FORMULATION AND EVALUATION OF HYDRODYNAMICALLY BALANCED SYSTEM OF MOLNUPIRAVIR.

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ABSTRACT

Molnupiravir were formulated to increase the bioavailabilty and to showcontrolled release of drug.Molnupiravir is anti-viral drug with oral bioavailability of 50%

It is the largest prescribed drug for this indication, worldwide. Floating drug delivery systems, that have been used to boost the gastric residence and the floatation time in the gastro intestinal tract. The study included formulation of floating tablets using polymers like HPMC and natural gumsgum as matrix forming agents. The tablets were prepared by direct compression technique. FTIR, conformed that there was no incompatibility between the polymer and the drug. The tablet showed good in vitro release. Drug release was through swelling and abided by the gellation mechanism

The main objective is to develop Twise-daily sustained release gastro-retentive floating system of Molnupiravir in an economical way by using HPMC and natural gums. Fourteen formulations of floating matrix tablets of Molnupiravir(F1 – F14) were prepared by using different polymers and additives (HPMC K100M, HPMC K15M, HPMC K4M, Guar gum Xanthan gum PEO, sodium bicarbonate, Avicel PH-102, Talc, Magnesium stearate) at different concentrations by direct compression method. The formula 11 was found to be optimum and released 98.47% of Molnupiravirin 24hrs. .

1. INTRODUCTION:

1.1 MODIFIED RELEASE ORAL DRUG DELIVERY SYSTEMS:

The oral route represents nowadays the predominant and most preferable route for drug delivery. Unlike the majority of parenteral dosage forms, it allows ease of administration by the patient and it's the natural, and therefore a highly convenient way for substances to be introduced into the human body.

Oral drug delivery systems (DDS) are mainly immediate release (conventional) drug delivery systems which are intended to disintegrate rapidly, and exhibit instant drug release. They are associated with a fast increase and decrease, and hence fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side effects. Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma concentration due to metabolismand excretion leading to poor patient compliance.

In order to overcome the drawbacks associated with conventional drug delivery systems, several technical advancements have led to the development of Modified release systems that could revolutionize method of medication and provide a number of therapeutic benefits.
Modified release systems, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance(reducing the frequency of dosing), as well as reducing the side effects.Oral modified release delivery systems are most commonly used for 1) delayed release (e.g., by using an enteric coating); 2) extended release (e.g., zero-order, first-order, biphasic release, etc.); 3) programmed release (e.g., pulsatile, triggered, etc.) and 4) site specific or timed release
(e.g., for colonic delivery or gastric retention). Extended, sustained or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery devices, with predictability and reproducibility in the drug release

Kinetics **.**Delayed release dosage forms are distinguished from the ones mentioned above as they exhibit a pronounced lag time before the drug is released. Oral extended release dosage forms offer the opportunity to provide constant or nearly constant drug plasma levels over an extended period of time following administration. Two basic types of extendedrelease dosage forms are designed to generate temporal input profile for drug delivery].
Matrix systems: It consists of rate controlling polymer, which is uniformly dissolved or dispersed with drug.
Reservoir system: This type of system separates drug compartment from polymer membrane that permits a diffusion barrier to yield drug flux of either zero order or first order.

2. MATERIALS AND METHODS:

TABLE 1 : LIST OF MATERIALS

S.No.	Materials	Source
1	Molnupiravir	Gift sample from Reddys pharmaLtd.,Hyderabad
2	HPMC K4M	Sd fine chem Ltd.
3	HPMC K15M	Sd fine chem Ltd.
4	HPMC K100M	Sd fine chem Ltd.
5	Xanthan gum	Sd fine chem Ltd.
6	Guar gum	Sd fine chem Ltd.
7	PEO	Colorcon Asia Pvt Ltd.,Goa
8	Sodium bicarbonate	S.D. Fine chemicals Ltd., Mumbai
9	Avicel PH-102	Signet chemical corporation, Mumbai
10	Talc	S.D. Fine chemicals Ltd., Mumbai
11	Magnesium stearate	S.D. Fine chemicals Ltd., Mumbai
12	Hydrochloric acid	LobaChemiePvt. Ltd., Mumbai

❖ METHODOLOGY :

2.1. PRE-FORMULATION STUDIES:

Pre-formulation testing is the first step in the rational development of dosage forms. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

The objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

The use of pre-formulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimization of the drug product quality.

- **Organoleptic evaluation:**

Organoleptic characters like color, odor, and taste of drug were observed and recorded using descriptive terminology.

- **Development of analytical method:**

A survey of literature reveals that few analytical methods such as , UV/VIS spectrophotometric methods were reported for the estimation of Molnupiravir in formulations.A simple, economic, convenient, reproducible and precise UV spectrophotometric method was employed for the assay as well as for the in-vitro dissolution studies.

- **UV Spectroscopy:**

A) Calibration curve forMolnupiravir

In the present study, Molnupiravir was analysed by UV spectrophotometer in distilled water as dissolution medium. Standard curves of Molnupiravirisprepared using different concentrations.

B) Determination of UV Absorption Maxima (λ_{max}) of Molnupiravir :

The lambda max of the drug was determined by scanning wavelength between 235-276nm using UV spectrophotometer.

C) Preparation of standard solution of Molnupiravir:

- Accurately weigh Molnupiravir was transferred to a 50 ml volumetric flask make up the volume upto the mark with distilled water.
- A stock solution contained 1000µg/ml of Molnupiravir.

D) Preparation of calibration curve of molnupiravir:

- Stock solution of Molnupiravir were pipette out (0.5 ml; 0.75ml; 1ml; 1.25ml; 1.5 ml) in five test tubes of 10ml.
- The volume is made up to the mark with the Distilled water and produce the concentration rom 50-150µg/ml.
- The absorbance of the solution was measured at against distilled water as a blank.

- **Determination of solubility:**

The following procedure was employed to determine the solubility of Molnupiravir indist Water.

Excess of BCF was added to 5mL of dist Water. in a 25mL stoppered conical flask and the mixture was shaken for 24 hours at room temperature (28±1^{o}C) on rotary shaker. After 24 hours of shaking 1mL aliquots were withdrawn at different time intervals and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for Molnupiravir by measuring the absorbance at 235-276nm. Shaking was continued until three consecutive estimations were same.

- **Drug–excipient compatibility study:**

In the preparation of the tablets, drug and other excipients may interact as they are in contact with each other, which could lead to the instability of dosage form. Preformulation studies regarding the drug-excipient interaction are therefore very crucial in selecting appropriate excipients. FT-IR spectroscopy was employed to ascertain the compatibility between the drug and the selectedexcipents. The drug alone and physical mixtures of drug with excipients (1:1 ratio) were scanned separately in the range of 4000-500 cm^{-1} using KBr disc method.

Procedure*:* 1-2mg of the sample to be examined was triturated with 300-400 mg specified quantity of finely powered and dried potassium bromide. These quantities are usually

sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The Infrared spectrum was recorded by using FT-IR spectrophotometer and observed for characteristic peaks of the drug.

- **Determination of micromeritic properties of the powder blends:**

The following tests were performed in-order to determine the flow properties of the powder blends.

Bulk Density:

Bulk density is of great importance when one considers the size of a high-dose drug product or homogeneity of a low-dose formulation. The homogeneity of a low-dose formulation in which there are large differences in drug and excipient could lead to segregation.

Apparent Bulk density (g/mL) was determined by pouring (pre-sieved 18-mesh) gently 10g of the sample through a glass funnel into a 50mL graduated cylinder. Then after pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as mL. The volume measure was called as the bulk volume and the bulk density was calculated by following formula.

Bulk density = Weight of powder / Bulk volume

Tapped Density:

Tapped density (g/mL) was determined by pouring gently 10g of sample through a glass funnel into a 50mL graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained (100 taps).Volume occupied by the sample after tapping was recorded as the tapped volume (mL) and tapped density was calculated from the formula.

Tapped density = Weight of powder / Tapped volume

Carr's Compressibility Index (%):

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density.

High density powders tend to possess free flowing properties. A useful empirical guide is given by the Carr's index or compressibility index calculated from bulk density and tapped density.

Compressibility index = 1 — 100

Where,V = volume of powder blend before tapping

V_0 = volume of powder blend after 100 tappings

Hausner'sratio:

Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value indicates better flow and vice versa.

Hausner's ratio = Tapped density /Bulk density

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. Angle of repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed funnel method and is the measure of the flowability of powder/granules.

A funnel with 10mm inner diameter of stem was fixed at a height of 2cm over the platform. The sample was slowly passed along the wall of funnel, till the cone of the powder formed. Angle of repose was determined by measuring the height of the cone of powder and radius of the heap of the powder. Angle of repose was calculated using the following formula

$\theta = \tan^{-1}(h/r)$

where,

θ = Angle of repose**,** h = Height of the powder cone **,**r = Radius of the powder cone

Table 2: Formulation of floating matrix tablets of molnupiravir :

Ingredients(%w/ wof500 mg tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Molnupiravir	400	400	400	400	400	400	400	400	400	400	400	400	400	400
HPMC K100M	30	40	20	25	30	40	40	—	—	40	—	—	—	—
HPMC K15M	—	—	—	—	—	—	—	40	—	—	40	—	—	—
HPMC K4M	—	—	—	—	—	—	—	—	40	—	—	40	—	20
Sodium bicarbonate	20	20	5	5	5	5	7	10	10	—	—	—	40	20
Avicel PH -102	30	20	55	50	45	35	33	30	30	20	20	20	20	20
Talc	10	10	10	10	10	10	10	10	10	33	33	33	33	33
Magnesium stearate	10	10	10	10	10	10	10	10	10	2	2	2	2	2
Total	500	500	500	500	500	500	500	500	500	5	5	5	5	5

2.2 POST-COMPRESSION PARAMETERS:

- **Hardness[51]:**

The hardness of the tablets was measured with a Monsanto hardness tester. The results reported were mean and standard deviation of 3 tablets for each formulation and expressed in kg/cm^2. Oral compressed tablets normally have a hardness of 4-9 kg/cm^2.

- **Friability (%F) [51]:**

20 tablets from each batch were selected randomly and weighed. These pre-weighed tablets were subjected to friability testing using Roche friabilator for 100 revolutions. The tablets were subjected to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the %friability

%F = 1 – (Final weight / Initial weight) 100

A maximum weight loss of not more than 1% of the tablet weight during the friability test is generally considered acceptable.

- **Weight variation:**

20 tablets were randomly selected from each batch, weighed individually. The average weight and standard deviation of 20 tablets was calculated.

- **Drug content uniformity:**

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. Accurately weighed powder sample (500mg) equivalent to 23mg ofMolnupiravir was transferred to a 100mL volumetric flask, and made upto volume distil water The contents of the volumetric flask were sonicated for 15 minutes inorder to extract the drug into dist Water. The solution was then filtered, suitably diluted with dist Water. and the absorbance was measured at 235-276nm.

- **In-vitro drug release study [43]:**

The tablet samples were subjected to in-vitro dissolution study using USP XXI type II (Paddle method) Dissolution rate test apparatus at a temperature of 37±0.5°C and 50 rpm speed. 900 mL of dist Water was used as the dissolution medium. Aliquot equal to 5mL was withdrawn at specific time intervals for 24 hours. The dissolution media volume was complimented with fresh and equal volume of blank media dist Water The aliquots were filtered and assayed for Molnupiravir by measuring the absorbance at 235-276nm against blank (dist Water).

Table 3: Dissolution parameters

Apparatus used	USP XXI tablet dissolution test apparatus-II
Dissolution medium	Dist Water
Dissolution medium volume	900 mL
Temperature	37±0.5ºC
Paddle speed	50 rpm
Sample volume withdrawn	5 mL
Absorbance measured at	235-276nm

- **MATHEMATICAL MODEL FITTING OF OBTAINED DRUG RELEASE DATA:**

The rate and mechanism of release of BCF from the prepared tablets were analysed by fitting the dissolution data into

Zero order kinetics
First order kinetics
Higuchi model Korsmeyer –Peppas model

A. Zero order kinetics:

This equation describes the systems where the release rate is independent of the concentration of the dissolving species. The equation describing the kinetics is given below

Qt= Qo + Ko t

Where

Q_t = amount of drug dissolved in time t
Q_o = initial amount of drug in the solution
K_o = zero order release constant

For zero order release kinetics, the graph was plotted between cumulative percent of drug released versus time.

Dosage forms following this profile, release same amount of drug per unit time, and it is the ideal method of release for a sustained release product.

B. First order kinetics:

Gibaldi and Feldman first proposed the application of this model to drug dissolution studies in 1967. The First order equation describes the release from systems where the release rate is dependent upon the concentration of the dissolving species. The equation is given below:

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Where, Co is the initial concentration of the drug, K is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative % of drug remaining Vs time which would yield a straight line with a slope of –K/2.303.

For first order release kinetics, the graph was plotted between log cumulative percent of drug remaining versus time.

C. Higuchi model:

Higuchi first proposed this model to describe dissolution of drug in suspension from ointment bases, but is widely applicable to other types of dosage forms. The equation is given below:

Where Q is the amount of drug released at time t per unit area A, C is the initial drug concentration, Cs is the drug solubility in the matrix media and D is the diffusivity of the drug molecules in the matrix substance.

Simplified Higuchi model

Ft = KH × t 1/2

Where K_H is the Higuchi dissolution constant. For Higuchi model, the graph was plotted between cumulative percent of drug released versus square root of time. The linearity of the graph indicates the diffusion controlled release.

D. Korsmeyer –Peppasmodel:

Korsmeyer and Peppas, in 1983 derived a mathematical equation which described the mechanism of drug release from a polymeric system. It is also known as Power law which is more comprehensive in describing the drug release mechanism as compared to Higuchi model. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer–Peppasmode

$Mt/M\infty = K\ tn$

Where M_t/M_∞ is a fraction of drug released at time t, K is the release rate constant and 'n' is the release exponent. For Korsmeyer-Peppas model, the graph was plotted between log cumulative percent of drug released versus log time.

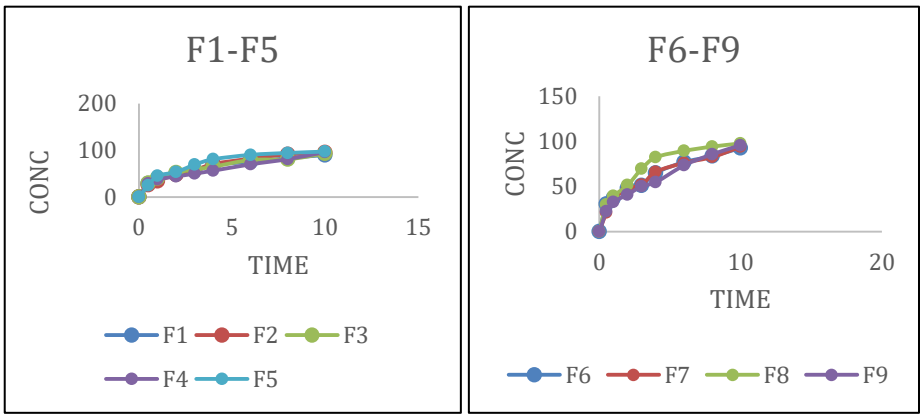
Based upon the buoyancy characteristics and percent cumulative drug release, the optimised formulation was selected.

3.RESULTS AND DISCUSSION:

TABLE4 :INVITRO DISSOLUTION PROFILES OF FORMULATIONS F1-F16 :

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	29.39 ±0.74	26.62 ±0.82	30.13 ±0.79	28.83 ±0.68	24.87 ±0.61	30.61 ±1.84	21.23 ±0.74	29.98 ±2.34	22.44 ±0.74	31.53 ±0.41	23.45± 0.34	19.58± 1.33	16.11±2 .30	24.49±0 .92
1	37.82 ±0.84	34.56 ±0.67	40.87 ±0.78	37.86 ±1.12	45.24 ±1.72	37.05 ±2.03	36.14 ±1.60	39.61 ±2.40	32.72 ±0.34	49.75 ±0.34	32.86± 3.04	28.40± 2.07	36.15±3 .12	36.23±1 .09
2	49.32 ±0.45	48.31 ±0.96	52.62 ±1.56	44.12 ±1.05	53.80 ±0.68	48.03 ±1.84	47.86 ±1.22	51.46 ±2.38	41.06 ±1.89	56.32 ±0.23	41.06± 2.71	38.49± 1.29	44.61±2 .38	50.74±2 .15
3	57.23 ±1.12	59.39 ±0.68	59.16 ±0.81	50.24 ±0.72	69.60 ±0.87	51.37 ±2.27	51.82 ±1.42	69.77 ±3.27	50.29 ±0.75	61.10 ±0.43	58.38± 2.56	47.36± 1.80	61.89±1 .57	67.61±1 .84
4	69.43 ±1.09	71.03 ±0.67	65.15 ±1.39	56.59 ±0.62	81.13 ±2.03	65.24 ±3.47	66.28 ±1.93	82.39 ±2.11	54.84 ±1.59	73.29 ±0.34	71.31± 4.56	64.46± 2.62	77.07±1 .67	79.73±0 .51
6	75.55 ±0.73	82.36 ±0.31	79.46 ±2.15	70.14 ±1.56	90.45 ±0.88	77.03 ±3.66	76.18 ±1.20	89.45 ±1.84	73.46 ±2.08	81.54 ±0.82	87.57± 1.23	81.89± 3.09	83.52±1 .76	86.09±0 .90
8	83.48 ±0.62	91.73 ±0.68	81.02 ±1.48	81.31 ±0.59	94.55 ±1.02	83.70 ±4.16	82.66 ±1.91	94.26 ±2.20	85.81 ±1.33	90.32 ±0.41	91.90± 0.48	90.59± 2.30	86.76±2 .54	90.23±0 .36
10	90.21 ±1.56	95.96 ±0.52	93.37 ±0.34	96.53 ±0.88	97.48 ±0.83	92.79 ±3.99	94.14 ±2.35	97.73 ±2.23	95.76 ±0.75	94.01 ±0.36	99.47± 0.71	93.02± 1.26	88.75±2 .11	96.53±1 .08

Fig 1:DISSOLUTION GRAPHS



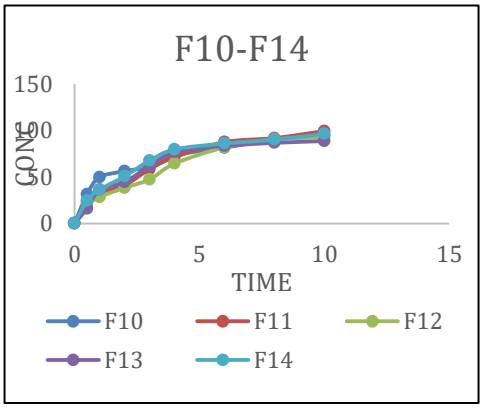


Fig 2 : Standard calibration curve of Molnupiravir in 0.1N HCl

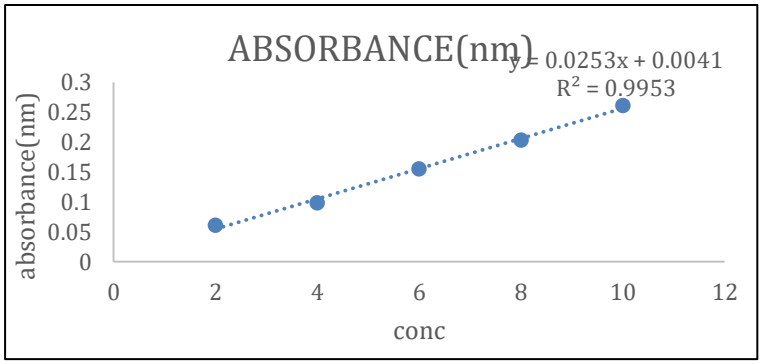


Table 5: Micromeritic properties of powder blends of various formulations

Batch code	Angle of repose(θ)	Bulk Density(g/mL)	Tapped density(g/mL)	Carr'sindex(%)	Hausner's ratio
F1	34.90°	0.222	0.256	13.28	1.15
F2	32.34°	0.266	0.310	14.19	1.17
F3	34.54°	0.258	0.291	11.30	1.13
F4	33.18°	0.281	0.321	12.46	1.14
F5	32.77°	0.242	0.279	13.26	1.15
F6	31.32°	0.240	0.280	14.28	1.17
F7	32.54°	0.250	0.290	13.79	1.16
F8	33.30°	0.298	0.345	13.62	1.15
F9	32.80°	0.266	0.309	13.91	1.16
F10	33.04°	0.311	0.355	12.39	1.14
F11	34.18°	0.240	0.270	11.11	1.13
F12	33.43°	0.296	0.342	13.45	1.16
F13	34.23°	0.311	0.356	12.64	1.14
F14	32.31°	0.250	0.287	12.89	1.15

3.1 Drug- excipient compatibility study:

- **FT-IR interpretation**:

FT-Infrared spectroscopy was employed to find out the compatibility of drug with the excipients. This study was carried out to find out the possible interaction between the selected drug Molnupiravir and the excipients. FT-IR spectrum ofMolnupiravirshowed the following characteristic peaks at 1093cm^{-1} (due to –C-Cl), 1526 cm^{-1} (due to -COOH), and 1626 cm^{-1} (due to –NH_2). These prominent peaks of drug were also present in the IR spectra of physical mixtures of drug with various excipients, thus revealing compatibility of the selected drug with the excipients.

Fig 3: FTIR spectra of drug -Molnupiravir

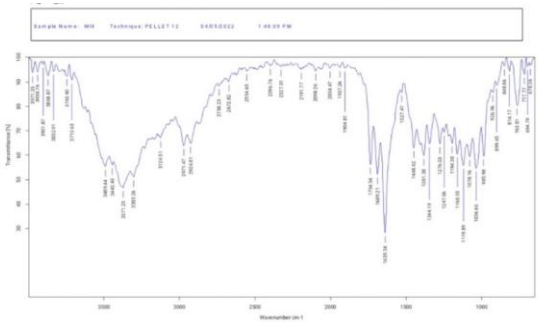


fig 4:Drug – polymer interaction (FTIR) study:

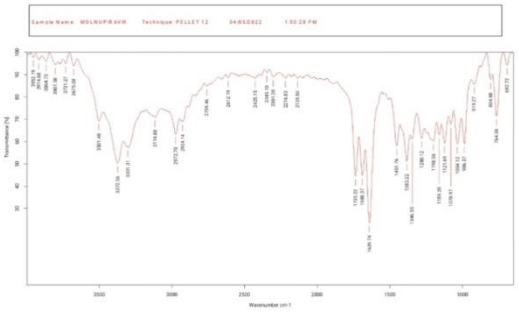
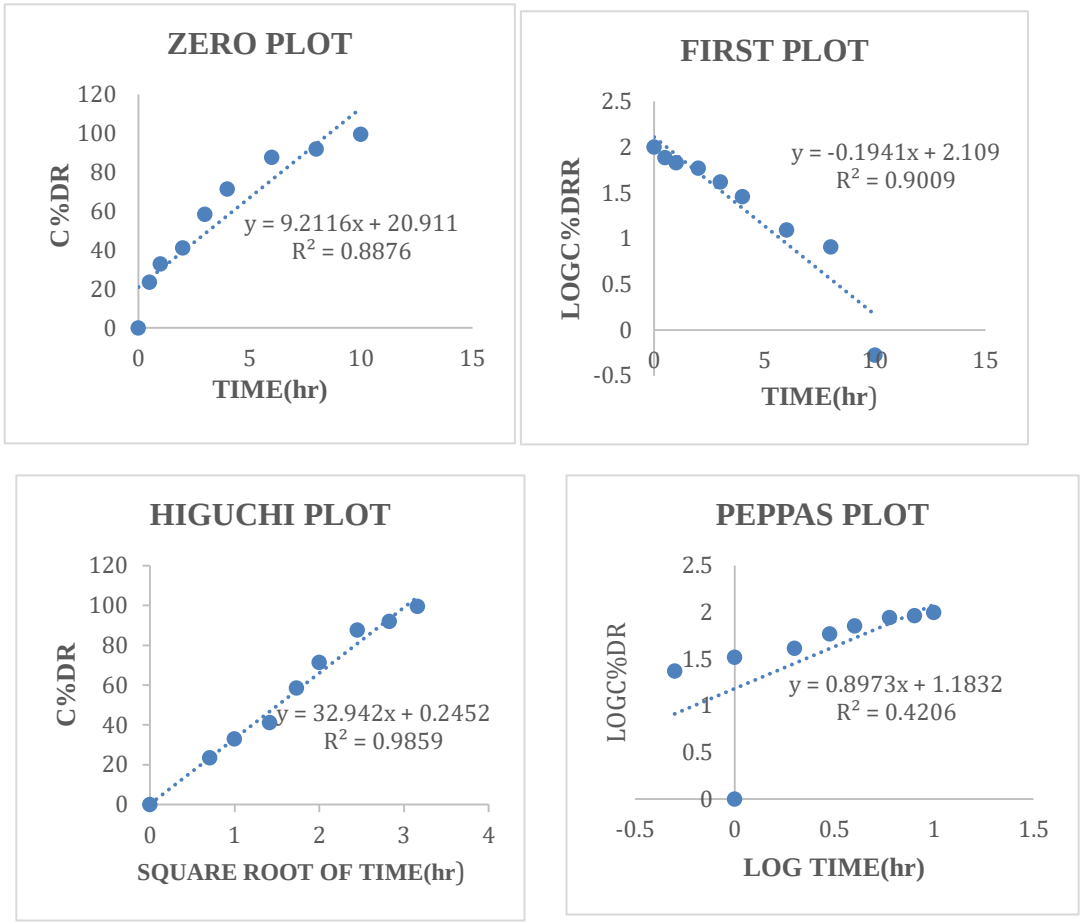


Table 6 :DRUG RELEASE KINETICS:

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
ZERO ORDER R2	0.8261	0.9715	0.820	0.9018	0.7834	0.8641	0.8739	0.7944	0.9307	0.781	0.8876	0.9119	0.794	0.8058
FIRST ORDER R2	0.9818	0.9963	0.9542	0.8767	0.9953	0.9778	0.9634	0.9932	0.9998	0.9988	0.9009	0.9049	0.932	0.8387
HIGUCHI R 2	0.9775	0.9942	0.9729	0.9825	0.9546	0.9847	0.989	0.959	0.9946	0.9542	0.9859	0.9841	0.9469	0.9629
PEPPAS R2	0.3426	0.3829	0.3282	0.9706	0.3705	0.3399	0.4002	0.3571	0.4081	0.3116	0.4206	0.4567	0.4464	0.3906

Fig 5: DRUG RELEASE KINETICS OF F11 FORMULATION



- Formulation (F11) containing xanthan gum-40%, sodium bicarbonate-12.5% exhibited a very less floating lag time of 20.33±6.03 seconds and total floating time of 24 hours . Formulation F11 released 98.47±0.71% of the drug in 24 hours. F11 showed better characteristics and drug release profile when compared to other formulations. Hence, it was selected as the optimized formulation.

4. ACKNOWLEDGEMENT :

We are special thanks to JNTUA-OTPRI Anantapuram for doing the project work.

5. CONCLUSION:

Finally, once-daily sustained release gastro-retentive floating tablets of Molnupiravir were successfully formulated in a relatively economical way when compared to the marketed formulation and found to be superior when compared to the marketed formulation.

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