Formulation And Evaluation of Ritonavir Sustained Release Matrix Tablets

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***Abstract*—Ritonavir is an antiretroviral drug which belongs to the class of protease inhibitor. It has short biological half-life (3 to 5hours) and the usual oral dosage regimen is 100-400mg in divided doses. The main aim of the study is to develop sustained-release matrix tablets of Ritonavir by using different ratios of polymers. A total of thirteen formulations are designed i.e., with varying concentration of polymer in each formulation. It has been observed that the formulations prepared in combination with HPMC K4M and Ethyl cellulose, HPMC K4M and Carbopol retarded the drug release over a period of 12hours. Among all these formulations F11 (HPMC K4M & Carbopol) has shown effective sustained release (95.62 ± 2.54) over an extended period of 12 hours. Hence, F11 was considered as best formulation. Results of the present study demonstrated that both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained release matrix tablets of Ritonavir. The investigated sustained release matrix tablet was capable of maintaining constant plasma concentration up to 12 hours. This can be expected to reduce the frequency of administration and decrease the dose dependent side effects.**

***Index Terms*—Ritonavir, Oral dosage forms, Sustained release**

I. INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drug via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process. The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended and specified period of time. This is generally accomplished by attempting to obtain "zero-order" release from the dosage form Zero-order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system (i.e. a constant release rate The overall objective is that, once the drug-carrier material has been injected or otherwise implanted or taken orally into the body, the drug is released at a predetermined rate for some desired period of time. Controlled release technology is relatively new field and as a consequence, research in this field has been extremely fertile and has produced many discoveries [1,2,3]. Non-immediate release delivery systems may be divided conveniently into 4 categories, Delayed release Sustained release Controlled release Prolonged release Site- specific release Drug properties relevant to sustained release formulations by Physiochemical properties and biological properties.

Hydrophilic Matrices

The matrix building material with fast polymer hydration capacity is the best choice to use in the hydrophilic matrix tablet formulations. Viscosity characteristics [4] of polymers are of great importance in determining the final release properties of the matrix tablet. Generally, the drug release rate is slower for a higher viscosity grade polymer.

Hydrophobic Matrices (Fat-Wax matrix tablets) [5]

The drug can be incorporated into a fat-wax granulation by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray drying technique. The mixture of active ingredients, waxy materials and fillers can also be converted into granules by compacting with a roller compactor or by direct compression. [6]

II. MATERIALS AND METHODS

Ritonavir [7] It is used to treat HIV infection and AIDS. Ritonavir is frequently prescribed with Highly Active Anti-Retroviral Therapy (HAART), not for its antiretroviral action, but as it inhibits the same host enzyme that metabolizes other protease inhibitors. This inhibition leads to higher plasma concentrations of other antiretroviral drugs, thus allowing them to lower their dose and frequency and also improving their clinical efficacy Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases.

III. METHODS

PRE-FORMULATION STUDIES

Determination of Solubility [9]

Phase solubility studies are carried out in order to determine the solubility of Ritonavir in various aqueous buffers via 0.1N HCl, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer, 4.5 pH acetate buffer and 0.1N NaoH. In this procedure, pure drug was dissolved in different aqueous buffers. Excess drug was added to buffer solutions in stoppered conical flask and kept on the rotary shaker for 48 hours at 25 ^{0}C. After 48 hours period the saturated solution was filtered through a filter paper, and analyzed by using UV spectrophotometer

❖ Construction of calibration curve of Ritonavir

• Preparation of Standard Curve

Accurately weighed amount of 50 mg of Ritonavir was transferred to a 50 ml volumetric flask. It was dissolved in sufficient amount of Methanol and volume was made up to 50 ml with 6.8 pH phosphate buffers, this gives a solution having concentration of 1mg/ml of Ritonavir stock solution. From this primary stock exactly 5ml of solution was withdrawn and diluted to 50 ml with 6.8 pH phosphate buffer. From this secondary stock 1, 2, 3, 4, 5, 6ml was taken separately and made up to 10 ml with 6.8 pH phosphate buffer to produce 10, 20, 30, 40, 50, 60, µg/ml respectively. The absorbance values were determined at 239 nm using U.V Spectrophotometer. A graph of absorbance Vs concentration was plotted. The same procedure was repeated in 7.4 pH phosphate buffer and 0.1N HCl.

Formulation development

Preparation of sustained release matrix tablets of Ritonavir

Matrix tablets were prepared by using kneading technique. First, the drug (Ritonavir) and polymer along with diluent MCC (microcrystalline cellulose) were passed through sieve no.80 and were mixed together uniformly by trituration in mortar- pestle (glass) for 10 minutes. To this mixture, distilled water was added in a small quantity to make a coherent mass. This coherent mass was then passed through sieve number 22 to obtain granules. These granules were dried in an oven at 60°C for 20 min. Then obtained dry Granule mixture was blended with 1% magnesium stearate and 0.5% talc for 5 minutes. After blending the granules for sufficient time the granule mixture was compressed using 12 station rotary tableting machine equipped with round, flat faced punches of 12-mm diameter. Polymer ratio was varied to get matrix tablets of varying polymer concentrations of ethyl cellulose, Carbopol and HPMCK4M. [10]

Table 1: Composition of Ritonavir sustained release matrix tablet

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Drug (Ritonavir)(mg)	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMC K4M (mg)	50	100	200	300	400	400	400	400	400	400	400	400	400
Ethyl cellulose (mg)	-	-	-	-	-	25	50	75	100	-	-	-	-
Carbopol (mg)	-	-	-	-	-	-	-	-	-	25	50	75	100
MCC(mg)	441	391	291	191	91	66	41	16	-	66	41	16	-
Magnesium stearate (mg)	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc (mg)	6	6	6	6	6	6	6	6	6	6	6	6	6

Evaluation of flow properties of the powder blend

i. Angle of Repose
ii. Bulk Density and Tapped Density
iii. Compressibility Index and Hausner Ratio

❖Evaluation of Ritonavir tablets [11]

There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters. The diameters and shape depend on the die and punches selected for the compression of tablets. The remaining specifications assure that tablets do not vary from one production lot to another. The following standards or quality control tests should be carried out on compressed tablets [The] formulated tablets of Ritonavir sustained release tablets were evaluated by the following studies:

General Appearance, Hardness test or Crushing Strength, [Uniformity] of weight or Weight variation test, Estimation of drug content, In-*vitro* dissolution studies

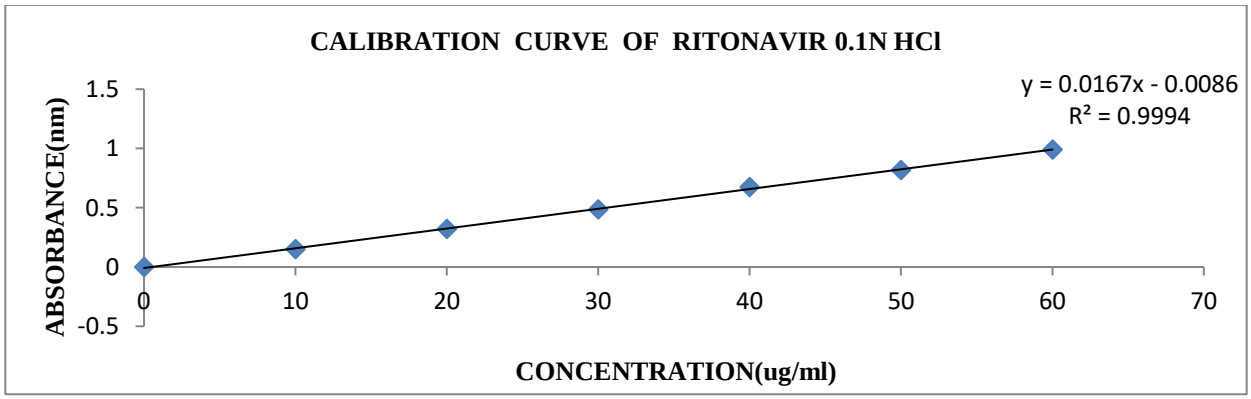
IV. RESULTS

Table 2: Solubility of Ritonavir in various buffers

S. No	Solvent used	Solubility(mcg/ml)	Inference
01	Methanol	87	Freely soluble
02	0.1N HCl	38.37	slightly soluble
03	pH buffer 7.4	30	slightly soluble
04	pH buffer 4.5	31.61	slightly soluble
05	0.1N NaOH	16.57	very slightly soluble
06	pH buffer 6.8	18.37	very slightly soluble
07	Distilled water	20.46	very slightly soluble

Table no 3: Standard graph of Ritonavir in 0.1N HCl

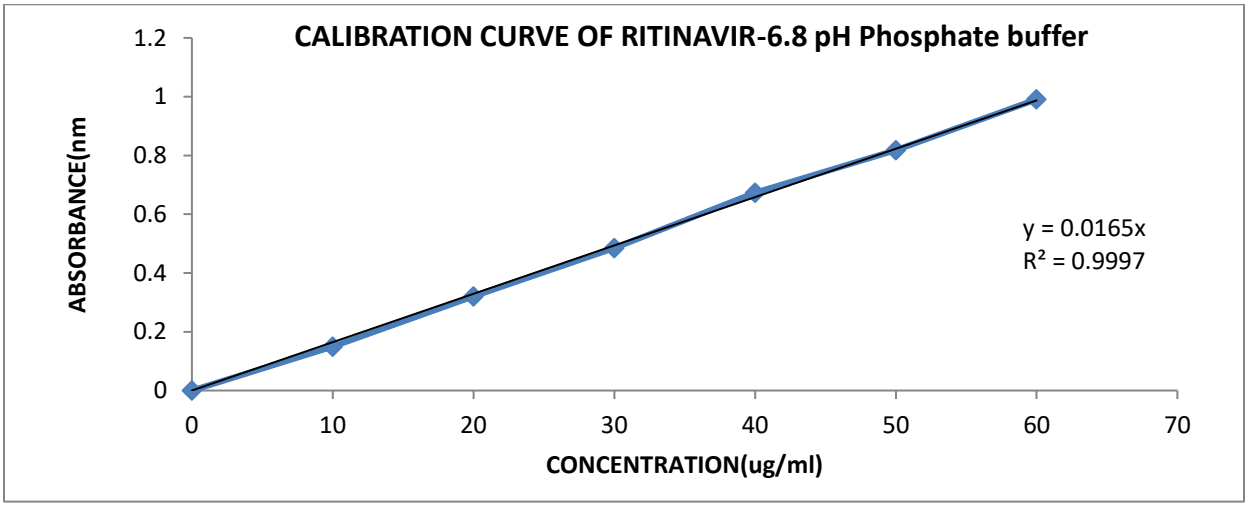
S.NO	Concentration(mcg/ml)	Absorbance(nm)
1	0	0
2	10	0.141
3	20	0.311
4	30	0.475
5	40	0.651
6	50	0.798
7	60	0.971



Graph:1 Standard graph of Ritonavir in 0.1N HCl

Table no 4: Standard graph of Ritonavir in 6.8 pH Phosphate buffer

S.no	Concentration(µg/ml)	Absorbance(nm)
1	0	0
2	10	0.149
3	20	0.321
4	30	0.485
5	40	0.673
6	50	0.818
7	60	0.991



Graph:2 Standard graph of Ritonavir in 6.8 pH Phosphate buffer

FTIR studies: Compatibility testing of drug with polymer

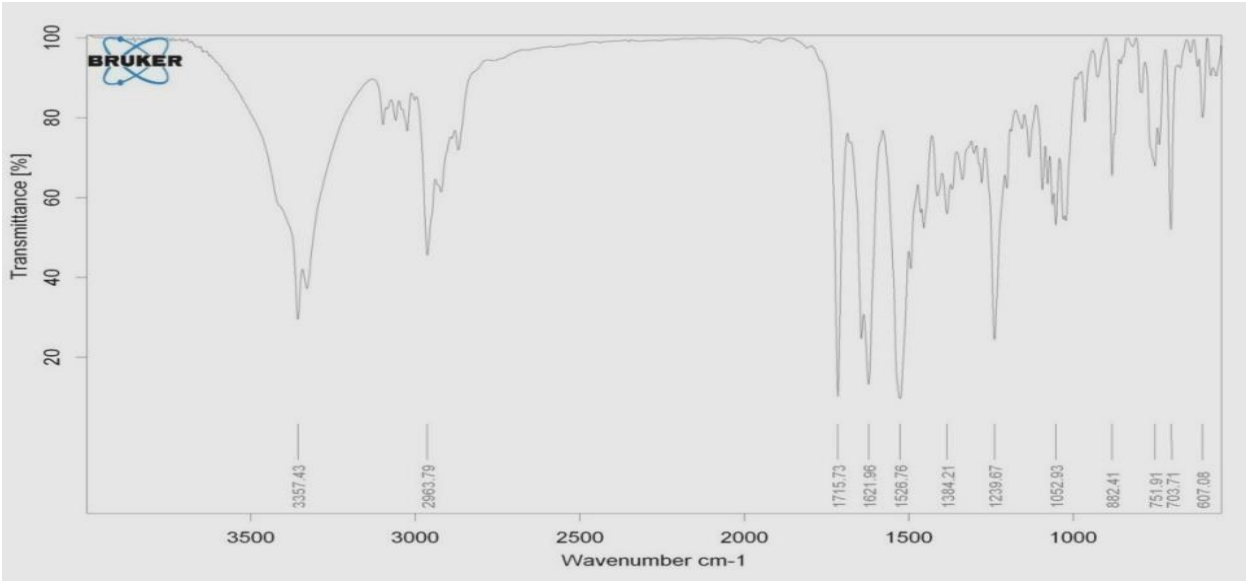


Figure no 1: FT-IR spectra of Ritonavir

Table no 5: Functional groups present in the Pure Ritonavir

S.No.	Wave number (cm^{-1})	Functional groups present
01.	3355.43	NH stretching
02.	2964.79	C-H stretching
03.	1714.73	C=O stretching
04	1621.66	C=O (amide) stretching
05	1526.7	N-H (2°-amide) bending
06	1384.21	O-H bending

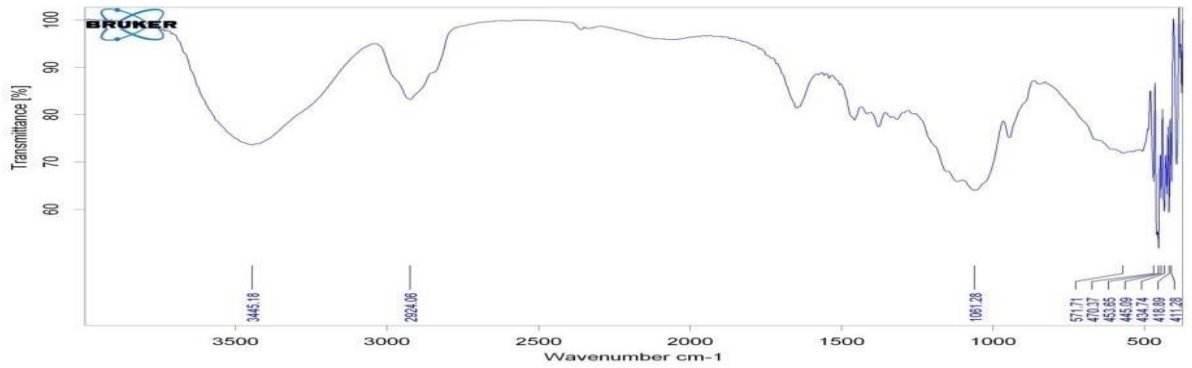


Figure no 2: FT-IR spectra of HPMCK4M

Table no 6: Functional groups present in the pure HPMC K4M

S.No.	Wave number (cm^{-1})	Functional groups present
01.	3435.34	OH stretching
02.	2931.90	CH stretching of methyl
03.	2839.31	CH stretching of CH_2
04.	1475.59	C-O stretching of secondary alcohol
05.	1123.57	C-O-C stretching
06.	1022.20	C-O stretching
07.	947.08	Overtone C-H deformation

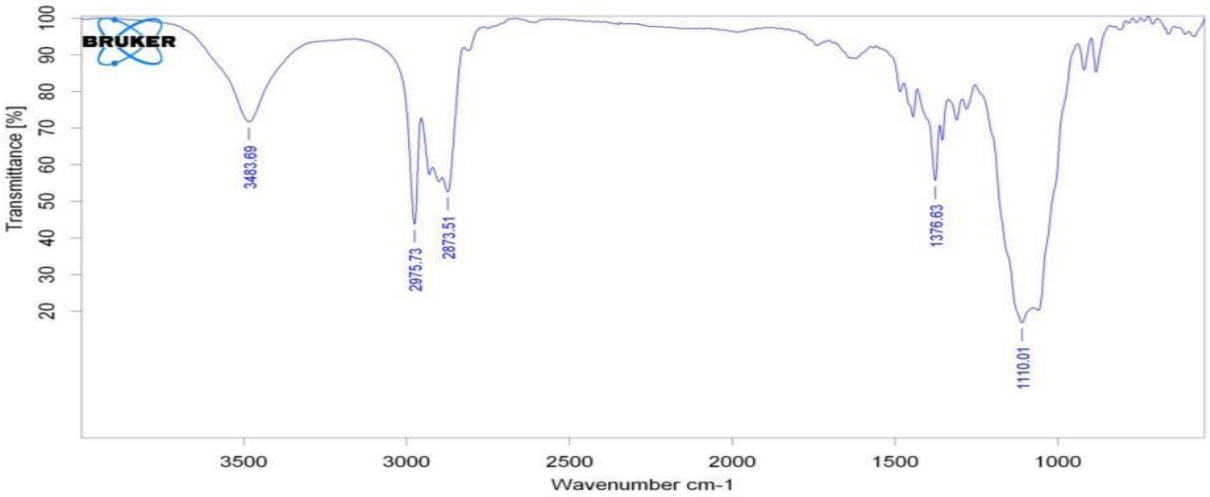


Figure no 3: FT-IR spectra of Ethyl cellulose

Table no 7: Functional groups present in the pure Ethyl Cellulose

S.No.	Wave number (cm^{-1})	Functional groups present
01.	3489.6	N-H (1°-amines) stretching
02.	2975.73	O-H stretching
03.	2873.51	C=O stretching
04	1370.63	CH_2 & CH_3 stretching
05	1110.01	C-C-C bending

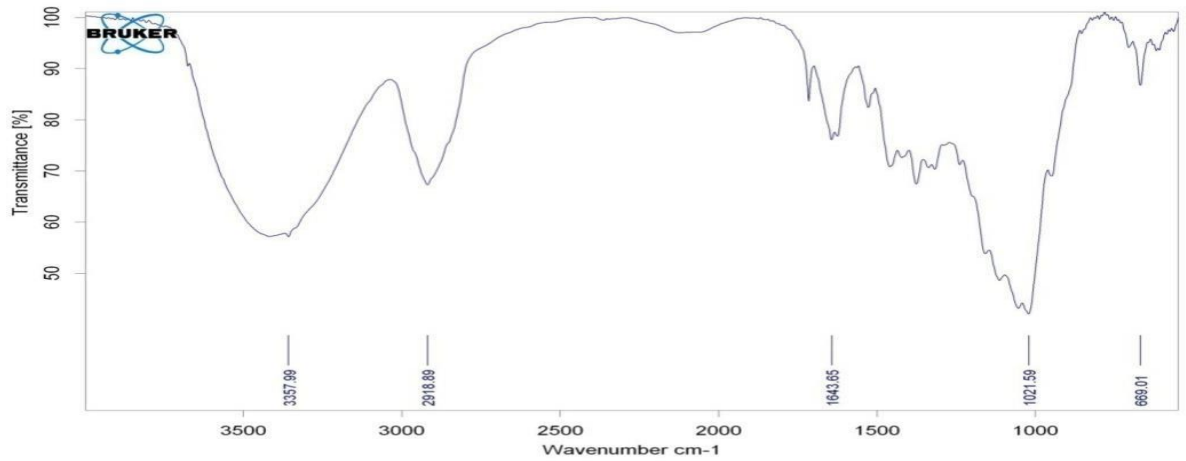


Figure no 4: FT-IR spectra of Ritonavir and HPMCK4M

Table no 8: Functional groups present in the Ritonavir and HPMC K4M

S.No.	Wave number (cm^{-1})	Functional groups present
01.	3357.9	O-H (alcohol)stretching
02.	2918.89	O-H (-COOH) stretching
03.	1643.65	C=C stretching
04	1021.59	C-N stretching

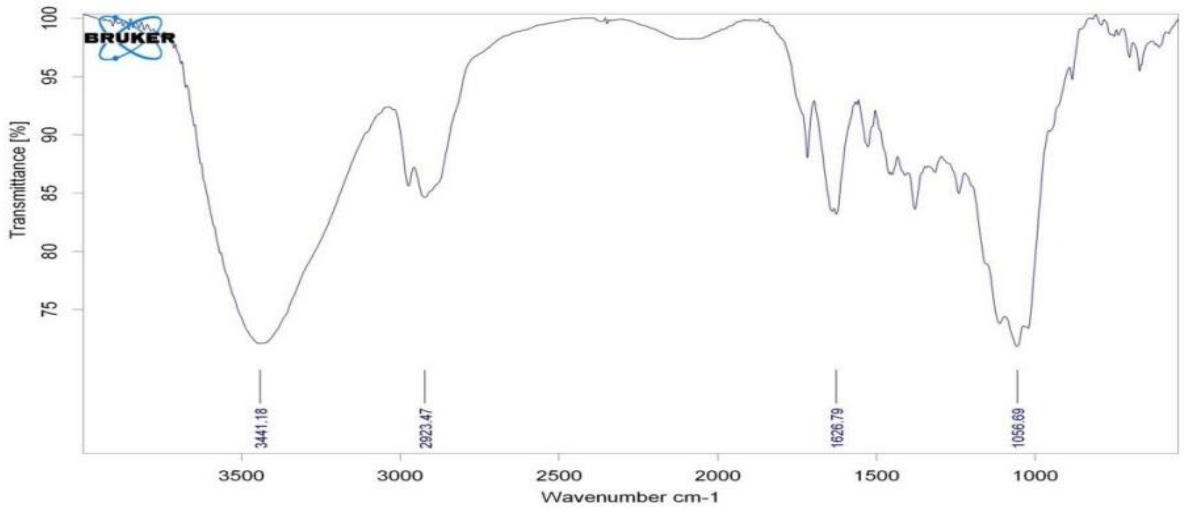


Figure no 5: FT-IR spectra of Ritonavir, HPMCK4M and Ethyl cellulose

Table no 9: Functional groups present in the Ritonavir HPMC K4M and Ethyl Cellulose

S.No.	Wave number (cm^{-1})	Functional groups present
01.	3441.18	N-H (1°-amines) stretching
02.	2923.47	CH_3, CH_2 & CH stretching
03	1628.69	C=C stretching
04	1058.59	C-N stretching

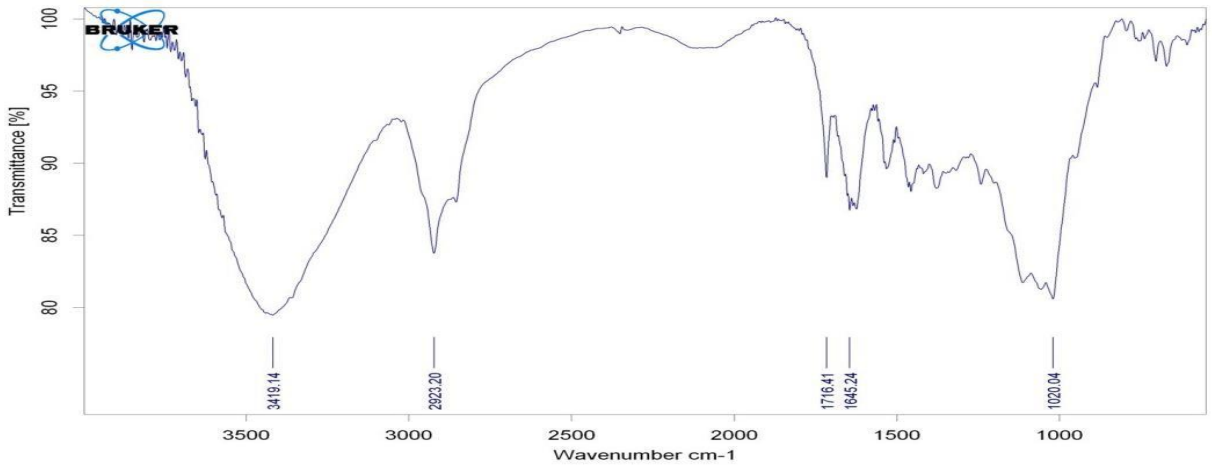


Figure no: 6 FT-IR spectra of Ritonavir, HPMCK4M and Carbopol

Table no 10: Functional groups present in the Ritonavir HPMC K4M and Carbopol

S.No.	Wave number (cm^{-1})	Functional groups present
01.	3419.18	O-H (alcohol) stretching
02.	2023.20	C=C stretching
03.	1716.41	C=O (saturated ketone) stretching
04	1645.59	C=C (symmetry)stretching
05	1020.06	C-N stretching

- Note**:** The incompatibility studies are performed for drug, polymers and physical mixtures for drug and polymers by Fourier transform infra-red (FTIR) spectroscopy. There is no incompatibility found between drug and polymers. The spectra obtained from FTIR studies at wavelength from 4000cm^{-1} to 450cm^{-1}

V. CHARACTERIZATION OF POWDER BLEND

Table11: PREFORMULATION PARAMETERS

Formulations	Angle of repose(è)*±SD	Bulk density (gm/cm3) *±SD	Tapped density (gm/cm3) *±SD	Carr's index (CI)*±SD	Hausner's ratio (HR)*±SD
F1	29.9±0.2	0.53±0.2	0.62±0.4	14.51±0.4	1.16±0.05
F2	28.3±0.1	0.51±0.5	0.61±0.1	16.39±0.2	1.19±0.02
F3	26.9±0.3	0.52±0.3	0.63±0.2	17.46±0.2	1.21±0.01
F4	26.4±0.3	0.47±0.4	0.54±0.1	12.96±0.1	1.14±0.03

F5	27.6±0.2	0.49±0.3	0.55±0.3	10.90±0.3	1.12±0.05
F6	23.7±0.5	0.48±0.1	0.57±0.6	15.78±0.1	1.18±0.04
F7	22.4±0.8	0.46±0.2	0.53±0.5	15.21±0.4	1.15±0.03
F8	24.3±0.2	0.51±0.4	0.58±0.2	17.60±0.3	1.13±0.01
F9	21.9±0.6	0.45±0.2	0.51±0.1	12.90±0.5	1.13±0.04
F10	26.5±0.3	0.52±0.3	0.58±0.6	10.34±0.2	1.11±0.02
F11	28.3±0.7	0.49±0.6	0.54±0.4	9.25±0.6	1.10±0.03
F12	29.6±0.2	0.53±0.5	0.59±0.3	10.16±0.1	1.11±0.01
F13	26.7±0.3	0.49±0.2	0.57±0.1	16.32±0.03	1.16±0.01

*All the values are expressed as mean± SD, n=3

VI. EVALUATION OF SUSTANIED RELEASE MATRIX TABLETS

Table 12: EVALUATION PARAMETERS

FORMULATION CODE	WEIGHT VARIATION (±SD)	FRIABILITY (%)	THICKNESS (mm) (±SD)	HARDNESS (kg/cm2)(±SD)	DRUG CONTENT (%)(±SD)
F1	598±2.9	0.43	4.3±0.07	6.2±0.2	99.5±1.4
F2	602±1.5	0.56	4.5±0.01	6.1±0.4	101.1±1.1
F3	609.±0.7	0.42	4.4±0.06	6.3±0.4	99.08±0.3
F4	602±2.4	0.64	4.5±0.02	6.5±0.1	102.4±0.6
F5	593±3.2	0.38	4.6±0.05	6.2±0.3	99.1±1.5
F6	603±1.3	0.75	4.3±0.04	6.1±0.4	98.2±0.4
F7	595±3.9	0.32	4.4±0.04	6.4±0.2	99.4±1.1
F8	606±0.4	0.58	4.3±0.05	6.6±0.1	98.5±1.8
F9	602±2.5	0.45	4.5±0.02	6.3±0.3	100.4±0.6
F10	597±1.8	0.63	4.4±0.05	6.2±0.2	99.7±1.5
F11	607±1.4	0.47	4.6±0.04	6.1±0.4	97.8±1.2
F12	599 ±2.3	0.68	4.5±0.03	6.3±0.1	102±0.3
F13	609.±1.1	0.42	4.4±0.06	6.2±0.3	101.2±1.4

*All the values are expressed as mean± SD, n=3

In-Vitro Dissolution Studies

Table13: *In-vitro* release of Ritonavir from formulations F1 to F5

Time (hrs)	F1	F2	F3	F4	F5
	%DR±SD	%DR±SD	%DR±SD	%DR±SD	%DR±SD
0	0	0	0	0	0
0.25	13.44±1.32	12.31±1.57	13.68±1.65	14.11±1.84	13.89±1.22
0.5	17.21±0.95	17.1±0.93	18.05±0.93	19.06±1.64	19.06±2.85
1	23.68±0.64	25.59±1.45	27.61±1.38	28.29±2.23	28.18±1.36
2	32.23±1.71	34.03±1.21	39.2±2.18	40.78±0.87	40.55±1.96
3	40.21±1.82	42.63±0.96	47.19±1.49	49.38±1.69	49.21±0.82
4	46.74±2.63	50.79±2.08	53.04±1.78	56.08±1.32	57.37±2.67
5	50.56±1.03	56.19±1.97	59.06±2.29	61.31±2.04	64.68±1.44
6	54.39±2.18	60.18±2.24	63.56±1.61	65.25±1.75	69.18±1.72

7	56.81±1.66	63.0±1.45	66.93±0.93	68.62±1.41	73.68±1.65
8	58.5±1.05	65.81±1.76	70.31±1.76	72.56±1.93	77.06±1.98

Values are represented as average ± standard deviation of (n=3)

Table14: *In-vitro* release of Ritonavir from formulations F6 to F9

Time (hrs)	F6	F7	F8	F9
	%DR±SD	%DR±SD	%DR±SD	%DR±SD
0	0	0	0	0
0.25	14±0.64	12.82±1.14	11.75±1.3	9.5±0.72
0.5	19.35±1.57	17.94±2.37	14.45±0.94	12.65±1.44
1	27.61±0.81	25.25±0.92	21.99±1.48	19.63±0.81
2	38.47±1.61	36.22±1.55	32.28±1.91	26.04±2.57
3	47.19±1.34	44.49±1.57	39.03±1.44	33.46±2.34
4	56.08±2.47	53.49±2.36	44.83±2.29	38.08±1.61
5	64.68±0.91	59.62±1.61	49.83±1.58	42.8±1.92
6	71.43±1.64	64.12±2.96	55.06±0.86	46.8±1.4
7	77.62±2.02	68.06±1.75	61.31±2.36	50.56±2.49
8	83.81±2.38	73.12±1.34	65.25±1.94	55.23±1.86
9	90±1.28	78.18±2.56	69.18±1.41	61.31±2.81
10	96±1.46	84.37±1.84	73.68±2.75	66.37±1.66
11	80.43±1.03	87.43±2.09	78.18±1.64	72.56±1.95
12	78.75±0.57	90.63±2.48	84.37±2.08	77.62±2.49

Values are represented as average ± standard deviation of (n=3)

Table no 15: *In-vitro* release of Ritonavir from formulations F10 to F13

Time (hrs)	F10	F11*	F12	F13
	%DR±SD	%DR±SD	%DR±SD	%DR±SD
0	0	0	0	0
0.25	13±1.62	12.43±1.18	11.7±1.63	10.06±0.64
0.5	16.48±1.14	15.52±1.58	14.23±0.84	12.09±0.81
1	20.05±0.93	20.41±0.91	18.28±1.36	16.7±0.79
2	29.08±1.58	28.06±1.04	25.2±0.92	22.1±1.23
3	39.09±1.33	37.01±2.37	33±1.75	29.08±1.11
4	48.26±1.66	45.5±1.54	42.24±3.02	37.06±1.62
5	57.37±2.12	53.38±1.61	50.11±0.86	44±2.48
6	65.25±1.54	60.75±1.03	56.08±2.34	51.8±1.73
7	75.37±2.02	69.75±3.02	64.68±1.92	59.06±2.05
8	82.12±2.27	78.18±2.74	74.25±1.38	66.37±1.84
9	88.87±1 .94	84.93±1.63	79.31±2.64	72.56±1.36
10	93.93±2.14	89.43±2.03	83.81±1.91	76.5±2.37
11	90.56±1.28	92.81±1.64	87.75±1.55	80.43±1.41

12	86.62±1.72	95.62±2.54	90±2.18	83.75±1.93

Values are represented as average ± standard deviation of (n=3)
F11 was found to be the best formulation

Release Kinetics
Table16: Release rate of Ritonavir from formulations (F11)

Formulation	R^2				Peppas n
	Zero	First	Higuchi	Peppas	
F11*	0.9594	0.9869	0.9726	0.9790	0.486

VII. DISCUSSSION

- The present aim of the study is to develop sustain release matrix tablets of Ritonavir prepared by wet granulation method using controlled release polymer i.e.., HPMC K4M, Ethyl cellulose and Carbopol.
- The drug (100 mg) was mixed with polymer and excipients and compressed in to tablets (600 mg) for these thirteen formulations are designed i.e.., F1,F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13 with varying concentration of polymer in each formulation.
- The drug solubility was studied spectrophotometrically with different solvents. It also found that Ritonavir was freely soluble in Methanol, slightly soluble in 0.1N HCl, pH buffer 7.4 and pH buffer 4.5 very slightly soluble in 0.1N NaOH, pH buffer 6.8 and distilled water.
- The incompatibility studies are performed for drug, polymers and physical mixtures for drug and polymers by Fourier transform infra-red (FTIR) spectroscopy. There is no incompatibility found between drug and polymers. The spectra obtained from FTIR studies at wavelength from 4000cm^{-1} to 450cm^{-1}
- Preformulation parameters are performed. Angle of repose was less than 40° and Carr's index values were less than 23 for all the formulations indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.
- The evaluation parameters are performed and results were satisfactory and within the acceptable limits for the uniformity of weight, hardness, thickness, friability and drug content of the tablets.
- The formulation F1, F2, F3, F4, F5 were prepared by HPMC K4M as the rate controlling polymer with different ratios i.e., 50mg, 100mg, 200mg, 300mg, 400mg of total weight of tablet (600mg) and the in-vitro drug release were found to be 58.5%, 65.8%, 70.31%, 72.56% and 77.06% for 8hrs respectively
- The release rate of F5 was found to be higher when compared to F1, F2, F3 and F4. This may be due to increase in the concentration of hydrophilic polymer (HPMCK4M) retards the release of drug from the dosage form.
- The formulation F6, F7, F8, F9 were prepared by HPMC K4M (hydrophilic polymer) along with Ethyl Cellulose (hydrophobic polymer) as the rate controlling polymer with different ratios i.e., 25mg, 50mg, 75mg, 100mg of total weight of tablet. The invitro drug releases were found to be 78.75%, 90.61%, 84.37% and 77.62% for 12 hrs respectively.
- The drug release was found to be lowest drug release with Ethyl Cellulose. This is because as Ethyl Cellulose was extensively hydrophobic in nature with lower wettability and due to this formation of pores and cracks did not occur to facilitate drug release.
- The formulation F10, F11, F12, F13 were prepared by HPMC K4M along with Carbopol as the rate controlling polymer with different ratios i.e., 25mg, 50mg, 75mg, 100mg of total weight of tablet which shows the drug release of 86.62%), 95.62%, 90%, 83.75% for 12hrs respectively.
- The formulations prepared by the combination of HPMCK4M and Carbopol extended the drug

release till the end of 12th hour. This is probably due to the formation of stronger hydrogen bonding between the carboxyl groups of Carbopol and hydroxyl groups of HPMC K4M

- From all the prepared sustained release matrix tablet of Ritnovir, it was concluded that F11 shows better sustainable drug release form the dosage form i.e., 95.62% for 12 hrs respectively.
- *In-Vitro* drug release study has revealed that by increasing concentration of polymer, release rate of drug was retarded and results confirmed that the release rate from matrix tablets depends on type and concentration of polymer.
- The drug release kinetics was studied for the best formulation (F11) and the results obtained were tabulated shown in table no.21 and fig no.12. From the results, it states that the drug releases from the dosage form follows *First-Order release* and *Erosion mechanism* of polymer.

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