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Nanosponge Formulation for the Encapsulation of Molnupiravir: Evaluation of Sustainable Oral Capsule Delivery

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Abstract

The current study was aim to formulate Molnupiravir nanosponges (MLV-NSPs) for a capsule system for controlled drug delivery. MLV-NSPwas fabricated using the emulsion solvent evaporation technique, employing β-cyclodextrin andethyl cellulose aspolymers.Dichloromethane was utilized as a cross-linking agent, and these NSPswere encapsulated within hard gelatine (formaldehyde-treated) capsules. The prepared NSPs were evaluated for physicochemical and morphological characteristics. Out of six NSPs formulations, the optimized NSPs were formulated into a capsule delivery system and further evaluated for drug release pattern.The FTIR demonstrated that there was no potential incompatibility existed among drug and other components. The % ofyield, encapsulation efficiency values are found to be 76.41 to 85.22 % and 69.87 to 77.48 %, respectively for F1-F6 formulations, F5 shows the highest entrapment efficiency of 77.48% with 3-fold enhanced solubilization incomparison with the unprocessed drug. The SEM images of the optimized formulation indicated that the NSPs had a spherical shape, featured a porous surface, and possessed a uniform and spongy texture. The optimised MLV-NSPs (F5) showed a narrow particle size distribution (PDI 0.201 ± 0.04) and a surface charge potential of –38.6 ± 2.1 mV, suggesting uniformity, colloidal integrity, and reproducibility. To enhance mucosal adhesion, prolong residence time, and to avoid dose-dependent side effects, F5 was loaded in treated capsule shells to extend the drug release up to 12 h. A total 8 formulations (S1-S8) were developed for the capsule delivery system. S2 showed 96.15% of medicament released by the 12th h. The dissolution profile of MLV from the optimised capsules (S2) followed a zero-order kinetic model (R^2 = 0.9945), exhibiting non-Fickian diffusion (n = 0.678), suggesting a sustained release that is controlled by both diffusion and polymer degradation.

Keywords: Nanosponges; Molnupiravir; Controlled release; Capsule delivery

Introduction

Molnupiravir (MLV) is an effective antiviral nucleoside analogue approved as an interim therapeutic option for managing mild-to-moderate COVID-19 innon-hospitalized population who are in high risk of infection (1, 2). After being given orally, MLV is quickly absorbed and broken down by esterases into at the time of absorption and the first pass through the liver (3); as a result, no substantial levels of MLV are found systemically in the plasma (4). Systemically distributed NHC converted into NHC active NHC-triphosphate (NHC-TP) (5). The NHC-

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TP functions by inducing viral replication errors, resulting in wrong bases incorporation during each viral replication cycle, leading to the generation of non-viable, non-infectious viruses (6).Oral antiviral treatments provide a more convenient option compared to drugs given through intravenous infusion. For treating Corona with MLV, capsules are prescribed, to be taken at a dose of 800 mg, which is equivalent to four capsules of 200 mg each, given twice a day for a duration of 5 days. A 200 mg capsule formulation was developed to speed up access to the treatment during the COVID-19 pandemic (7). 400 mg film-coated tablets were then formulated to make administration easier.

To avoid a greater number of doses and a pill burden to the patient, the current study aimed to formulate MLV-NSPs for a capsule delivery system, to enhance mucosal adhesion, prolong residence time, and to avoid dose-dependent side effects.

The porous and nanosized polymeric structures increase the surface area and interaction with biological membranes, thereby improving mucosal adhesion and permeability of MLV. In capsule delivery of NSPs it offers protection of MLV from premature degradation (e.g., hydrolysis or enzymatic breakdown), ensuring drug stability during gastrointestinal transit sustainable oral delivery reduces the need for frequent dose administration(8).

Materials and methods

Chemicals

Molnupiravir was sponsored by Dr Reddy's, Visakhapatnam. All the remaining chemicals of AR grade utilized in making of NSPs and capsules delivery system were purchased from Molychem, Mumbai, India.

Formulation and characterization of MLV-NSPs

The NSPs formulation for the encapsulation of MLV was prepared by utilizing the emulsion solvent diffusion technology, inspired by previously published work (9, 10).Six variations of NSPs formulations (F1-F6) were prepared according to the parameters defined in (Table 1). Firstly, a continuous phase was prepared in 10 mL of distilled water by mixing a calculative amount of β-cyclodextrin (BCD) and heated at 40^{o}C using a heating mantle. Now, cool the mixture at room temperature.Secondly, in another beaker required amount of dichloromethane (DCM), ethyl cellulose (EC), and MLV were added. Later, to the continuous phase (i.e., first prepared mixture) is placed on a magnetic stirrer, the dispersed phase, i.e., second mixture, is added dropwise to the continuous phase. Stirring is continued for 2 hat 1000 rpm (rotation per min). The obtained mixture is filtered by using the Buchner funnel, in which filter paper is placed. The collected NSP powder was subjected to vacuum drying below 50 °C under approximately 50–100 mbar for 24 h and the NSPs were collected.

Percentage yield of NSPs

After complete drying, the MLV-NSPs were weighed, and the resulting percentage yield values were tabulated using equation 1.

$$\%\text{Yield} = \frac{\text{PM}-\text{NSPs} \times 100}{\text{TMS}} \quad (1)$$

Table 1: Composition of MLV-NSPs

Formulation	F1	F2	F3	F4	F5	F6
Molnupiravir (mg)	100	100	100	100	100	100
EC (mg)	100	150	200	100	150	200
BCD (mg)	100	100	100	150	150	150
DCM (ml)	5	5	5	5	5	5
Distilled water (ml)	10	10	10	10	10	10
EC- ethyl cellulose, DCM– dichloromethane						

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PM-NSPs- Practical mass of NSPs; TMS-Theoretical mass of solids

Entrapment efficiency

An exact weight of vacuum-dried NSPs corresponding to 10 mg of MLV was taken and re-dispersed in 10 mL of buffer (pH 6.8) through gentle mixing to make an even suspension. The free drug was isolated from the re-dispersed NSPs using centrifugal ultrafiltration units such as the Amicon Ultra, with a 50 kDa molecular weight cut-off. The prepared sample was spun at 6,000 rpm for 15 min at 4 °C, and the filtrate containing the unentrapped drug was carefully collected. The residue was washed once with phosphate buffer, and then centrifuged again; the wash filtrate was combined with the primary filtrate. The diluted filtrate was suitably quantified at 239 nm via UV–VIS spectroscopy. A standard plot was prepared in a blank filtrate, derived from drug-free NSPs that were dispersed and filtered in the same procedure, spanning the concentration range 2–40 µg/mL, taken in triple replicate measurements.

$$\text{Entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad (2)$$

Solubility at saturation

An evaluation was performed to test the improvement in MLV solubility within NSPs by dissolvingan excess amount of NSPs in 10 mL of distilled water (9).

Surface morphological analysis

The size and external morphological features wereinvestigated under scanning electron microscopy (SEM), which operated at an applied voltage of 15kV and 30 kV with a work extent of 14 mm and 41 mm. Samples for imaging were prepared by drop casting a diluted solution of NSPs on copper-coated deposited onto a carbon grid and permitted to dry under room temperature conditions overnight.

Particle characterization parameters

The stability of optimised NSPs was assessed with a Malvern Zetasizer Nano ZS, a device produced by Malvern Instruments, UK. The samples were then diluted with double-distilled water to eliminate the risk of multiple scattering effects occurring prior to analysis. Duplicate measurements were taken at a temperature of 25 degrees Celsius. The polydispersity index (PDI) was used to assess the uniformity of the particle size distribution. The zeta potential was measured through electrophoretic light scattering utilising a disposable folded capillary cell. Values are shown as mean ± standard deviation.

Differential scanning calorimetry (DSC)

To check compatibility or the interaction of API and polymers, differential scanning calorimetry (DSC) was conducted on NSPs and compared to the individual polymers and the API. The DSC was calibrated beforehand using Indium and lead reference standards. Aluminium pans with crimped edges, containing samples weighing between 3-5 mg, were heated under a nitrogen atmosphere, with a temperature ranging from 30-350 oC, at a rate of 10oC/min. The enthalpy of fusion and melting point were calculated using automation processes.

FTIR (Fourier Transform Infrared Spectroscopy)

Fourier transformed infrared spectroscopy (FTIR) spectra were obtained for the prepared formulations. The samples prepared underwent compatibility analysis, and the outcomes of this analysis were discussed in the results section.

Dissolution profiling

The in-vitro drug release of MLV-NSPs was evaluated using a USP type II (paddle) dissolution apparatus (DS 8000) with a dialysis membrane (MWCO 12–14 kDa, HiMedia, India). The membrane was pre-soaked overnight in phosphate buffer (pH 7.4) to ensure hydration. An accurately weighed amount of NSPs, equivalent to 100 mg of drug, was sealed in the membrane bag and immersed in 50 mL of dissolution medium maintained at 37 ± 0.5 °C with stirring at 100

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rpm. At 10 min intervals, 5 mL samples were withdrawn up to 60 min and replaced with fresh buffer to maintain sink conditions. Samples were appropriately diluted and analyzed at 239 nm using a UV–visible spectrophotometer.

Data were expressed as mean ± SD (n = 3). Entrapment efficiency (EE) and drug release (%) across formulations (F1–F6, S1–S8) were compared by one-way ANOVA using GraphPad Prism (v9.5.1), with significance set at $p < 0.05$.

Preparation of capsules

The powdered form of NSPs was transformed into capsules according to the procedure previously reported. Firstly, defined quantities of NSPs were mixed with excipients such as microcrystalline cellulose (MCC) and lactose in different concentrations as shown in (Table 2). Secondly, the shells were treated with formaldehyde solution in different concentrations (i.e., 0-3.5 %) under strict process control. Finally, such treated capsule shells were loaded with the excipient-NSP mix.

Evaluation of MNC

Weight variation

The weight variation test specified in the Indian Pharmacopoeia was performed on 20 individual capsules to determine their mean weight and calculated using formula 3.

$$\%\ \text{Weight variation} = \frac{\text{Individual Weight} - \text{Average Weight}}{\text{Average Weight}} \text{X } 100 \quad (3)$$

Drug content

The average weight was calculated by selecting five capsules randomly. A certain amount of powder was adjusted to the total volume of 100mL by adding phosphate buffer, andit was kept 12 h. 1ml of fluid was further mixed to get total volume of 50ml in the separate container and absorbance was recorded at 239 nm.

Content Uniformity

Weight variation of fillings in hard gelatine capsules with high drug loads and high fill weights (230 mg per capsule) can be used to assess the uniformity of active ingredient content. The potency method must be employed to individually assess the content of the active ingredient in each capsule, particularly for formulations with low drug loads and fill weights. When the predetermined standards for the active ingredient's range and variation are met, uniformity of content is ensured.

Moisture permeation test

Expose the sealed unit to a pre-determined relative humidity for a set period to evaluate its moisture penetration characteristics. Inspect the desiccant pellet for any changes in its colour. A colour change signifies the absorption of moisture.

Permeability and sealing

Capsule shellsundergo mechanical robustness testing to ensure there is no leakage, typically through visual inspection. In

Table 2: Composition of MLV-NSPs loaded capsules

Code	MNC-1	MNC-2	MNC-3	MNC-4	MNC-5	MNC-6	MNC-7	MNC-8
Pure drug	100	_	_	_	_	_	_	_
MLV-NSPs (Equivalent to 100mg of pure drug)	–	145	145	145	145	145	145	145
MCC	65	10	25	35	40	50	60	75
Lactose	65	75	60	50	45	35	25	10
Total weight	230	230	230	230	230	230	230	230
*All the ingredients are taken in mg; MNC-Molnupiravir Nanosponge capsule								

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the same way hard gelatine capsules also tested to identify such breaches like damage or cap–body separation.

Microbial content

Microbiological tests are conducted to verify the presence of bacteria and mould within the capsules. The test was performed by placing the capsule's components in a culture medium and then measuring growth after a specified period and ensuring aseptic conditions are maintained throughout the test.

***In-vitro* drug release pattern**

Testing for dissolution was conducted with a USP apparatus (model- DS8000) type 2 (paddle) at a speed of 50 rpm, keeping all other conditions as per the pharmacopoeial guidelines. The method utilising pH change was used to replicate gastrointestinal transit, which involved the use of 0.1 N HCl (pH 1.2) for 0-2 h, acetate buffer (pH 4.5) for 2-4 h, phosphate buffer (pH 6.8) for 4-8 h, and phosphate buffer (pH 7.4) for 0-12 h. At regular time points, 5 mL of the medium was sampled and replaced with equivalent volumes of freshly prepared medium. The samples were filtered through a 0.45 µm pore size and analyzed under UV at a wavelength of 239 nm. The results were presented as the mean ± standard deviation, with data from three separate tests. A one-way analysis of variance (ANOVA) was used to evaluate differences in the cumulative percent of drug release between formulations. A p-value of less than 0.05 was taken to be statistically significant.

Evaluation of release kinetics

To understand how MLV is released from NSPs loaded in capsules designed for extended release, the release kinetics were examined using a zero-order (where Cumulative release of the drug was plotted versus time). The release kinetics were determined using the provided equation.

$$C = k_o t \quad (4)$$

In this context, ko= zero-order rate constant, C= the quantity of drug released at time "t".

Results and Discussion

Formulation and assessment of MLV-NSPs

MLV is an active antiviral pharmaceutical used for treating RNA viruses, causing burst release due to its greater aqueous solubility. To promote a prolonged sustainable release, a NSP formulation of MLV, has been developed via the emulsion solvent diffusion technique using some copolymers. The procedure has been inspired and modified from previously published work(11). Briefly, an aqueous solution of Beta-cyclodextrin was added dropwise to a pre-prepared solution mixture of MLV and Ethyl cellulosedissolved in dichloromethane. Ethyl cellulose is a hydrophobic polymer with compatibility to encapsulate like MLV, while the cyclodextrin in this encapsulation strategy, acts as hydrophilic shell to confer water solubility to the NSP(12). The drop-wise addition of β-cyclodextrin solution into the organic phase gradually initiates the polarity changes, which force APIs to entrap within the EC core. β-cyclodextrin in the reactions functions not only as a hydrophilic domain, but also as a surfactant to stabilize the structures. As defined in Table 1, various optimizing conditions were explored by manipulating the amount of EC and β-cyclodextrin. Among those conditions displayed in (Table 3), F5 produced NSPs with excellent entrapment efficiency, likely due to the usage of a balanced proportion of co-polymers (13). In addition, NSPs exhibited amorphous surface, with pseudo-spherical shape of size range between 190-210 nm (14). NSPs have a mean size of 204 nm, was shownin (Fig. 1). Table 3 displays the values for evaluation of MLV-NSPs.

The EE of NSPs formulations (F1–F6) were calculated by first separating the free (unentrapped) drug via centrifugal ultrafiltration and then quantifying it using UV–VIS spectrophotometry.

The EE for the NSPs formulations were listed in (Table 3). All formulations showed high EE, varying between 69.87 ±

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Table 3: Evaluation of MLV-NSPs			
Code	Entrapment efficiency (%)	Saturated Solubility (gm/100ml)	%Yield
Pure drug	-	2.17±0.11	-
F1	72.57±0.15	3.11±0.18	76.41±0.13
F2	69.87±0.23	2.67±0.21	80.17±0.21
F3	70.25±0.19	3.76±0.23	81.63±0.23
F4	74.73±0.22	4.01±0.16	78.63±0.15
F5	77.48±0.14	4.91±0.18	85.22±0.16
F6	71.08±0.16	2.98±0.22	79.91±0.14
Mean ± standard deviation			

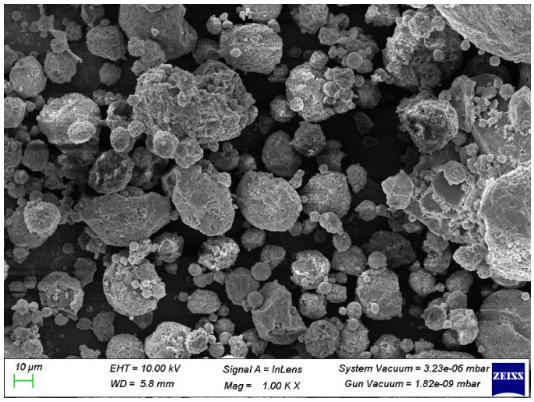

Fig. 1: SEM photographs of MLV-NSPs

0.23% and 77.48 ± 0.14%. Formulation F5 showed the highest EE at 77.48 ± 0.14%, which was greater than F4 at 74.73 ± 0.22%. The results indicated that the NSPs system successfully held onto a significant portion of the drug, implying strong interactions between the drug and the polymer, as well as effective encapsulation. The method demonstrated high precision, with triplicate measurements resulting in relative standard deviations (RSD) of less than 2% across all concentrations, thereby verifying assay repeatability and reliability

The entrapment efficiency of the nanosponge formulations varied from 69.87 ± 0.23% (F2) to 77.48 ± 0.14% (F5) (Table 3). ANOVA indicated a notable impact among the formulations ($p < 0.0001$). A comparison of individual means revealed that formulation F5 had a significantly higher entrapment efficiency compared to remaining NSPs formulations.

The release of the drug at 60 min fell within a range of 86.57 ± 0.15% (F1) to 97.48 ± 0.14% (F5). ANOVA analysis showed a significant disparity amongst the formulations ($p < 0.0001$). ANOVA confirmed a significant variation in EE and drug release among the NSP formulations, with F5 demonstrating superior entrapment anddelivery pattern among others. The improvedEE of F5 can be attributed to the optimized polymer–drug ratio, which established a beneficial matrix structure for drug incorporation. The higher % of drug release of F5 suggests an improved dissolution profile, which is likely due to better wettability and lower crystallinity of the drug within the NSP matrix. Formulation F5 was chosen as the optimised version from the six examined formulations due to its beneficial qualities concerning solubility, drug EE, and drug release as per the study by Sengupta (16). The optimized formulation was subsequently reformulated into a capsule format, as illustrated in (Table 2).

The percentage yields of the non-starch polysaccharides fell within a range of 76.41-85.22%, with the highest yield of 85.22% achieved in the F5 formulation. The percentage yield decreased as the concentrations of co-polymer differed. A combination of 150 mg of β-cyclodextrin and ethyl cellulose co-polymer was chosen as the optimised formulation. The F5 formulation resulted in an entrapment efficiency of 77.48%. Low entrapment rates have been attributed to the adhesive properties of the ethyl cellulose polymer. Preparation of the NSPs enhanced their solubility. The F5

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formulation yielded a solubility that was three times higher.

The spherical-shaped numerous MLV-NSPs were characterised using SEM analysis and are depicted in (Fig. 1). The porous nature of the NSPs is demonstrated.

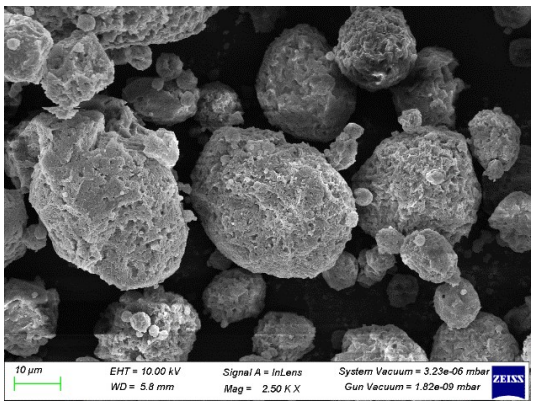

Fig. 2: The porous nature is demonstrated the NSPs

A feature observed in the pores is an inward tunneling pattern, which appears to result from the migration of DCM from the NSP outer layer, as illustrated in (Fig. 2).

The MLV-NSPs demonstrated a narrow size distribution with a PDI of 0.201± 0.04, indicating a high degree of homogeneity in F5 formulation (Fig. 3). A zeta potential of –38.6 ± 2.1 mV indicates sufficient electrostatic repulsion between particles to guarantee colloidal stability (Fig. 4). Values obtained from the experiments indicate that the formulation F5 exhibited stability and repeatability under the conditions that were examined.

The spectra of FTIR of pure drug (MLV) and MLV-NSPs optimised formulation are shown in (Figs. 5 and 6). From the spectral study, no alteration in the peaks of optimized formulation (MLV-NSPs, MCC, lactose). Therefore, it can be inferred that there was no chemical incompatibility among the components of optimized formulation.

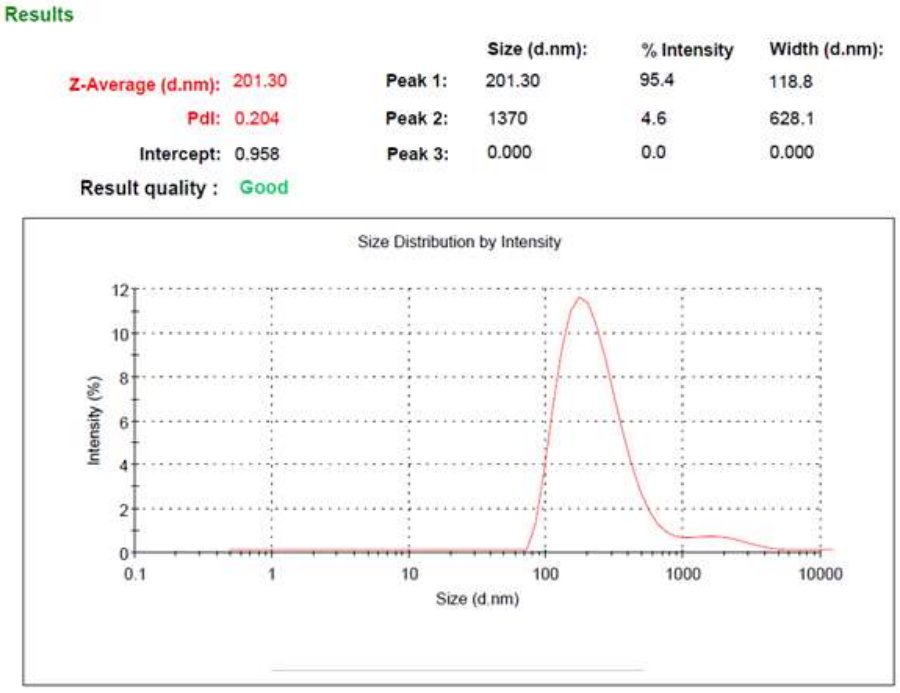

Fig. 3: Size distribution of optimized NSPs

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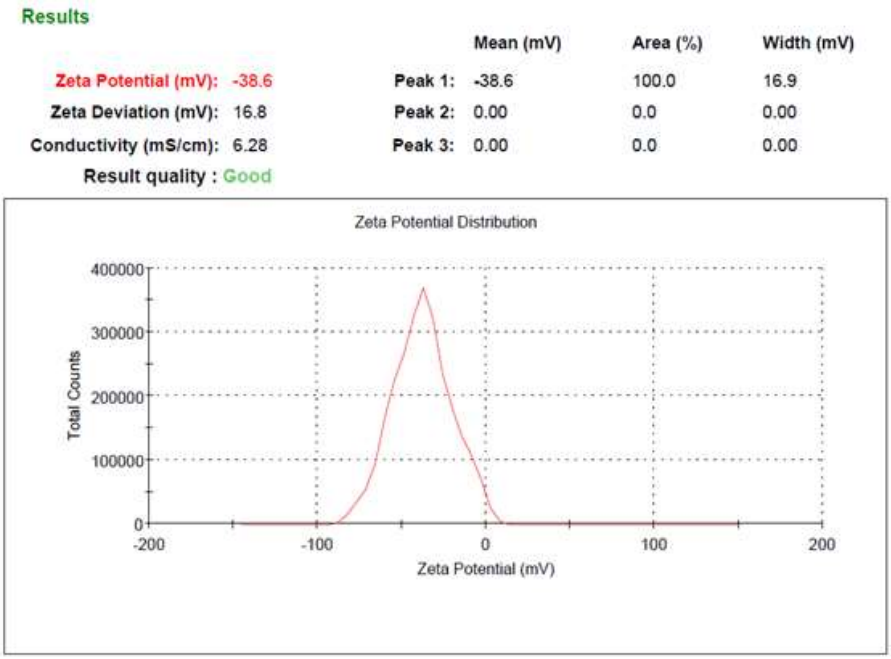

Fig. 4: Zeta potential of optimized NSPs

The thermogram for pure MLV exhibits a distinct curve at 162.9 ºC, coinsides to its melting point as illustrated in (Fig. 7). MLV-NSPs exhibited a comparable endothermic peak at 169.2 ºC, as depicted in (Fig. 8), thereby substantiating the lack of polymer-drug interaction (15).

Weight variation test

In order to ensure the consistency and uniformity of the capsule dosing, a weight variation test has been performed on 20 capsules, expecting each capsule to be in the weight range of 230 mg. Weight variation test presented an excellent uniformity, with an average weight of 226±0.13 to 232±0.18 mg that with a weight variation of 0.4 %, which is well fit within the acceptable limits, set by regulatory guidelines (±5%).

Moisture permeation analysis

The moisture permeation analysis on samples revealed an absorption value of 5 %, indicating the need for careful attention to maintain recommended storage and packaging conditions,to prevent the degradation of API and maintain the stability. In contrast, the uniformity test on capsules revealed a consistent distribution of active ingredient i.e, 100 mg with a SD of 1.5 mg (a RSD of 1.5 %), which reportedly fulfils the regulatory standards.

Microbial content

Microbial content within the final capsule formulation was evaluated according to a standard protocol. Results showcased in the (Table 4), highlights low microbes' content in the formulation. The values reported were within the acceptable range, with total aerobic bacteria at 10^3 CFU/mL and total yeasts andmolds at 10^2 CFU/g. Significantly, the traces of commonly found microbeswere not detected in the respective sample, which confirms the safety and microbial quality of the formulation(17, 18).

Formulation and assessment of controlled release capsules

The *in-vitro* drug release profile of MLV-NSPs encapsulated in gelatin capsules

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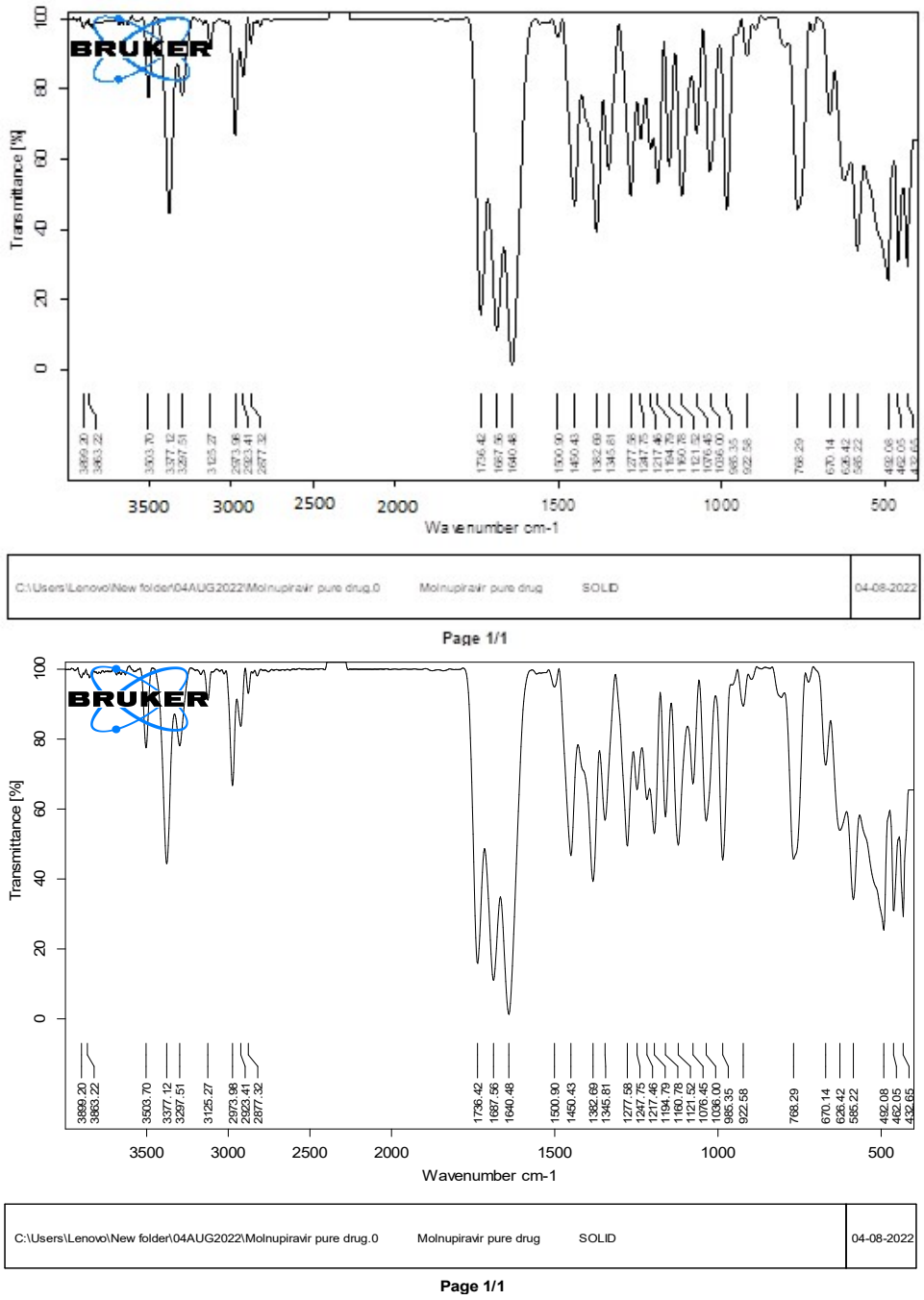

Fig. 5: FTIR of MLV pure drug

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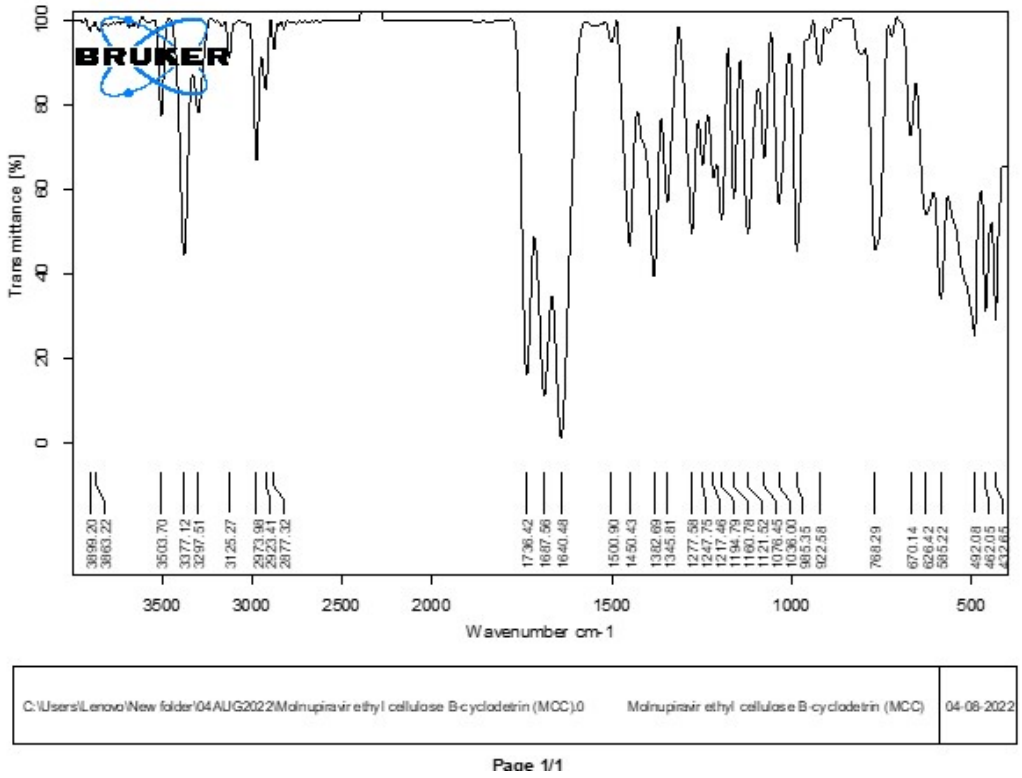

Fig. 6: FTIR of optimised formulation (S2)

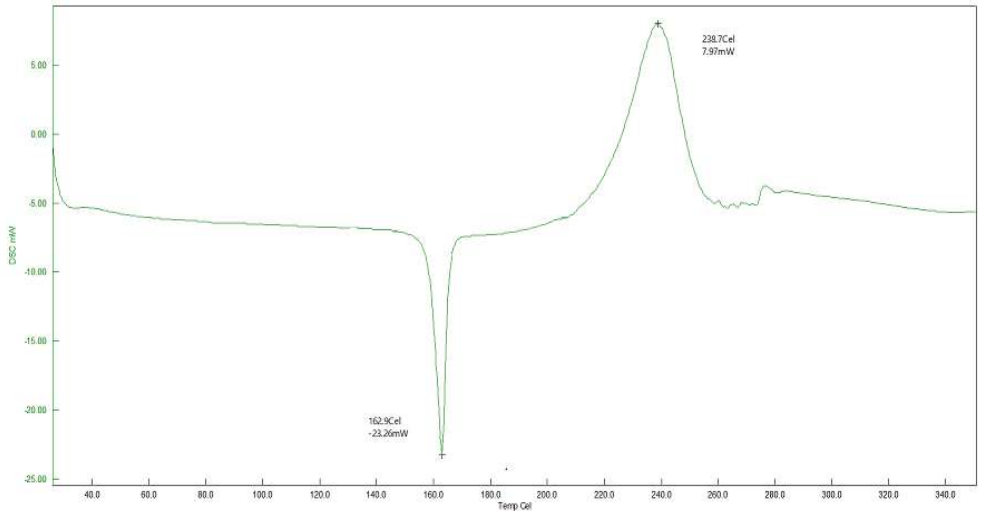

Fig. 7: Thermal analysis for MLV

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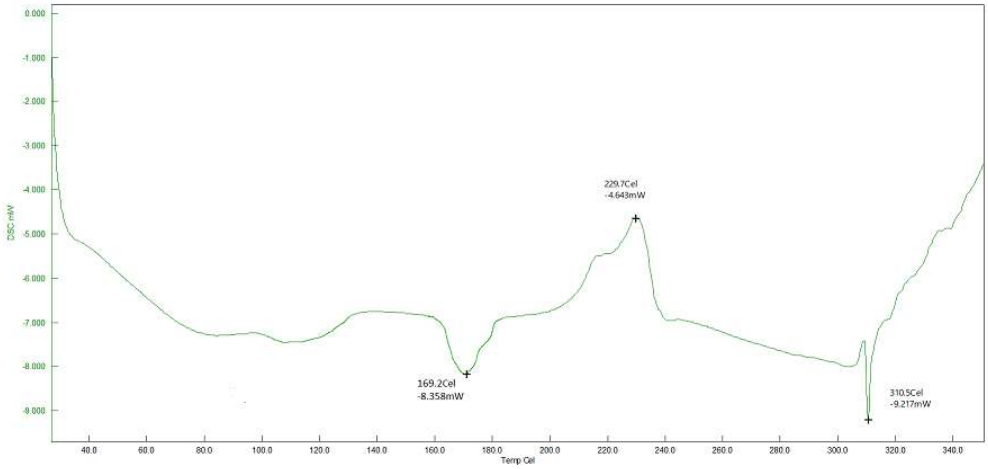

Fig. 8: Thermal analysis for drug loaded NSPs

Table 4: Microbial limit of MLV-NSPs loaded capsule		
Microbes indicator	Limit	Result
Total aerobes	≤ 10^3 CFU/g	Under the limit
Yeasts and fungi	≤ 10^2 CFU/g	Under the limit
P. aeruginosa	Not present in 1 g	Not found
S. aureus	Not presentin 10 g	Not found
E. coli	Not present in 1 g	Not found
Salmonella spp.	Not presentin 1 g	Not found

treated with formaldehyde was assessed in a phosphate buffer with a pH of 7.4 for 12 h. The cumulative release percentages are shown in (Table 5 and depicted in Fig. 9). An initial rapid release was seen in formulation S1 (98.8 ± 0.15% at 12 h), whereas other formulations (S2-S8) showed a prolonged drug release pattern, with final drug release rates ranging from 75.9 ± 0.26% to 96.1 ± 0.18% at 12 h. Formulations S3–S6 exhibited a gradual release pattern over 12 h, with 80–88% release, thereby confirming the controlled release capabilities of the nanosponge-loaded capsule system.

Additional dissolution studies were conducted under various pH conditions to simulate gastrointestinal environments. In a low pH environment (pH 1.2), the release remained insignificant with ≤12% in 2 h, confirming the protective effect of formaldehyde-treated capsule shells. At pH 4.5, the cumulative release was approximately 22-28% after 4 h, whereas at pH 6.8, release increased further to approximately 50-55% by 8 h. Maximum release was achieved in a pH 7.4 buffer, as outlined in (Table 5), with the release ranging from 76-98% at 12 h depending on the specific formulation. The results show that drug release was limited in gastric-like conditions, moderate in intestinal transition pH, and optimal in colonic pH, which validates the controlled release design of the capsule formulations.

MLV capsules were evaluated for drug release pattern and results were given in

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Table 5: % Drug release of MLV-NSPs in capsule formulation

Time (mins)	S1	S2	S3	S4	S5	S6	S7	S8
0	0	0	0	0	0	0	0	0
5	22.92± 0.21	4.78±0. 22	3.9±0.3 3	3.36±0. 32	3.12± 0.32	3.97± 0.32	3.72± 0.33	3.22± 0.25
10	36.4±0. 17	7.45±0. 31	6.29±0. 21	4.02±0. 22	4.09± 0.23	7.5±0. 36	5.11± 0.35	5.89± 0.27
30	48.49± 0.23	8.61±0. 12	7.45±0. 15	7.41±0. 17	7.69± 0.26	10.69 ±0.24	8.69± 0.26	8.67± 0.35
60	58.57± 0.15	15.41± 0.16	13.56± 0.22	10.31± 0.13	11.61 ±0.17	15.11 ±0.26	11.74 ±0.24	11.76 ±0.33
120	65.22± 0.16	24.13± 0.15	20.56± 0.14	20.56± 0.22	18.2± 0.14	21.39 ±0.22	12.95 ±0.18	14.27 ±0.30
180	73.64± 0.13	31.51± 0.11	28.79± 0.23	30.32± 0.24	26.3± 0.13	27.51 ±0.15	22.3± 0.26	20.74 ±0.26
240	86.31± 0.12	41.1±0. 33	37.36± 0.34	41.78± 0.28	35.2± 0.14	32.98 ±0.18	28.47 ±0.28	26.12 ±0.25
300	98.15± 0.11	49.27± 0.24	42.67± 0.25	46.98± 0.15	41.16 ±0.26	38.72 ±0.18	35.55 ±0.26	35.33 ±0.26
360	98.26± 0.32	55.37± 0.34	50.06± 0.17	52.12± 0.13	45.41 ±0.25	43.87 ±0.24	38.84 ±0.33	40.66 ±0.28
420	98.37± 0.24	62.12± 0.16	58.99± 0.23	56.78± 0.17	51.6± 0.34	50.01 ±0.28	45.39 ±0.37	46.62 ±0.18
480	98.58± 0.18	70.14± 0.22	65.42± 0.13	63.62± 0.23	58.39 ±0.27	55.46 ±0.23	53.45 ±0.17	54.17 ±0.27
540	98.66± 0.32	76.81± 0.24	71.98± 0.22	71.76± 0.32	66.8± 0.13	61.09 ±0.28	58.7± 0.19	57.76 ±0.24
600	98.76± 0.25	86.21± 0.15	80.1±0. 27	76.86± 0.23	71.17 ±0.11	68.32 ±0.31	64.54 ±0.11	67.7± 0.17
660	98.78± 0.26	91.97± 0.13	86.21± 0.32	87.90± 0.27	79.19 ±0.26	75.98 ±0.20	70.57 ±0.22	72.11 ±0.22
720	98.80± 0.15	96.15± 0.18	91.31± 0.12	88.55± 0.26	85.74 ±0.24	81.21 ±0.14	79.29 ±0.26	75.89 ±0.26

(Table 5). Drug release patternof MLV-NSPs in capsule system was done three times.

In S1, MLV pure API was used, kept the other ingredients same as other formulations. In S2, 145 mg of NSPs is equivalent to 100mg of drug. The capsule shells which were used for S2-S8 formulation were treated with formaldehyde solution in different concentrations (i.e., 0 – 3.5 %). S1 released 98.15% at the 5^{th} h but S2 released 96.15% at the end of the 12^{th} h (Fig. 7). Treated capsule has extended the drug release beyond the pure drug. The elimination half-life of MLV is 3-4 h. Treatment with formaldehyde leads to the reaction with amino groups in gelatine, resulting in cross-linking of gelatine molecules via methylene bridges. Capsule shell is

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Table 6: *In-vitro* kinetic analysis (R^2 values)

Formulation	Zero order	First order	Higuchi	Korsemeyerpeppa's R^2value - n value
S1	0.9853	0.9761	0.9904	0.9784 - 0.6552
S2	0.9945	0.8768	0.9917	0.9901 - 0.678
S3	0.9901	0.9652	0.9469	0.9814 - 0.6678
S4	0.9359	0.9517	0.9507	0.9777 - 0.6548
S5	0.9476	0.9797	0.9536	0.9687 - 0.7063
S6	0.8179	0.9342	0.9473	0.9765 0.6902
S7	0.9371	0.9917	0.9905	0.9711 0.6595
S8	0.8882	0.9528	0.9489	0.9743 0.687

becoming less water soluble, more rigid, dense, and resistant to enzymatic degradation, and extends the drug release, so the elimination half-life was increased. As the concentration of formaldehyde increases there is more retardation of drug release.

Statistical analysis using one-way ANOVA indicated a significant variation ($p < 0.0001$) among formulations at various intervals (from 60 min to 720 min). Analysis after the fact showed that S2 released significantly more compared to S5, S6, S7, and S8 ($p < 0.01$), whereas S7 and S8 released at a slower pace ($p < 0.05$ compared to S1–S3). By the end of 720 min, S2 had the highest cumulative release rate (96.15 ± 0.18%), while S7 and S8 showed the lowest release rates (79.29 ± 0.26% and 75.89 ± 0.26%, respectively), indicating substantial differences among the formulations.

ANOVA revealed that the delivery features of the drug from capsule system (S1–S8) were considerably distinct throughout the study duration.ANOVA data hasconfirmed that the capsule formulation has a pronounced effect on drug delivery, and statistical analysis supports the choice of the most effective systems for further assessment.The release pattern of drug from the capsule system were analyzed using various kinetic approaches described by Lakshmi *et al*. (19).

In-vitro kinetic analysis

Release pattern of MLV-NSPs loaded capsule system was fitted into the various pharmacokinetic effects and the results shown in (Table 6 & Fig. 9).

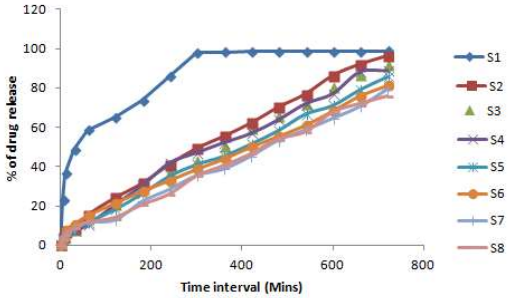

Fig. 9: Cumulative % of release of drug

The optimized formulation (S2) showed the highest correlation with the zero-order model ($R^2 = 0.9945$), implying that the release rate remained nearly constant over the observed period. A good fit to the Higuchi model ($R^2 = 0.9917$) at the same time implies that diffusion through the polymeric matrix is a major contributing factor. The Korsmeyer–Peppas analysis produced a value of $n = 0.678$ for the exponent, a result that falls within the range for non-Fickian diffusion, indicating that the drug discharge is influenced by the combined process of diffusion and polymer relaxation. The optimized capsules exhibit anomalous drug release, which can be characterised as zero-order kinetics, primarily driven by the diffusion through the polymericnetwork, with polymer swelling and erosion also playing a contributing role. This dual mechanism accounts for the sustained and controlled release behavior noted in the formulations (20).

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Conclusion

Successfully formulated a controlled-release capsule containing molnupiravir nanosponges (MLV-NSPs) through the emulsion solvent evaporation technique, employing β-cyclodextrin and ethyl cellulose as the polymers used. Formulation F5, out of the six NSPs formulations (F1–F6), displayed the highest entrapment efficiency at 77.48% and exhibited a threefold increase in solubility relative to the pure drug. Analysis by scanning electron microscopy showed that spherical, porous, and uniform NSPs had formed. Formaldehyde-treated gelatine capsules were used to further develop F5 into a capsule dosage form that would release MLV over up to 12 h. Eight different capsule formulations (S1 through S8) were developed, with formulation S2 exhibiting the highest level of drug release (96.15 % at 12 h). Infrared spectroscopy (FTIR) analysis confirmed the absence of substantial interaction among the formulation ingredients, and all evaluated parameters following formulation were within acceptable pharmacopeial standards. The optimized capsules exhibited anomalous drug release, which can be characterised as zero-order kinetics, primarily driven by the diffusive transport of the drug in the polymer network, with polymer swelling thereby playing erosion also. The capsule system based on MLV-NSPs technology presents a promising approach for achieving long-term release of MLV, increasing its solubility, boosting its ability to adhere to mucous membranes, extending the time the drug stays in the body, and potentially reducing side effects associated with high doses.

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