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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MOLNUPIRAVIR ENCLOSED MICROBEADS

AUTHOR:1 **AUTHOR:2** **AUTHOR:3**

V PHANIDEEPTHI **C H SRINIVASAKUMARI** **GUDA VINEETH REDDY**

ASST.PROFESSOR **ASST.PROFESSOR** **STUDENT**

PHARMACEUTICS **PHARMACEUTICS** **B.PHARMACY**

AUTHOR:4 **AUTHOR:5**

KAMIREDDY RUCHITHA **M S DHANDAPANI**

STUDENT **STUDENT**

B.PHARMACY **B.PHARMACY**

JAWAHARLAL NEHRU TECHNOLOGICAL UNIVERSITY ANANTAPUR

OIL TECHNOLOGICAL AND PHARMACEUTICAL RESEARCH INSTITUTE

ANANTHAPURAMU, A.P., INDIA – 515 001

ABSTRACT: Microbeads of Molnupiravir were formulated to increase the bioavailabilty and to show controlled release of drug. Molnupiravir is anti-viral drug with oral bioavailability of 50%. Molnupiravir microbeads were prepared by Ion gelation method using different polymers. Polymers used were Sodium alginate, Calcium chloride, Carboxy methyl cellulose, EDTA, HPMC, Propylene glycol, Ethanol. Microbeads were prepared

Key words: Molnupiravir , microbeads, EDTA, HPMC

1.INTRODUCTION:

1.1 NOVEL DRUG DELIVERY SYSTEM:

1.3.1 Novel drug delivery system (NDDS) refers to the approaches, formulations, technologies and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects. It may involve scientific targeting with in the body, or it might involve facilitating systemic pharmacokinetics. NDDS is advanced drug delivery system which improves the drug potency, control drug release to give a sustained therapeutic effect, provides greater safety

1.3.2 Density of dosage form:

Dosage forms having a density lower than that of the gastric fluid experience floating behaviour and hence gastric retention. A density of < 1.0 gm/cm^{3}is required to exhibit floating property. However, the floating tendency of the dosage forssm usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.

1.3.3 Size and shape:

Dosage form unit with a diameter of more than 7.5mm are reported to have an increased gastric residence time competed to with those with a diameter of 9.9nm. The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 KSI are reported to have better GIT at 90-100% retention for 24 hrs compared with other shapes.

1.3.4 Fed or Unfed state:

Under fasting conditions, the GI motility is characterised by periods of strong motor activity at MMC that occurs every 1.5 to 2 hrs. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the gastric residence time of unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerable longer.

1.3.5 Nature of the meal:

Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric residence time and prolonging the drug release.

1.3.6 it is to target a drug specifically to a desired tissue. and evaluated for various physic-chemical properties for selection with suitable polymer. Then, drug loaded microbeads were prepared with five optimised formulation and evaluated for various parameters. The FTIR study shown its characteristic peaks in pure drug and proved its compatability with the excipients used. The monograph of molnupiravir has its melting point range of 169-172^{0}C. Micromeritic properties of all formulations was found to be satisfactory. Percentage drug release for the optimised six formulations were found to be 93.62, 96.54, 94.78, 93.22, 97.12, 93.32 for F1, F2, F3, F4, F5 and F6formulations respectively till 10th hour. From the results of micromeritic properties, percentage yield, and percentage drug release studies for al

1.3.7 Caloric content:

Gastric residence time can be increased between 4-10 hrs with a meal that is high in proteins and fats.

1.3.8 Frequency of Feed:

The gastric residence time can increase by over 400 min when successive meals are given compared with a single meal due to low frequency of MMC.

1.3.9 Effect of gender ,posture and age:

Females showed comparatively shorter mean ambulatory gastric residence time than males and gastric emptying time in women was slower than in men.

The floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained or a longer period , shoeing prolonged gastric residence time, but the non-floating units settled to the lower part of the stomach and undergone faster emptying as a result of peristaltic movements, and the floating units remained away from the pylorus.

1.5 Alginate beads:

Multi unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hrs. These floating beads gave a prolonged residence time of more than 5.5 hrs.

1.6 MICROBEADS

Microbeads: Microbeads are nearly spherical, small with diameter of 0.5- 1000 µm. The solid and free-flowing particulate carriers containing dispersed drug particles either in solution or crystalline form allow a sustained release or multiple release profiles of treatment with various active agents without major side effects. Additionally, the microbeads maintain functionality under physiological conditions, can incorporate drugs to deliver locally at high concentration, ensuring that therapeutic levels are reached at the target site while reducing the side effects by keeping systemic concentration low. The microbeads are produced from several polymers such as cationic polymers, e.g., chitosan, anionic polymers, e.g., sodium alginate, and binding components, e.g., gelatin, chondroitin sulfate, avidin in a predetermined ratio. Microencapsulation has become a common technique in the production of controlled release dosage forms. One approach for the controlled release formulation of different therapeutic agents in the production of polymeric gel beads. The beads are discrete spherical microcapsules that serve as the solid substrate on which the drug is coated or encapsulated in the core of the beads. Beads can provide sustained-release properties and a more uniform distribution of drugs within the gastrointestinal tract. Furthermore, the bioavailability of drugs formulated in beads has been enhanced. Numerous studies have been reported concerning the use of alginate beads as a controlled release carrier 14, 15, 16,

1.6.1 Ideal characteristics of Microspheres:

- The ability to incorporate reasonably high concentration of the drug.

- Stability of the preparation after synthesis with a clinically acceptable shelf life.
- Controlled particle size and dispersability in aqueous vehicles for injection.
- Release of active reagent with a good control over a wide time scale.
- Biocompatibility with a controllable biodegradability.
- Susceptibility to chemical modification.

1.6.2 ADVANTAGES OF MICROBEADS:

- Limiting fluctuation within therapeutic range.
- Reducing side effects.
- Decreasing dosing frequency.
- Improving bioavailability.
- Improving patient compliance.

1.6.3 LIMITATIONS:

- Floating system is not feasible for those drugs that have solubility or stability problem in GIT.
- These systems require a high level of fluid in the stomach for the drug delivery to float and work efficiently.
- The drugs that are significantly absorbed through the GIT, which undergo significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating systems causes irritation to gastric mucosa.

1.7 Criteria for Formulation of Sustained Release Microbeads Dosage forms: 3, 5:

A number of formulation methods have been developed to overcome the barrier seen with immediate release oral dosage forms. These processes include inert insoluble matrices, use of coatings, hydrophilic matrices, as well as the combinations of hydrophilic and hydrophobic polymers, embedding of the drug in plastic matrix, ion exchange resins, osmotic pumps and microencapsulation. The physiology of the gastrointestinal tract, the physicochemical property of the drug, the drug release pattern, the pharmacological action of the drug are the parameters that must be considered too. The physicochemical properties of the drug involve parameters like aqueous solubility, stability, pKa, and permeability values. **1.7.1 The Biopharmaceutical Classification System (BCS) involves placing a drug into four classifications:**

- High solubility and high permeability.
- Low solubility and high permeability.
- High solubility and low permeability.
- Low solubility and low permeability.

Class 1 is considered the preferred category, while Class 4 is the worst category. A drug having high solubility in the intestine is a good drug for a co ntrolled oral dosage form. The drug permeability value must also be considered and should be more than the

prescribed value. A biological half-life of a required drug is between two and six hours is the best choice of formulation because this type of criteria of the drug is avoiding the accumulation of the drug in the body.

1.8 Drug Release Kinetics Criteria: 3, 5, 47

The purpose of a sustained-release system is to deliver a drug at a necessary rate to achieve and maintain a constant drug blood level. It means that the rate of drug delivery should be independent of the amount of drug remaining in the dosage form and constant over a certain time. It implies that the rate should follow zero-order kinetics. Zero-order release may be theoretically desirable. Non zero-order release rates may be clinically equivalent to constant release in many cases. In order to achieve a therapeutic level promptly and maintain that level for a given period of time, the dosage form generally should consist of two parts. With the controlled oral dosage forms, the total drug in the dosage form should consist of two portions, a loading dose and a maintenance dose. The initial loading dose is released immediately on its administration. The release of the drug is characterized by a firstorder kinetic process. The loading dose immediately obtains the acceptable therapeutic plasma levels. The remaining dose is released at a slow and a controlled rate to maintain the constant plasma concentration of the drug. The release pattern has to follow zero-order kinetics. Therefore, the rate of release of the drug is independent of the remaining fraction of the dose. The controlled oral dosage form involves releasing the maintenance dosage at a rate that is equivalent to the elimination rate of the drug.

1.9 Drug Release Mechanism: 5, 47, 48:

Drug release from the microbeads formulation occurs by a general mechanism including dissolution, diffusion, polymer degradation, and hydrolysis/erosion.

1.9.1 Dissolution Controlled System:

In this system, the rate-controlling step is dissolution. The drug is embedded in slow-dissolving or erodible matrix or by coating with a slow dissolving substance. It is of two types is Encapsulation and Matrix

1.9.1.1 Encapsulation:

The drug particle is coated or encapsulated by microencapsulation techniques with slow dissolving materials like cellulose, polyethylene glycol, polymethacrylates, waxes, etc. The dissolution rate is dependent upon the solubility and thickness of the coating.

1.9.1.2 Matrix:

It is also called monoliths. They employ waxes such as beeswax, carnauba wax, hydrogenated castor oil, which controls drug dissolution by controlling the rate of fluid dissolution penetration into the matrix by altering porosity of rate. The wax embedded drug is generally prepared by dispersing the drug in molten wax and congealing and granulating the same.

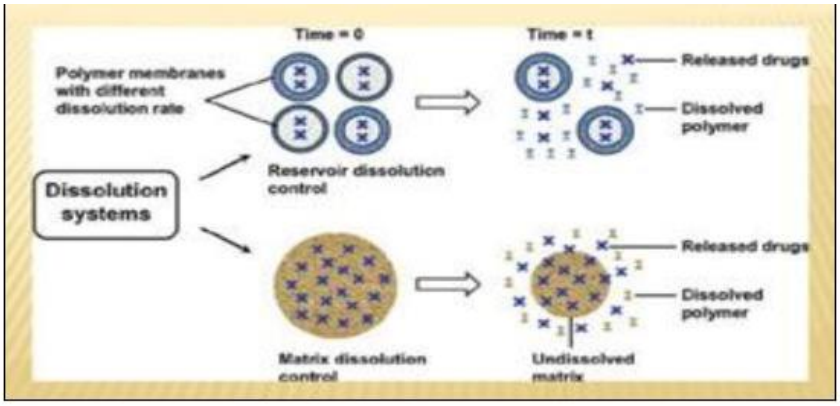


FIG.1.2 : RELEASE MECHANISM DISSOLUTION CONTROLLED SYSTEM[49]

1.9.2 Diffusion Controlled System:

Rate limiting step is diffusion of drug through inert water-insoluble membrane barrier. In the case of a polymer matrix, the diffusion of the active ingredient can be through the intact polymer network or through the pores filled with water. Water-soluble drugs may also dissolve in the aqueous pore networks. Water uptake causes polymer chains to swell, indicating the formation of new pores and/or osmotic pressure.

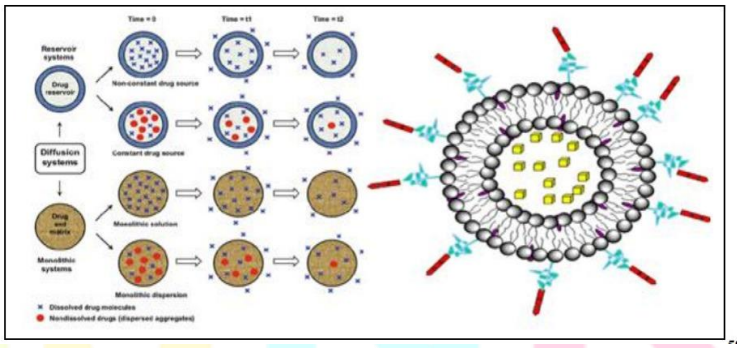


FIG. 1.3: RELEASE MECHANISM DIFFUSION CONTROLLED SYSTEM[50]

During swelling, the volume increases, the effective diffusion coefficient of the drug is increased, and more pharmacon molecules enter the aqueous part. The rate of release also depends upon where the polymer degradation by homogeneous or heterogeneous mechanism. The drug release depends on the rate of drug dissolution in the dissolution fluid, rate of penetration of dissolution fluid to the microbeads, and rate at which the dissolved drug escapes from the microbeads.

1.9.2.1 Erosion:

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle. The polymer erosion, i.e. loss of polymer, is accompanied by accumulation of the monomer in the release medium. The erosion of

the polymer begins with the changes in the microstructure of the carrier as the water penetrates within it leading to the plasticization of the matrix.

1.10 Techniques used for Formulation of Microbeads:

1.10.1 Ionotropic Gelation Method:

It involves the interaction of an ionic polymer with oppositely charged ions to initiate crosslinking. Unlike simple monomeric ions, the interaction of polyanion with cations cannot be completely explained by the electro-neutrality principle. The three-dimensional structure and presence of other groups influence the ability of cations to conjugate with anionic functionalities or vice-versa. There are two sub-methods by which beads can be generated using ionotropic gelation technique. The methods differ from each other in the source of the crosslinking ion 19, 21, 23. In one of the methods, the cross-linker ion is positioned externally, whereas, in the other method, the cross-linker ion is incorporated within the polymer solution in an inactive form. Ionotropic gelation methods classified into two types:

- External gelation method.
- Internal gelation method.

1.10.1.1 External Gelation Method:

The external gelation method involves the use of a metal ion solution as a source of the crosslinking ion. The polymer solution containing the drug is extruded through a needle into this solution with mild agitation. As soon as the polymeric drop comes in contact with the metal ion solution, instant gelation occurs, resulting into self-sustained bead formation. The beads are cured for a specified time period into the gelation medium following which, they are removed and dried. The external gelation occurs as a result of rapid diffusion of the cross-linker ions into the partially gelled beads 19, 21, 23.

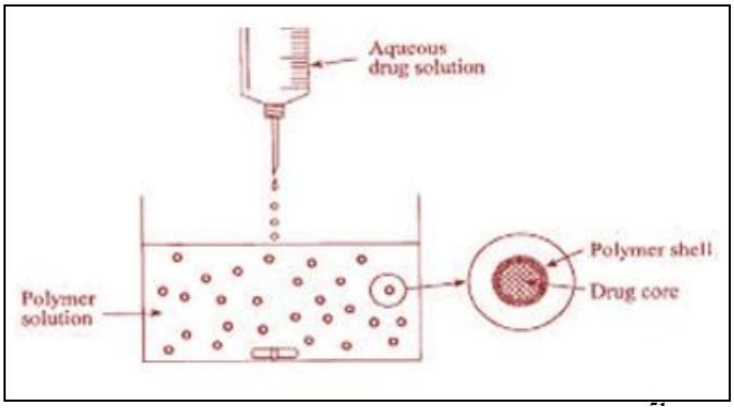


FIG. 1.4: EXTERNAL GELATION METHOD[51]

1.10.1.2 Internal Gelation Method:

The internal gelation method involves the generation of the cross-linker ion 'in situ'. This method involves the use of insoluble metal salt (such as calcium carbonate and barium carbonate) as a source of crosslinking cation. The cation is released, in-situ, by lowering the pH of the solution, thereby solubilizing the metal salt and releasing the metal ion 19, 21, 23.

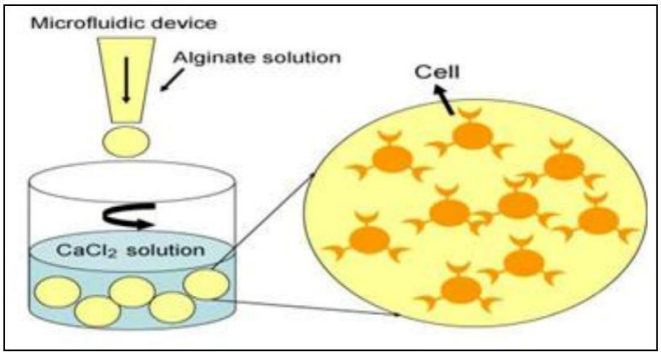


FIG.1.5: INTERNAL GELATION METHOD[52]

1.10.2 Emulsion Gelation Method:

Another method of microbead preparation is emulsion gelation techniques. The sodium alginate solution is prepared by dispersing the weighed quantity of sodium alginate in deionized water. An accurately weighed quantity of drug is added to the polymeric solution of Sodium alginate, and the drug is stirred magnetically with gentle heat to get a homogenous drug polymeric mixture.

A specific volume of the crosslinking agent is added to form a viscous dispersion, which is then extruded through a syringe with a flat-tipped needle of size no. 23 into oil containing span 80 and 0.2% glacial acetic acid being kept under magnetic stirring at 1500 rpm. The microbeads are retained in the oil for 30 min to produce rigid discrete particles. They are collected by decantation, and the products thus separated are washed with chloroform to remove the traces of oil. The microbeads are dried at 400 ºC for 12 h[18,22].

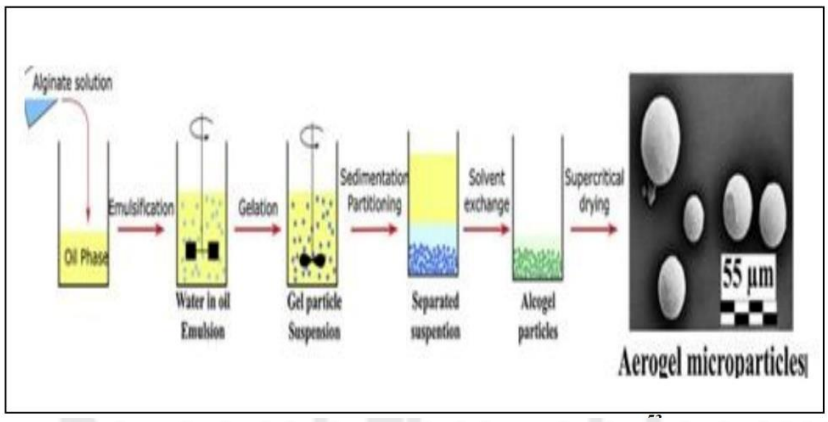


FIG.1.6: EMULSION GELATION METHOD

1.10.3 Polyelectrolyte Complexation Method:

Another method of microbeads preparation is the complex coacervation of oppositely charges polyelectrolytes, polycation, and polyanion materials. Alginate chitosan microcapsules with biocompatibility and biodegradability may be prepared under mild conditions. Even physiological conditions, so they are suitable for application in biomedical fields. In recent years, there has been an increasing interest in the study of the use of alginate– chitosan microcapsules as the drugdelivery systems of proteins and polypeptides. With this method, specific conditions of polyion concentration, pH and ionic strength, the mixture

will separate into a dense concretive phase containing the microbeads and a dilute equilibrium phase. For example, complex coacervation between alginic acid and chitosan was achieved by spraying the sodium alginate solution into the chitosan solution, producing strong microbeads that remained stable over a large range of pH. For the best yield with coacervative bead preparation, conditions should be set to a pH of 3.9, ionic strength of 1 mm, and a 0.15% w/v total polyion concentration .

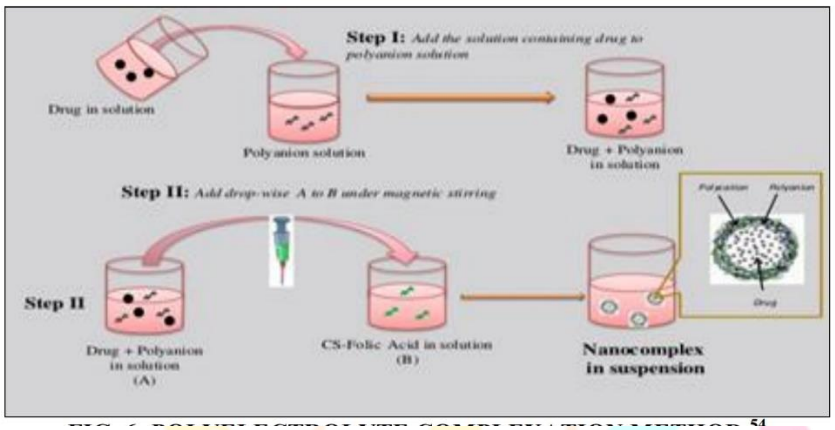


FIG. 1.7: POLYELECTROLYTE COMPLEXATION METHOD[54].

1.11 Polymers used for the Preparation of Microbeads:

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microbeads. These materials include polymers of natural and synthetic origin and also modified natural substances. Some examples of polymers are Albumin, Gelatin, Sodium alginate, Chitosan, Starch, Dextran, Polylactide, and olyglycolide Polyanhydride, Polyphosphazene, etc. Sodium alginate micro Beads are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability, and to target the drug to specific sites. Multiple unit dosage forms such as microspheres or beads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastrointestinal tract, more uniform drug absorption, reduced local irritation, and elimination of unwanted intestinal retention of polymeric material when compared to non-disintegrating single unit dosage form .

1.11.1 Alginates:

Alginates are natural polysaccharide polymers isolated from the brown seaweed (Phaeophyceae). Alginic acid can be converted into its salts, of which sodium alginate is the major form currently used. Alginates offer various applications in drug delivery, such as in matrix type alginate gel beads, in a liposome, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications. The bioadhesive character of alginates makes them useful in the pharmaceutical industry. The application areas of sodium alginate-based drug delivery systems are many, and these systems can be formulated as gels, matrices, membranes, nanospheres, microspheres, and microbeads, etc. Alginate beads can be administered by filling in capsules or by compressing them into a tablet. A new approach of alginate polymer in the pharmaceutical field is the development of systems that are capable of adjusting drug release according to physiological needs

(e.g., pH-responsive systems based on polymer swelling, magnetically triggered delivery systems). Alginate also possesses the physic-chemical properties required to make it an important contributor to this area of future research.

1.11.2 Chitosan:

Chitosan is a cationic natural polysaccharide that is derived from the chitin of crustaceans, with crabs and shrimp-shell wastes as its principal source. Its properties include the extent of deacetylation and the average molecular weight of the polymer and low toxicity, and good bioavailability makes it a novel excipient in a pharmaceutical formulation as relatively new development. Chitosan is a biopolymer that could be used for the preparation of various polyelectrolyte complex products with natural polyanions such as xanthan, alginate, and carrageenan. Many formulations were recently prepared and evaluated within different dosage forms such as ophthalmic, nasal, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, transdermal as well as gene carrier, which is based on the application of chitosan and its derivatives. Chitosan is biocompatible and shows anti-microbial and antifungal activities, which makes it a favorable option for biomedical applications. In many researches, researchers proved that the chitosan is very useful in tissue growth, tissue repair, and accelerating wound-healing and bone regeneration therapies .

1.11.3 Pectin:

Pectin is used as a thickening agent and a gelling agent. Basically, it is a polymer of a-Dgalacturonic acid with 1-4 linkages. The chemistry and gel-forming characteristics of pectin have enabled this naturally occurring biopolymer to be used in the pharmaceutical industry. It has also been used potentially in pharmaceutical preparation and drug formulation as a carrier of a wide variety of biologically active agents, not only for sustained release applications but also as a carrier for targeting drugs to the colon for either local treatment or systemic action .

1.11.4 Xanthan Gum:

Xanthan gum is a natural, biosynthetic, edible gum, and extracellular polysaccharides. Xanthan gum consists of glucose, mannose, and glucuronic acid. Xanthan is highly soluble in cold and hot water, and this behavior is related to the polyelectrolyte nature of the xanthan molecule. Xanthan gum is mainly considered to be a nongelling agent and is used for viscosity. It hydrates rapidly in cold water without lumping to give a reliable viscosity. Xanthan gum is used as a thickener stabilizer, emulsifier, and foaming agent. Xanthan has the potential advantage of drug release with zero-order release kinetics. However, its major drawback is that the drug release is influenced by the pH and the presence of ions in the medium 37,38

1.12 APPLICATION OF MICROBEADS:

- Ophthalmic drug delivery
- Oral drug delivery
- Gene delivery
- Nasal drug delivery
- Intratumoral and local drug delivery

- Buccal drug delivery
- Gastrointestinal drug delivery
- Transdermal drug delivery
- Colonic drug delivery
- Vaginal drug delivery
- Targeting by using microparticulate carriers.

1.12.1 Ophthalmic drug delivery:

Microspheres developed using polymer exhibits favourable biological behaviour such as bioadhesion, permeability-enhancing properties and interesting physic-chemical characteristics, which make it a unique material for the design of ocular drug delivery vehicles.Eg. chitosan, alginate, gelatin.

1.12.2 Oral drug delivery:

The ability of microspheres containing polymer to form films permit its use in the formulation of filming dosing forms, as an alternate to pharmaceutical tablets. The pH sensitivity, coupled with reactivity of the primary amine groups, make microspheres more suitable for oral drug delivery applications. Eg: chitosan, gelatin.

1.12.3 Gene delivery :

Microspheres could be a useful oral gene carrier because of its adhesive and transport properties in the GI tract. Eg: chitosan, gelatin, viral vectors, cationic liposomes, polycation complexes.

1.12.4 Nasal drug delivery:

Polymer based drug delivery systems, such as microspheres, liposomes, and gels have been demonstrated to have good bioadhesive characteristics and swell easily when in contact with the nasal mucosa increasing the bioavailabilty and residence time of the drugs to the nasal route.Eg: starch,dextran, albumin, chitosan.

1.12.5 Intratumoral and local drug delivery:

In order to deliver paclitaxel at the tomour site in therapeutically relevant concentration, polymer films are fabricated. Mixture of drug has promising potential for use in controlled delivery in the oral cavity Eg: chitosan, gelatine, PLGA, chitosan and PCL.

1.12.6 Buccal drug delivery:

Polymer is excellent to be used for buccal delivery because it has muco/bioadhesive properties and can act as an absorption enhancer. Eg: chitosan, sodium alginate.

1.12.7 Gastrointestinal drug delivery:

Polymer granules having internal cavities prepared by de acidification when added to acidic and neutral media are found buoyant and provided a controlled release of drug. Eg: eudragit,ethylcellulose, carbapol BSA, gelatin.

1.12.8 Transdermal drug delivery:

Polymer has good film forming properties. The drug release from the devices is affected by the membrane thickness and crosslinking of the film. Eg: chitosan, alginate, PLGA.

1.12.9 Colonic drug delivery:

Polymer has been used for the specific delivery of insulin to the colon. Eg: chitosan.

1.12.10 Vaginal drug delivery:

Polymer, modified by the introduction of thioglycolic acid to the primary amino groups of the polymer is widely used for the treatment of mycolic infections of the genitourinary tract. Eg: chitosan , gelatin, PLGA.

1.12.11 Targeting by using microparticulate carriers: Pellets are prepared with the polymer by using the extrusion/spheronisation technology. Eg: chitosan, microcrystalline cellulose. l formulations, F5 formulation was selected as best formulation

4. MATERIALS AND METHODS :

4.1 Materials:

Table 4.1 List of materials

S.NO	Materials	Suppliers/Manufacturer
1.	Drug (Molnupiravir)	Reddy's laboratory, Hyderabad.
2.	Sodium alginate	Sd fine chem Ltd.
3.	Ethanol	Sd fine chem Ltd.
4.	EDTA	Sd fine chem Ltd.
5.	Calcium chloride	Sd fine chem Ltd.
6.	HPMC	Sd fine chem Ltd
7.	Sodium carboxy methyl cellulose	Sd fine chem Ltd
8.	Propylene glycol	Sd fine chem Ltd

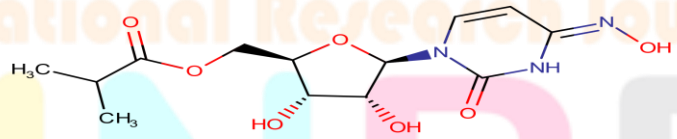
4.2 Equipments:

Table 4.2 List of equipments

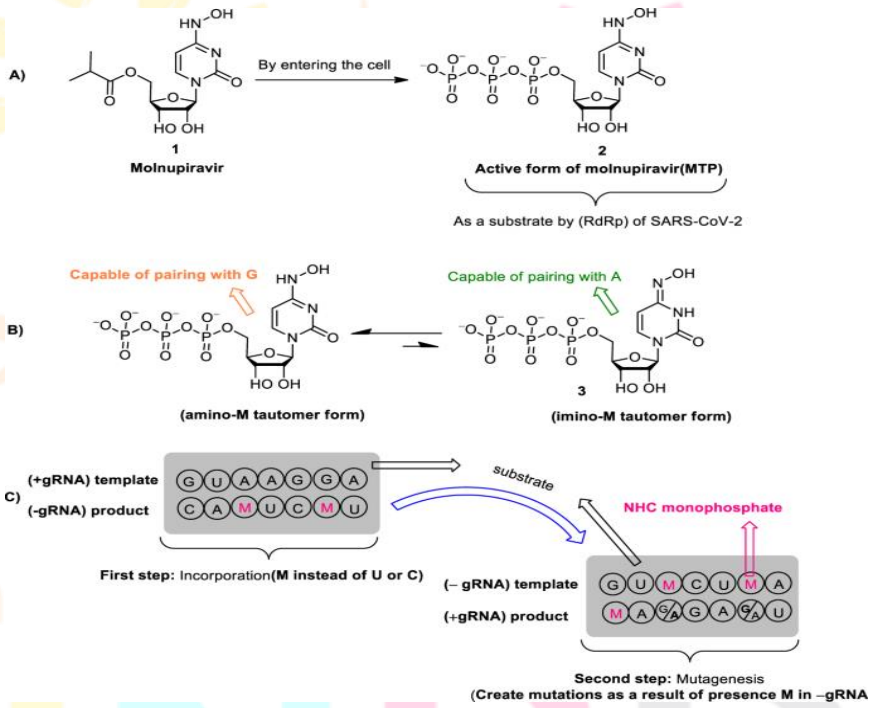
S.NO	Instruments	Manufacturers
1.	Digital balance	Vibra technologies
2.	Magnetic stirrer	Remi
3	Melting point apparatus	Sisco Ltd. Hyd, India
4.	FTIR	Bruker alfa
5.	UV visible spectroscopy	Shimadzu model no S1210
6.	Dissolution test apparatus	Electro lab USP Tdl-081

4.3 DRUG PROFILE:

Table 4.3.1 Drug profile

1	**Drug name**	Molnupiravir
2	**IUPAC name**	**[(2R,3S,4R,5R)-3,4-dihydroxy-5-[4-(hydroxyamino)-2-oxopyrimidin-1-yl]oxolan-2-yl]methyl 2-methylpropanoate**
3	**Structural formula**	
4	**Empirical formula**	C13H19N3O7
5	**Molecular weight**	329.3g/mol
6	**Physical description**	White to off- white powder
7	**Melting point**	169-172^{0}C

8	**Route of Administration**	Oral
9	**Metabolism**	Hepatic
10	**Biological half life($t_{1/2}$)**	3.3 hrs
11	**Excretion**	97%- Renal (inactive metabolite) <3%- renal (active metabolite)
12	**Class**	Broad spectrum anti-viral
13	**BCS class**	Class III
14	**Category**	Anti-viral agent
15	**Dose**	200 mg
16	**Solubility**	Soluble in water; freely soluble in methanol; sparingly soluble in 2-propanol; Slightly soluble in methyl acetate ; practically insoluble in n-heptane.
19	**Mechanism of action**	Molnupiravir inhibits viral reproduction by promoting widespread mutations in the replication of viral RNA by RNA-directed RNA polymerase. It is metabolized into a ribonucleoside analogue that resembles cytidine, β-D-N^4-Hydroxycytidine 5′-triphosphate (also called EIDD-1931 5′-triphosphate or NHC-TP). During replication, the virus's enzyme incorporates NHC-TP into newly made RNA instead of using real cytidine.
20	**pH**	1.5-2.5
21	**Adverse effect**	➢ Nausea ➢ Diarrhoea ➢ Dizziness
22	**Uses**	Covid 19
23	**Indication and use**	➢ Medical uses Molnupiravir is indicated for the treatment of **mild-to-moderate coronavirus disease (COVID-19)** in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19

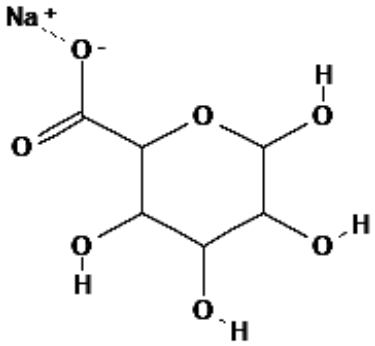
24	**Side effects**	➢ Nausea ➢ Diarrhoea ➢ Dizziness
25	**Interactions**	There are no known drug interactions, although based on limited data available.
26	**Pharmacokinetics and metabolism**	**Molnupiravir is hydrolyzed to** N4-hydroxycytidine/ **N4-hydroxy uridine which distributes into tissues. Once inside cells, N4-hydroxycytidine/ N4-hydroxy uridine is phosphorylated to the 5'-triphosphate form, they both existing tautomeric forms.** 

EXCIPIENT PROFILE :

Sodium alginate :

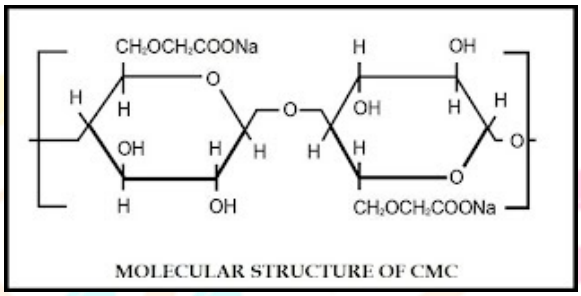
Table 4.3.2 Sodium alginate polymer profile

Nonproprietary Names	Sodium alginate Natrii alginas
Synonyms	Algin, alginic acid, sodium salt, E401, Kelcosol, Keltone, Protanal, sodium polymannuronate.
Chemical Name	Sodium alginate

Empirical Formula	Sodium alginate consists chiefly of the sodium salt of alginic acid, which is a mixture of polyuronic acids composed of residues of D- mannuronic acid and L-guluronic acid.
Description	Sodium alginate occurs as an odorless and tasteless, white to pale yellowish brown colored powder
Viscosity	20–400 mPa s .
Loss on drying	≤15.0%
Structural Formula	
Stability and Storage Conditions	Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humidities and a cool temperature. Aqueous solutions of sodium alginate are most stable at ph 4–10. The bulk material should be stored in an airtight container in cool, dry place.
Incompatibilities:	Sodium alginate is incompatible with acridine derivatives, crystal violet, phenylmercuric acetate and nitrate, calcium salts, heavy metals, and ethanol in concentrations greater than 5% Low concentrations of electrolytes cause an increase in viscosity but high electrolyte . concentrations cause salting-out of sodium alginate; salting out occurs if more than 4% of sodium chloride is present.
Safety	It is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may be harmful.

SODIUM CARBOXYMETHYL CELLULOSE :

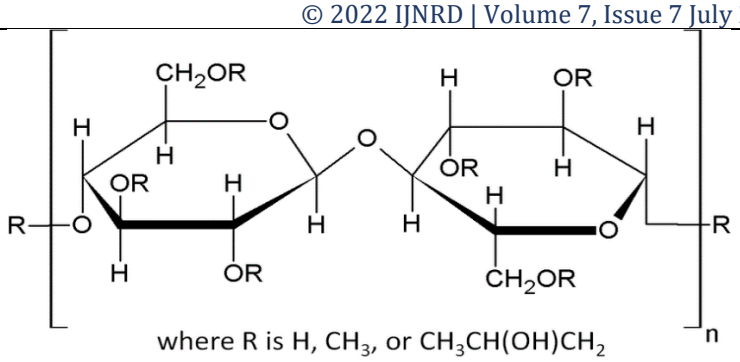
Table 4.3.3 Sodium carboxy methyl cellulose polymer profile

Synonyms	Cellulose gum, CMC Powder
Chemical name	Sodium carboxy methyl cellulose
Structural formula	 MOLECULAR STRUCTURE OF CMC
Emperical formula	**[C6H7O2 (OH)x (OCH2COONa)y]n**
Molecular weight	Avg wt: 90,000 daltons
Description	It is white or slightly yellow fibrous powder. Hygroscopic, odourless, tasteless, non-toxic easy to ferment.
Solubility	Easily dispersed to form colloidal solution in water, insoluble in acids, alcohols and organic solvents.

Hydroxy propyl methyl cellulose

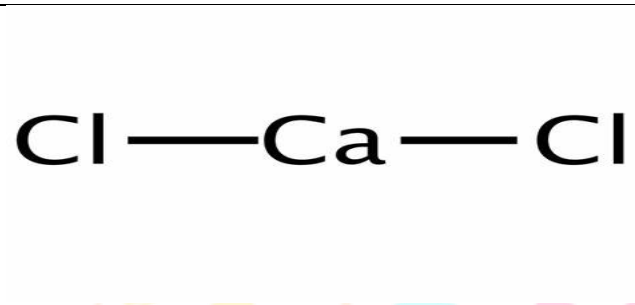
Table 4.3.4 HPMC polymer profile

Synonym	Hydroxy propyl methyl cellulose, Hypromellose
Chemical name	Hydroxy propyl methyl cellulose

Structure	 where R is H, CH_3, or $CH_3CH(OH)CH_2$
Empirical formula	$C_{56}H_{108}O_{30}$
Molecular formula	$C_{56}H_{108}O_{30}$
Molecular weight	1261.4
Description	White or off-white powder
Solubility	Non-ionic and water soluble
Viscosity	400-75000 mPa.s
Density	1.39 g/cm^3

Calcium chloride:

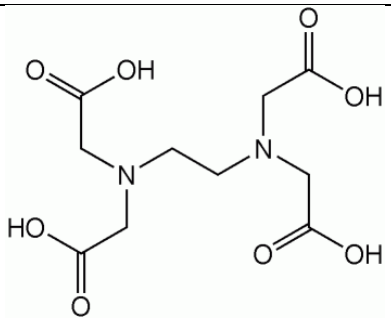
Table 4.3.5 Calcium chloride polymer profile

Synonyms	Calcium dichloride, Cal plus
Chemical name	Calcium chloride
Structural formula	
Emperical formula	**CaCl2 · 2H2O.**
Molecular formula	CaCl2
Molecular weight	110.98 g/mol
Description	It is a white odourless powder, granules or flakes
Solubility	It is highly soluble in water, acetic acid, acetone, alcohol. Insoluble in hexane.
Density	2.15 g/cm^3

ETHYLENE DIAMINE TETRA ACETICACID

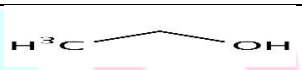
Table 4.3.6 EDTA polymer profile

Synonyms	ETHYLENE DIAMINE TETRA ACETICACID, Edetic acid

Chemical name	2,2',2",2"'-(Ethane-1,2-diyldinitrilo)tetra acetic acid
Structure	
Empirical Formula	$C_{10}H_{16}N_2O_8$
Chemical formula	$C_{10}H_{16}N_2O_8$
Molecular weight	292.2438 g/mol
Description	White crystalline powder
Solubility	Slightly soluble in cold water, insoluble in ethanol and in organic solvents
Density	0.860 g/cm^3

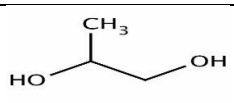
ETHANOL

Table 4.3.7 Ethanol Profile

Synonym	Alky, Fire Water
Chemical name	Ethyl alcohol
Structure	
Empirical formula	C_2H_5OH
Chemical formula	C_2H_5OH
Molecular weight	46.07gm/mol
Description	Colourless, clear liquid
Solubility	Water
Density	789 kg/m^3

Propylene Glycol

Table 4.3.8 Propylene Glycol Profile

Synonym	Methyl ethyl glycol, 1,2-propanediol
Structure	
Empirical formula	$C_3H_8O_2$
Chemical formula	$C_3H_8O_2$
Molecular weight	76.095gm/mol
Description	Colourless liquid
Density	1.036 gm/cm^3

4.4 Preformulation

Preformulation testing is the initial step in the development of dosage forms of a drug. It is an investigation of physical and chemical properties of a drug substance alone and along with excipients. The objective of these studies is to generate information useful in the formulation design and bioavailable dosage forms which can be mass-produced.

4.4.1 Solubility:

Solubility of molnupiravir ethanol,

4.4.2 Melting point apparatus:

Melting point of molnupiravir was determined by open capillary method.

4.4.3 Calibration curve for Molnupiravir:

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

4.4.3.2 Determination of λ_{max} :

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

4.4.3.3 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.

FORMULATION OF MICROBEADS

4.4.3.4 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.

4.5 METHODOLOGY:

4.5.1 Preparation of empty microbeads :

Method used : Ionotropic - gelation technique

Microbeads were prepared using sodium alginate, calcium chloride, EDTA, propylene glycol, Sodium carboxy methyl cellulose, ethanol HPMC. Weighed quantity polymer were added to 100ml of sodium alginate solution with stirring about 300 rpm. The resultant solution was added drop wise to 100 ml of calcium chloride solution under constant stirring using 12.7mm gauge needle syringe. The obtained microbeads were filtered and then dried for 6hrs. The microbeads that were prepared by sodium alginate, HPMC, EDTA Sodium carboxy Methyl cellulose. have shown good consistency

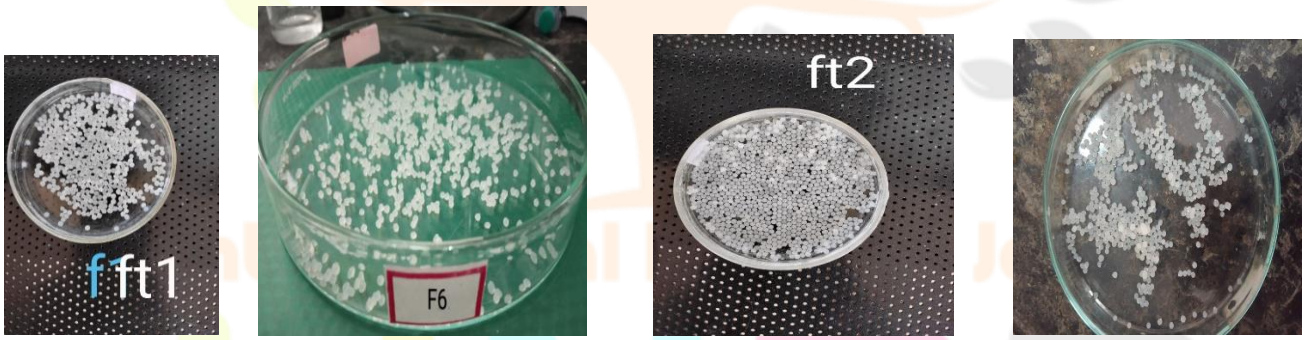


Fig 1 Microbeads of molnupiravir

4.5.2 Formulation design:

Table 4.5: Formulation design for Molnupiravir microbeads

Formu-lation code	Ingredients (gm)							
	Drug	Sodium Alginate	Sodium carboxymethyl cellulose	HPMC	EDTA	Ethanol	Propylene glycol	Calcium chloride (% w/v)
F1	0.2	3	0.5	0.5	0.3	0.1	0.1	4
F2	0.2	3	1	0.5	0.4	0.2	0.2	4
F3	0.2	3	0.5 _	1	0.4	0.2	0.1	4
F4	0.2	3	1	0.5	0.4	0.1	0.2	4
F5	0.2	3	1	1	0.5	0.2	0.1	4
F6	0.2	3	0.5	0.5	0.2	0.2	0.2	4

Preparation of molnupiravir microbeads:

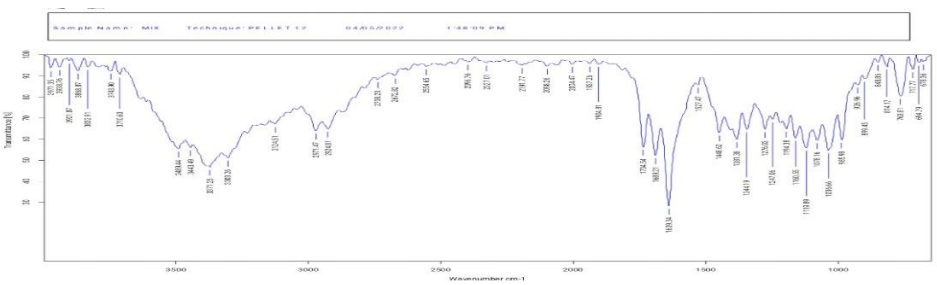
Method used : Ionotropic - gelation technique

Microbeads of molnupiravir were prepared using sodium alginate, sodium carboxy methyl cellulose, HPMC, EDTA and calcium chloride. Weighed quantity of drug and polymer were added to 100ml of sodium alginate solution with stirring about 300 rpm. The resultant solution was added drop wise to 100 ml of calcium chloride solution under constant stirring using 12.7 gauge needle syringe . The obtained microbeads were filtered and then dried for 6hrs.

4.6 Evaluations of Molnupiravir microsbeds:

4.6.1 Drug- polymer interaction (FTIR) study :

FTIR spectroscopy was performed on Fourier transformed infrared spectrophotometer. The drug and polymers mixture was scanned in the wave number ranging 3971.35-678.36 cm^{-1}. FTIR study was performed on Molnupiravir, physical mixture of drug and polymers.



4.6.2 Micromeritic properties :

4.6.2.1 Angle of repose :

. 5 gms of the sample was taken in a funnel fixed in a holder (6 cm) above the surface at an appropriate height and graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was measured and angle of repose was determined using the formula.

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

h = height

r = radius

θ = angle of repose

4.6.2.2 Bulk density and tapped density determination :

A quantity 5gm of the powder (W) from each formula was introduced in to a 25ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density and tapped density were calculated using the following the formula

Bulk density (ρ_b) = m/ v_b

Tapped density(ρ_t) = m / v_t

Where,

m = mass of the powder

v_b = initial or bulk volume

v_t = final or tapped volume

4.6.2.3 Determination of compressibility index and hausner ratio:

Compressibility index and Hausner ratio are measured by using the following formula

$$\%\text{compressibility (carr's index)} = \frac{\text{Tapped density-Intial bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio = v_b / v_t

Where,

v_b = initial or bulk volume

v_t = final or tapped volume

4.6.3 Percentage yield:

The prepared microbeads of all batches were accurately weighed. The weight quantity of prepared microbeads was divided by the total amount of all the excipients and drug used in the preparation of the microbeads, which give the total percentage yield of microbeads. It was calculated by using following equation,

$$\text{Percentage yield} = \frac{\text{Actual yield of product}}{\text{Total weight of excipients and drug}} \times 100$$

4.6.4 Percentage drug entrapment:

Practical drug content: According to dose 10 mg actual drug present in total microbeads is calculated. That amount mixed in 0.1 M HCL by sonication. From that pipette 1ml into 10ml volumetric flask and made upto 10ml using buffer. The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically at 296 nm against appropriate blank.

Theoretical drug content: It is calculated by assuming that the entire drug present in the polymer solution get entrapped and no loss occurs at any step of preparation. The amount of drug entrapped in the microbeads was calculated by the following formulae.

$$\text{Percentage drug entrapment} = \frac{\text{Practical drug content}}{\text{Theoretical drug content.}} \times 100$$

4.6.5 Invitro dissolution studies:

Procedure: The release rate of molnupiravir microbeads was determined using USP dissolution apparatus . Dissolution was performed using 900 ml of 0.1 m HCL in 37 ± 0.5 ^{0}C at 50 rpm. molnupiravir microbeads equivalent to 100 mg were placed in basket. Sample of solution was withdrawn with an interval of 1hr for 8 hrs and replaced with fresh dissolution medium after every withdrawl of sample. Absorbance of each sample was measured at 287 nm. Dissolution profiles were analysed by plotting drug release versus time.

5. EXPERIMENTAL RESULTS

5.1 Preformulation studies :

5.1.1 Solubility :

It was determined as per the procedure given in the preformulation in material and equipment part. The results are illustrated in the following table.

Table 5.1 solubility of molnupiravir microbeads:

Test	Specification	Result
Solubility	Soluble in water, ethanol and insoluble in 2-propanal	Compiles (as per specification)

5.1.2 Melting point :

It was determined as per the procedure using melting point apparatus. The results are illustrated in the following table.

Table 5.2 Melting point of Molnupiravir:

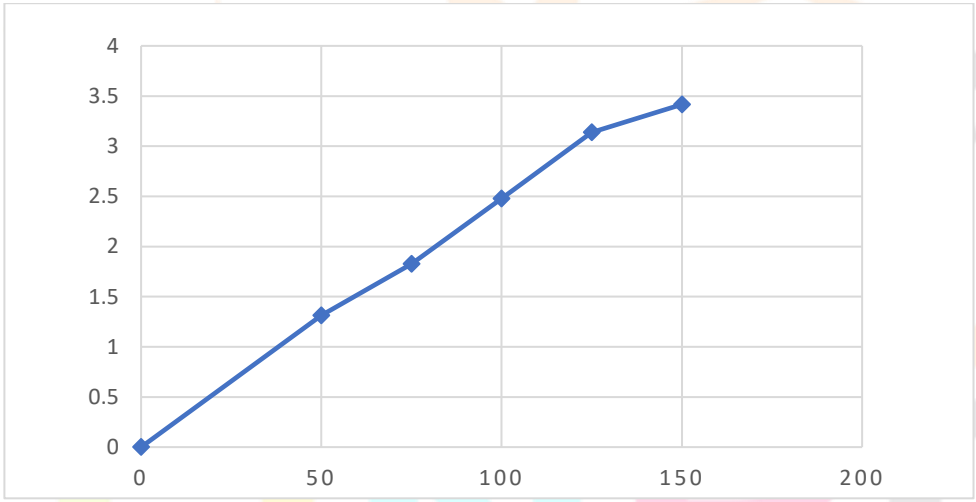
Material	Melting point	Result
molnupiravir	169-172^{0}C	Compiles (as per specification)

5.1.3 UV Spectroscopic method for analysis of Mlnupiravir:

Calibration curve :

Table 5.3 Calibration data of drug

S.NO	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	50	1.312
3	75	1.825
4	100	2.479
5	125	3.138
6	150	3.416



CONCENTRATION (µg/ml)

On X-axis =Concentration(µg/ml)

On Y-axis=Absorbance(nm)

Fig 5.1 Standard calibration curve of Molnupiravir

5.2 Evaluation of Molnupiravir:

5.2.1 Drug – polymer interaction (FTIR) study:

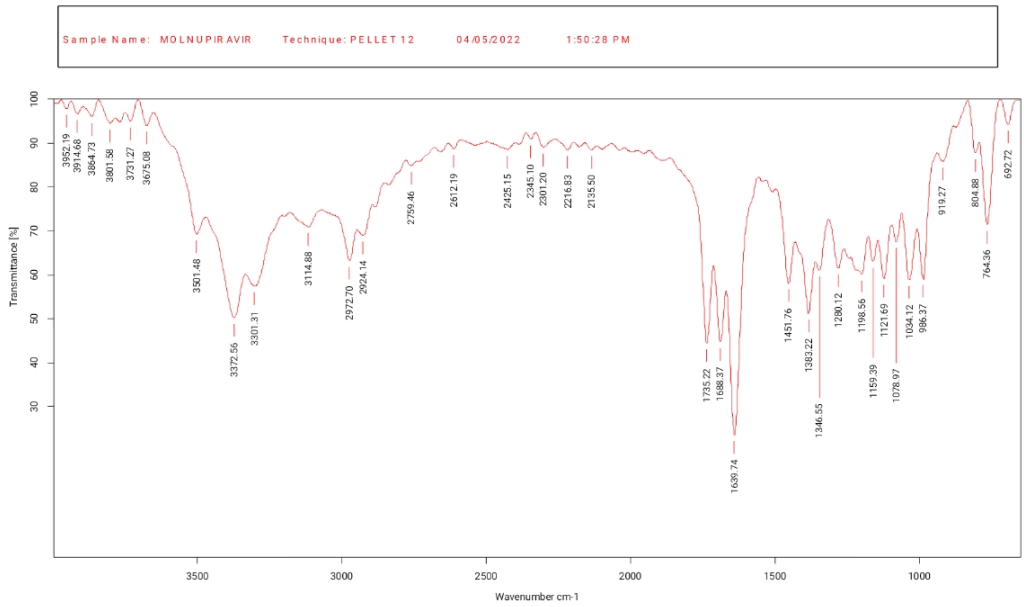
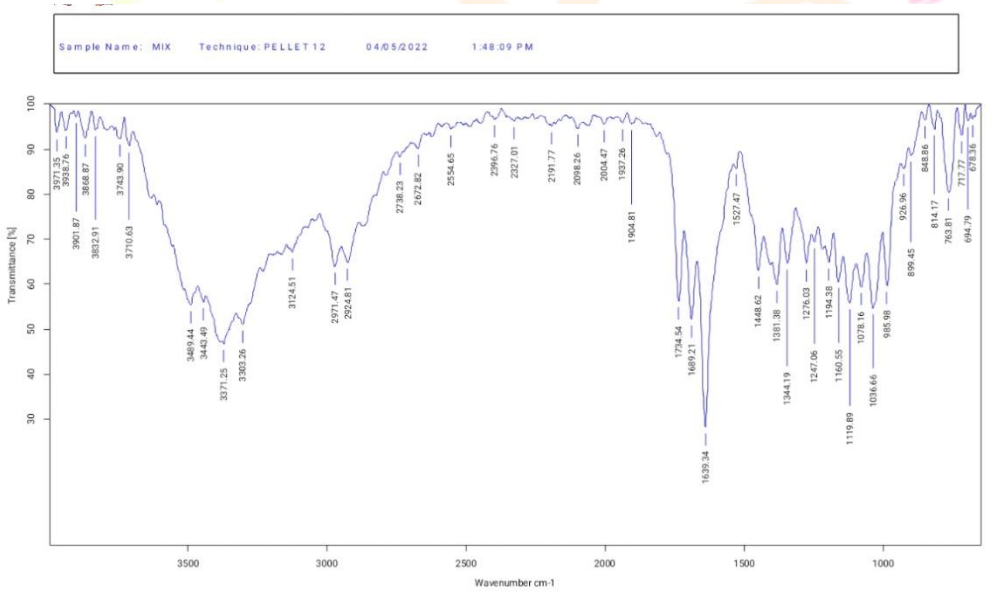


Fig 5.2 FTIR spectra of drug -Molnupiravir



5.2.2 Micromeritic properties :

Table 5.4 Micromeritic properties of Molnupiravir Microbeads

Formulation code	Bulk density(g/ml)	Tapped density(gm/ml)	Carr's index	Hausner ratio	Angle of repose(^{0})
F1	0.478	0.525	08.95	1.09	31.87
F2	0.336	0.435	11.03	1.12	33.49
F3	0.452	0.517	12.57	1.14	32.88
F4	0.592	0.653	09.34	1.22	33.39
F5	0.622	0.693	14.41	1.11	34.24
F6	0.563	0.613	8.96	1.10	32.98

5.2.3 Percentage yield ; percentage drug entrapment ; buoyancy percentage and floating time:

Table 5.5 Efficiency of molnupiravir microbeads

Formulation code	Percentage yield (%)	Percentage drug entrapment (%)	Swelling Index(%)
F1	62.5	73.73	13
F2	78.1	68.55	23
F3	68.7	66.22	15
F4	65.6	71.06	22
F5	81.6	76.47	56.5
F6	64.32	70.54	21.5

5.2.4 Invitro dissolution studies :

Table 5.6 Invitro dissolution properties of molnupiravir microbeads

Time (hr)	Cumulative percentage drug release (%)					
	F1	F2	F3	F4	F5	F6
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	23.18±8.8	24.73± 1.2	25.43± 0.6	22.23± 0.3	26.14± 0.2	26.14± 0.2
2	29.01 ±0.3	31.15 ± 1.2	36.53±0.8	33.48±0.3	37.31±1.2	33.31±1.2
4	34.48±1.2	44.99±0.3	41.74±2.3	48.69±1.3	52.16±2.5	56.16±2.5
6	48.12±0.3	51.03±1.6	58.53±1.2	56.76±0.5	61.32±0.6	60.47±0.6
8	77.38±0.5	79.97±0.8	79.18±0.6	86.73±1.5	88.88±1.6	81.58±1.6
10	93.62±0.8	96.54±1.5	94.78±2.3	93.22±1.2	97.12±0.3	93.32±0.3

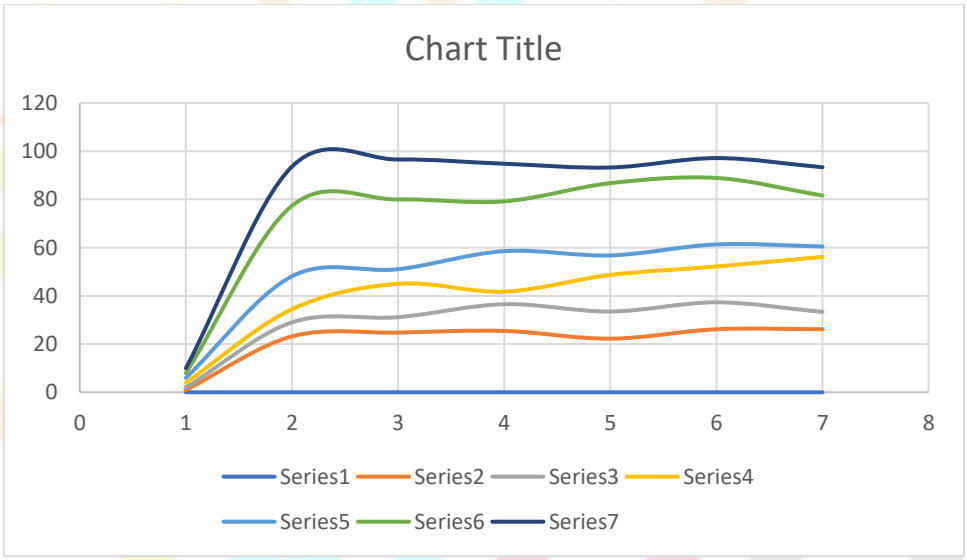


Fig 5.5 *IN-VITRO* Dissolution graph of different formulations

7. SUMMARY

Molnupiravir is anti-viral drug with oral bioavailability .In this work, an attempt was made to formulate and evaluate the microbeads of Molnupiravir which increase the bioavailabilty and to show sustained release of drug. In our work we have formulated six empty microbeads formulations by using various combinations of polymers. Both natural and synthetic polymers like were used. All formulations F1-F6 have been prepared by Ion gelation method & evaluated for their mechanical and *in-vitro* properties. From these parameters, it was observed that the microbeads prepared by Sodium Alginate, Sodium CMC, HPMC, EDTA, Ethanol, Propylene Glycol showed good consistency. Based on the results obtained we have selected formulation the formulations from F1-F6

Molnupiravir shown its characteristic peaks in pure drug and proved its compatibility with the excipients used. The melting point of Molnupiravir shown its purity. Formulations shown uniformity in drug content.

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