	112.13±0.30	20.0±0.03

Table 13:- *In-Vitro* Mucoadhesion Strength Measurement with Two-Armed Physical Balance:

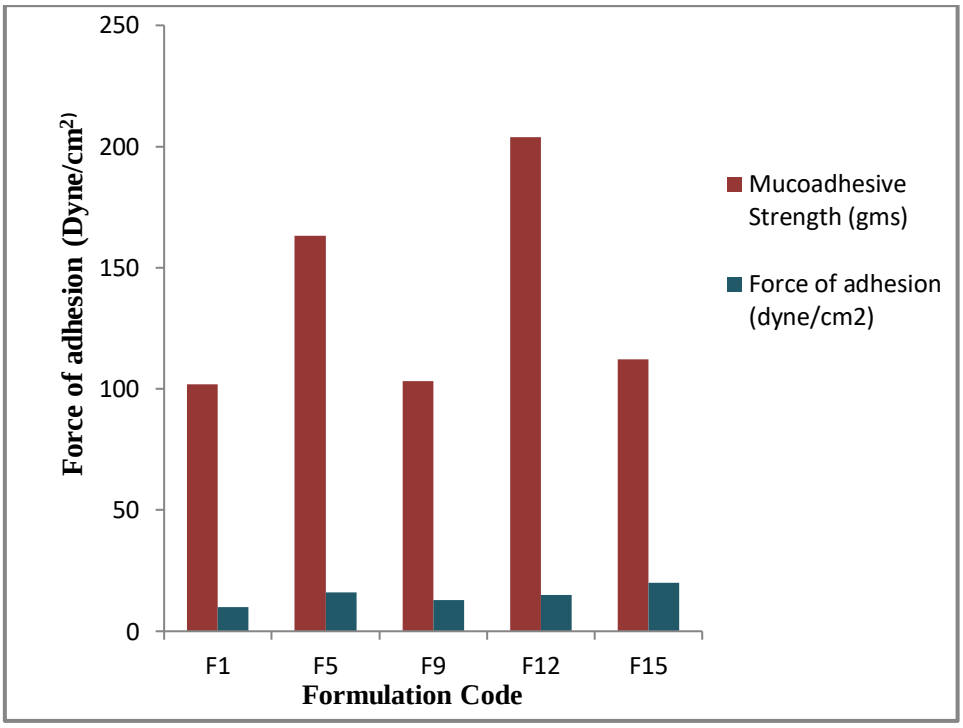

Fig 9:- *In-vitro* mucoadhesion strength measurement with two-armed physical balance

The bioadhesion characteristics were found to be affected by the nature and proportions of the bioadhesive polymers used. The peak detachment force is considered to be dependent on the formation of hydrogen bonds between the functional groups of the bioadhesive and the mucus. Physical entanglement is also related to the peak detachment forces as it induces chain inter-locking due to the inter-diffusion of the polymer chains into the mucus glycoproteins. Polyox-303 WSR and HPMC K-100M, are known to be good mucoadhesive polymers. It can be seen that all mucoadhesive polymers differ in their adhesion properties.

Each of the formulations comprising of mucoadhesive polymer can be arranged in order of their mucoadhesion as follows:

HPMC- K100: Polyox WSR-303 > Polyox WSR-303 > Xanthan gum > HPMC- K100 > Gantrez

V. CONCLUSION

Metronidazole is use as antiinfective activity and its half life is 8 hr and protein binding having less than 20% bound to plasma protein. Metronidazole is presently available in tablet dosage form and dose for women is 200mg once daily. The present work aim was to formulate and evaluate mucoadhesive vaginal tablets. the tablets were formulated using like HPMC K100M, Poyox-WSR-303, Xanthum Gum and Gantrez.

The polymer and their combination blends were prepared with polymer concentration of 10%, 20%, 30%, 40% and HPMC K-100M : Polyox (1:1), Gantrez : HPMC K-100M (1:1) as having ratio 1:1 of total weight of a tablet. evaluated for low bulk density, tapped bulk density, carr's compressibility index, Hausner ratio and angle of repose. It was found that, all polymer and their combination, blends with drug did not good flow properties and good compressibility. Then after adding binder mixed all the components, then passed through 60-mesh sieve, then add

70% ethanol was used as wetting agent to prepare the damp mass, the granules were prepared by passing through 18 mesh sieve and dried at 55°C.The dried granules were mixed with lubricants, glindant and compressed using single punch tableting machine by using 12mm punch.

The prepared tablets were evaluated for thickness, hardness, average weight, friability and percent drug content. It is found that, tablet passes all these parameters. *In-vitro* drug release studies the tablets with 10% have showed a good sustained release over a period of 8h. It is found that, as the polymer concentration increases, the drug release decreases. The tablet 20%, 30%, and 40% showed slow released than the 10%. The tablet prepared with showed good result HPMC K-100M:Polyox (1:1) than Gantrez:HPMC K-100M (1:1) of drug release 90.93±0.35% over a period of 8h.

The tablet formulations were evaluated for % Water uptake, IR and *in-vitro* mucoadhesive strength measurement. From all these evaluation parameters it is found that

- The % Water uptake by various polymers can be arranged in following order:
  Polyox WSR-303> HPMC K100M > Polyox WSR-303> HPMC K100M> Xanthan Gum.> Gantrez
- The *in-vitro* mucoadhesive strength by various polymers can be arranged in following order:
  Polyox WSR-303 > Gantrez > Xanthan gum > HPMC

Any presence of interactions in drug and polymers was checked by IR . It is found that, there is no interactions between drug and polymers.

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