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Development And Optimization of Apixaban-Loaded Mesoporous Silica Nanoparticle Incorporated into Oral Disintegrating Films Using Quality by Design Approach

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ABSTRACT:
Apixaban, a BCS Class II anticoagulant, exhibits poor aqueous solubility and dissolution-limited oral absorption that may compromise its therapeutic performance, motivating development of an Apixaban-loaded mesoporous silica nanoparticle (MSN)-based oral disintegrating film (ODF) to enhance dissolution and improve patient compliance. Mesoporous silica nanoparticles were synthesized via a surfactant-templated sol-gel method and loaded with the drug through solvent immersion–evaporation, following preliminary screening for suitable film-forming polymers and superdisintegrants. The optimized nanoparticles were incorporated into films prepared by solvent casting, with a 3^2 factorial Quality by Design approach optimizing the HPMC E5: Pullulan Concentration and Kollidon® CL-SF concentration. Films were evaluated for physicochemical and mechanical properties like drug content, *In vitro* disintegration, moisture behaviour, dissolution, release kinetics, and stability under ICH conditions. The optimized MSN formulation achieved high entrapment efficiency, satisfactory drug loading, and enhanced solubility; among the factorial batches, formulation ASMF5 was superior, showing a folding endurance of 379.67 ± 1.53, drug content of 99.73 ± 0.25%, disintegration within 9.18 ± 0.91 s, and cumulative release of 62.41 ± 0.78% at 2 mins. and 99.75 ± 0.85% at 14 mins. Response surface analysis confirmed that polymer composition and superdisintegrant concentration significantly influenced critical quality attributes, while checkpoint analysis showed excellent agreement between predicted and experimental responses. Release followed the Higuchi model, indicating diffusion-controlled transport from the mesoporous matrix, and stability studies confirmed retention of physicochemical, mechanical, and dissolution performance over six months. This QbD-optimized platform represents a promising patient-centric strategy for delivering poorly water-soluble drugs to pediatric, geriatric, and dysphagic patients.

INTRODUCTION:

Apixaban is a selective factor Xa inhibitor widely prescribed for the prevention and treatment of venous thromboembolism, deep vein thrombosis, pulmonary embolism, and stroke associated with non-valvular atrial fibrillation. Despite its predictable pharmacokinetic profile, minimal drug interactions, and freedom from routine monitoring, its classification as a BCS Class II drug results in poor aqueous solubility, limiting dissolution and oral bioavailability.[1] Mesoporous silica nanoparticles (MSNs) have emerged as an effective strategy to overcome this limitation owing to their high surface area, tunable pore structure, biocompatibility, and ability to convert crystalline

drugs into stable amorphous forms, thereby enhancing dissolution and preventing recrystallization.[2] Oral disintegrating films (ODFs) further improve therapeutic performance by providing rapid disintegration without water, making them particularly suitable for pediatric, geriatric, dysphagic, and bedridden patients while facilitating faster drug release and improved patient compliance.[3] The performance of ODFs is strongly influenced by the composition of the polymer matrix and superdisintegrants, necessitating optimization to achieve an appropriate balance between mechanical strength, flexibility, disintegration, and dissolution.[4] Quality by Design (QbD), recommended by ICH guidelines, offers a systematic framework for formulation optimization using statistical experimental designs, with a 3^2 full factorial design enabling efficient evaluation of formulation variables and their interactions.[5] Although nanotechnology-based systems and oral films have been investigated separately, studies integrating apixaban-loaded MSNs into ODFs with QbD-driven optimization remain scarce.[6] Therefore, the present study developed and optimized apixaban-loaded MSN-based ODFs using solvent casting and a 3^2 full factorial QbD approach, followed by comprehensive physicochemical, mechanical, dissolution, release kinetic, statistical, validation, and stability evaluations to establish a robust and patient-friendly delivery system.[7] The present study aimed to develop and optimize Apixaban-loaded mesoporous silica nanoparticle-based oral disintegrating films using a Quality by Design (QbD) approach. The study focused on enhancing the drug's solubility and dissolution rate while achieving rapid disintegration, desirable mechanical properties, formulation robustness, and stability to improve oral drug delivery and patient compliance.

MATERIALS AND METHODS:

Materials:

Cetyltrimethylammonium bromide (CTAB), Sodium Hydroxide (NaOH), Sodium Starch Glycolate (SSG), Croscarmellose Sodium (CCS), Hydroxypropyl Methylcellulose (HPMC E5), Polyvinyl Alcohol (PVA), Citric Acid, Sucralose, Pregelatinized Starch, D-Mannitol, Aspartame, Sodium Lauryl Sulfate (SLS), and Magnesium Stearate were procured from Chemdyes Corporation, Rajkot, India. Tetraethyl orthosilicate (TEOS), Triethanolamine (TEA), Ethanol, and Propylene glycol were purchased from Actylis Lab Solution, Ahmedabad, India. Deionized water and Hydrochloric Acid (HCl) were obtained from Finar Chemicals, Ahmedabad, India. Pullulan, Polyvinylpyrrolidone K-30 (PVP K-30), Sodium Alginate, and Talc were supplied by Astron Chemicals, Ahmedabad, India. Kollidon® CL-SF and Poloxamer 188 were generously provided by BASF India Ltd., India. All chemicals and reagents used in the study were of analytical reagent (AR) grade.

Pre-formulation studies:

Determination of Melting Point of Apixaban:

The melting point of Apixaban was determined using a digital melting point apparatus with the capillary tube method, following Indian Pharmacopoeia guidelines. Powdered drug was packed into a sealed capillary and heated gradually. Onset and complete melting temperatures were recorded in triplicate, and the average was compared against reported standard values to confirm identity and purity. A narrow melting range indicated good crystalline purity, while any notable deviation would suggest impurities or changes in crystalline structure.[8]

Determination of Apixaban by UV Spectroscopy

A stock solution of Apixaban at 100 ppm was prepared in pH 1.2 buffer, pH 6.8 phosphate buffer, methanol, and distilled water. Serial dilutions ranging from 5 to 25 ppm were scanned on a double-beam UV-Visible spectrophotometer, and the wavelength of maximum absorption was identified at 278 nm. Calibration curves plotted as absorbance versus concentration demonstrated good linearity across all media. This method was then applied for quantitative estimation of Apixaban in drug content, solubility, and dissolution studies.[9,10]

Determination of Drug–Excipient Compatibility by FTIR

Drug–excipient compatibility was evaluated using Fourier Transform Infrared (FTIR) spectroscopy with a Bruker Platinum ATR-FTIR spectrophotometer (Bruker Optics, Germany). FTIR spectra of pure Apixaban, blank MSNs, and Apixaban-loaded MSNs were recorded over a wavenumber range of 4000–400 cm^{-1} to identify characteristic functional groups and assess possible interactions between the drug and formulation components. The obtained spectra were compared for any significant shifts, disappearance, or appearance of new absorption bands. The absence of notable spectral changes confirmed the chemical stability of Apixaban and its compatibility with the excipients and materials used in the preparation of MSNs.[11]

Mesoporous Silica Nanoparticles (MSNs)

MSNs were synthesized using a surfactant-templated sol-gel method employing CTAB as the structure-directing agent and TEOS as the silica precursor. A total of 16 formulation batches (ASM1–ASM16) were prepared by systematically varying the concentrations of CTAB, TEOS, TEA, and NaOH to investigate their influence on the physicochemical characteristics of the nanoparticles. Briefly, CTAB was dissolved in an ethanol–deionized water mixture, followed by the addition of TEA and NaOH as catalytic agents. After pH adjustment with dilute hydrochloric acid, TEOS was added dropwise under continuous stirring at controlled temperature to facilitate silica condensation around the CTAB micelles. The obtained nanoparticles were recovered by centrifugation, washed thoroughly, dried, and subsequently calcined at 550 °C to remove the surfactant template and generate the mesoporous structure. Apixaban was then incorporated into the optimized MSNs using the solvent immersion–evaporation technique. All formulations were evaluated for particle size, PDI, zeta potential, entrapment efficiency, drug loading, practical yield, and saturation solubility enhancement.[12,13,14]

Apixaban MSN loaded ODFs

Trial Batches

Following the successful optimization of Apixaban-loaded MSN (ASM12), the optimized formulation was incorporated into oral disintegrating films (ODFs) to create a patient-friendly dosage form offering rapid disintegration and improved dissolution. Six preliminary formulations (ASF1–ASF6) were first prepared by solvent casting to identify a suitable polymer–superdisintegrant combination before proceeding to statistical optimization. Each formulation contained a fixed drug load of 133 mg Apixaban-loaded MSNs, while the polymer and superdisintegrant compositions were varied. Other excipients listed in the table were used for the formulation. The prepared films were evaluated for clarity, surface appearance, stickiness, thickness, weight variation, surface pH, folding endurance, drug content, *In vitro* disintegration time, and moisture characteristics.

3^2 Factorial Design batches

Among the trial batches, ASF5 and ASF6—formulated with Pullulan–HPMC E5 and Kollidon® CL-SF—exhibited superior film integrity, lower moisture uptake, and the shortest disintegration times, confirming that this polymer–superdisintegrant combination offered the most favorable balance between mechanical strength and rapid disintegration. These findings justified the selection of these variables for further optimization using a Quality by Design approach. A 3^2 full factorial design was subsequently employed with two independent variables: the HPMC E 5: Pullulan Concentration (X_1) governing film formation and mechanical properties, and Kollidon® CL-SF concentration (X_2) controlling disintegration behavior. Four dependent variables were monitored—folding endurance (Y_1), *In vitro* disintegration time (Y_2), cumulative drug release at 2 mins. (Y_3), and at 14 mins. (Y_4). Experimental data were fitted to a second-order polynomial model and statistically analyzed using ANOVA. Response surface methodology, including three-dimensional surface and contour plots, was then used to elucidate variable–response relationships and identify the formulation providing the best compromise between mechanical robustness, rapid disintegration, and enhanced drug release.[15,16] Formulation table for factorial design batches are shown in below table 1.

Formulation of Apixaban MSN loaded ODFs

Table 1: Formulation table of Apixaban MSN loaded ODFs by 3^2 Factorial Design

Ingredients (mg)	ASMF 1	ASMF 2	ASMF 3	ASMF 4	ASMF 5	ASMF 6	ASMF 7	ASMF 8	ASMF 9
Apixaban MSNs	133	133	133	133	133	133	133	133	133
HPMC E5	70	70	70	105	105	105	140	140	140
Pullulan	30	30	30	45	45	45	60	60	60
Kollidon CL-SF	2.4	4.2	6	2.4	4.2	6	2.4	4.2	6
Propylene Glycol (PG)	30	30	30	30	30	30	30	30	30
Poloxamer 188	1	1	1	1	1	1	1	1	1
Citric acid	1	1	1	1	1	1	1	1	1
Sucralose	2	2	2	2	2	2	2	2	2
Peppermint flavour	1	1	1	1	1	1	1	1	1
Water:Ethanol (80:20)	**q.s.**	**q.s.**	**q.s.**	**q.s.**	**q.s.**	**q.s.**	**q.s.**	**q.s.**	**q.s.**

Evaluation Parameters for ODFs

Appearance, Surface Texture, and Clarity of Formulated Film: The appearances of the prepared films were evaluated by visual observation of transparency or opaqueness.[17]

Film Thickness: The thickness of the film was measured by micrometer screw gauge at three different places, at the corners, and at the center, and an average of three values and the SD were calculated. This is essential to ascertain uniformity in the thickness of the film which is directly related to the accuracy of dose in the film[18]

Weight Variation: 10 films were randomly selected from each formulation, and the average weight variations were determined. The weight of each film was taken using digital weighing balance. The standard deviation (SD) of weight was computed from the mean value.[19]

Surface pH: The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done.[20]

Folding Endurance: It was determined by repeatedly folding a small strip (6 cm^2) at the same place till it broke. The number of times a film can be folded at the same place without breaking gave the value of folding endurance. Further, less folding endurance value indicates more brittleness.[21]

Drug Content: Content uniformity of the optimized MSN-loaded oral disintegrating films (ODFs) was established through a validated UV–Visible spectrophotometric method. Three films were randomly selected from each optimized APX formulation, cut into small pieces, and transferred to a 100 mL volumetric flask. A suitable solvent was added, and the resulting dispersion was sonicated for 15–20 minutes to achieve complete extraction of the drug from both the polymeric film matrix and the MSN. The volume was then made up to 100 mL with the same solvent, and the solution was passed through a 0.45 µm membrane filter to remove undissolved polymer residue or silica particles. An aliquot of the clear filtrate was diluted further, and absorbance was recorded on a UV–Visible spectrophotometer at the respective λ_{max} at 278 nm. Drug concentration was derived from the corresponding calibration curve and expressed as a percentage of the theoretical drug content. Each analysis was carried out in triplicate, and the mean value was used to evaluate content uniformity across the optimized ODF formulations.[22]

***In vitro* Disintegration Time:** The *In vitro* disintegration time of the oral disintegrating films was determined using a modified Petri dish method. Briefly, a film strip of unit-dose size was placed in a Petri dish containing 10 mL of pH 6.8 phosphate buffer maintained at 37 ± 0.5 °C. The dish was gently swirled at regular intervals, and the time required for the film to completely disintegrate was recorded using a stopwatch. The test was performed in triplicate, and the average disintegration time was calculated.[23]

% Moisture loss: The % moisture loss study was carried out to check the physical stability and integrity of the films. In the present study, the moisture loss capacity of the film was determined by the Known weight and predetermined by placing size of the film in a desiccator containing anhydrous calcium chloride for three days. The films were removed and reweight and the percentage moisture loss of the film was measured by using the following formula[24]

$$\%\ \textbf{moisture loss} = \frac{\textbf{Initial weight} - \textbf{Final weight}}{\textbf{Final weight}} \times 100$$

% Moisture uptake: The prepared films were weighed and kept in desiccators containing anhydrous silica at Room temperature for 24 h. It was then taken out from the desiccators, weighed and exposed to relative humidity of 75% (saturated solution of sodium chloride) in desiccators. The film was weighed until it showed a constant weight. Percent moisture uptake was determined using the formula[25]

$$\%\ \textbf{moisture uptake} = \frac{\textbf{Final weight} - \textbf{Initial weight}}{\textbf{Initial weight}} \times 100$$

***In vitro* Drug Release:** The *In vitro* drug release study of the oral disintegrating films was performed using USP

Dissolution Apparatus II (paddle method) containing 900 mL of pH 6.8 phosphate buffer maintained at 37 ± 0.5 °C and stirred at 50 rpm. Each film was secured with a stainless-steel sinker to prevent floating during the study. At predetermined time intervals, aliquots were withdrawn, filtered, and replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The samples were analyzed using a UV–Visible spectrophotometer at the respective λ_{max} of the drug, and the cumulative percentage drug release was calculated using the corresponding calibration curve.[26]

Drug Release Kinetics: The *In vitro* drug release data of the optimized formulations were fitted to various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas, to elucidate the mechanism of drug release. Zero-order and first-order models were used to evaluate concentration-independent and concentration-dependent release patterns, respectively, while the Higuchi model assessed diffusion-controlled drug release from the matrix system. The Korsmeyer–Peppas model was applied to determine the drug release mechanism by calculating the release exponent (n). The model exhibiting the highest correlation coefficient (R^2) was considered to best describe the release kinetics of the optimized formulation.[27]

Stability Studies: Stability studies of the optimized formulations were performed according to ICH guidelines under accelerated conditions (40 ± 2 °C/75 ± 5% RH) for 6 months. The optimized Apixaban-loaded MSN containing ODFs were packed in aluminium foil and stored in a stability chamber. Samples were withdrawn at 1, 2, 3, and 6 months and evaluated for critical quality attributes, including wetting time, disintegration time, and *In vitro* drug release. The results were compared with the initial values to assess the physical stability and performance of the optimized formulations during storage.[28]

RESULT & DISCUSSION:

Physical Characteristics: Apixaban was obtained as a white to off-white crystalline, odorless powder with a slightly bitter taste. The drug exhibited good flow characteristics and was found to be non-hygroscopic under normal laboratory conditions, indicating its suitability for the development of ODFs.

Melting Point: The melting point of Apixaban was determined to confirm its identity and purity. The observed melting point ranged from 236–240 °C, which was in close agreement with the reported literature value (238–240 °C). The sharp and narrow melting range indicated the high crystalline purity of the drug and confirmed its suitability for further formulation studies.

Estimation of Apixaban by UV–Visible Spectroscopy

The UV–Visible overlay spectra of Apixaban in pH 6.8 phosphate buffer exhibited a distinct absorption maximum (λ_{max}) at 278 nm, which was consistent across all tested concentrations, indicating the spectral stability of the drug in the selected medium. The calibration curve constructed over the concentration range of 5–25 ppm demonstrated excellent linearity, with the regression equation $y = 0.0286x + 0.0886$ and a correlation coefficient ($R^2 = 0.9993$), confirming compliance with Beer–Lambert's law. The low variability among replicate measurements further indicated the precision and reproducibility of the analytical method. Based on these findings, 278 nm was selected as the analytical wavelength for the quantitative estimation of Apixaban in subsequent drug content, dissolution, and formulation studies. UV overlay spectra is shown in figure 1, the results of calibration data and calibration curve are shown in table 2 and figure 2 respectively.

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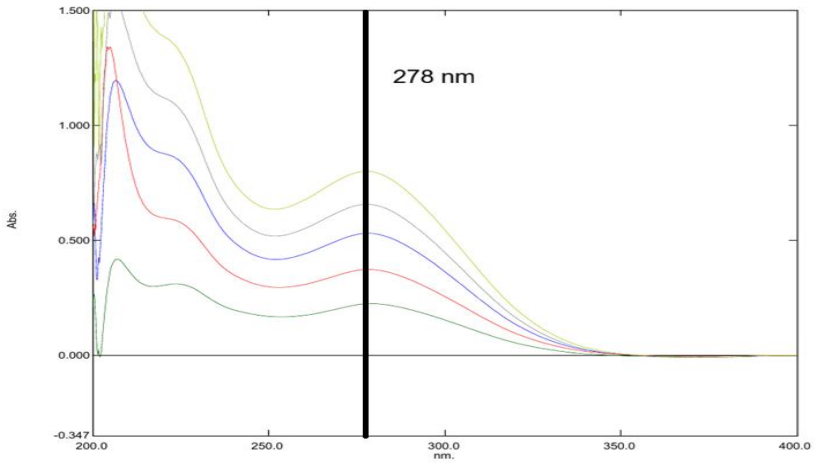

FIGURE 1: OVERLAY SPECTRA OF APIXABAN IN PH 6.8 PBS

Table 2: Absorbance of different concentration of Apixaban in pH 6.8 PBS

Sr. No.	Concentration (ppm)	Absorbance			Mean Absorbance ± SD
		I	II	III	
1	**5**	0.224	0.231	0.228	0.228 ± 0.0035
2	**10**	0.378	0.372	0.374	0.375 ± 0.0031
3	**15**	0.529	0.531	0.524	0.528 ± 0.0036
4	**20**	0.663	0.652	0.656	0.657 ± 0.0056
5	**25**	0.799	0.805	0.802	0.802 ± 0.0030

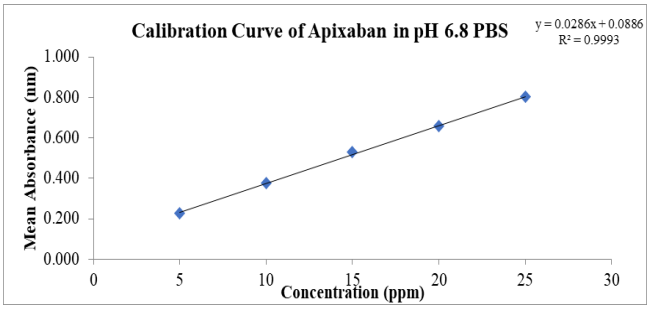

Figure 2: Calibration curve of Apixaban in pH 6.8 PBS

FTIR Analysis (Drug-excipient Compatibility Study)

FTIR spectroscopy was performed to evaluate the compatibility of Apixaban with the excipients used in the formulation. The spectra of the pure drug, individual excipients, physical mixtures, and the optimized Apixaban-loaded MSN were compared. The characteristic absorption peaks of Apixaban were retained without any significant shift, disappearance, or appearance of new peaks in the spectra of the physical mixtures and optimized formulation. These findings indicate the absence of any chemical interaction between Apixaban and the selected excipients, confirming the compatibility of the drug with all formulation components and the suitability of the excipients for the development of the optimized formulation.

Evaluation data for Apixaban loaded MSNs

The prepared nanoparticles exhibited particle sizes ranging from 199.1 to 442.4 nm, PDI values between 0.15 and 0.294, and zeta potentials from −26.82 to −34.26 mV, indicating good colloidal stability with narrow particle size distribution. Entrapment efficiency varied from 56.54% to 83.82%, while drug loading ranged from 6.74% to 18.38%, depending on the formulation variables. Pure Apixaban showed poor solubility in water, 0.1 N HCl, and phosphate buffer pH 6.8, whereas every MSN formulation achieved a substantial gain over this baseline. Batch ASM12 emerged as the top performer among the developed formulations, recording saturation solubility values of

1.717 ± 0.008 mg/mL in water, 2.046 ± 0.016 mg/mL in 0.1 N HCl, 2.002 ± 0.016 mg/mL in phosphate buffer pH 6.8, and 5.477 ± 0.075 mg/mL in methanol. This enhancement is most plausibly attributable to amorphization of Apixaban within the mesoporous framework, the increased surface area afforded by the silica matrix, improved wettability of the drug particles, and inhibition of drug recrystallization through confinement within the mesopores. These combined effects point toward a favorable potential for improved dissolution and enhanced oral bioavailability of Apixaban. Among all the developed formulations, ASM12 demonstrated the most desirable characteristics, exhibiting a particle size of 201.1 nm, PDI of 0.269, zeta potential of −32.41 mV, the highest entrapment efficiency (83.82%), excellent practical yield (86.84%), and remarkable enhancement in drug solubility. Therefore, ASM12 was selected as the optimized MSN formulation for further characterization and subsequent development of apixaban-loaded ODFs.

Results of Trial batches of Apixaban MSN loaded ODFs

Transparent films were obtained with ASF2 and ASF4, whereas ASF3 and ASF5 were slightly transparent and ASF1 and ASF6 exhibited slight opacity, indicating the influence of polymer composition on film homogeneity. ASF1, ASF2, ASF5, and ASF6 were non-sticky, while ASF3 and ASF4 showed slight tackiness, reflecting differences in polymer or plasticizer content. Film thickness remained uniform (0.237 ± 0.24 – 0.274 ± 0.27 mm), with minimal weight variation (24.18 ± 0.10–24.34 ± 0.05 mg), confirming reproducibility of the solvent-casting process. All formulations exhibited near-neutral surface pH (6.65 ± 0.01 – 6.95 ± 0.01), satisfactory flexibility (folding endurance: 182.33 ± 2.08 – 215.00 ± 2.65), and uniform drug content (98.22 ± 0.14 – 99.81 ± 0.08%), indicating excellent mechanical integrity and homogeneous incorporation of Apixaban-loaded MSNs. Disintegration time varied from 26.04 ± 0.32 s (ASF6) to 39.95 ± 0.60 s (ASF3), while moisture loss (3.81 ± 0.19 – 5.70 ± 0.16%) and moisture uptake (1.84 ± 0.92 – 3.62 ± 0.59%) indicated comparatively lower hygroscopicity and improved storage stability for ASF5 and ASF6. Dissolution studies exhibited a biphasic release profile, with cumulative drug release at 2 mins. ranging from 28.46 ± 0.39% (ASF3) to 50.50 ± 0.83% (ASF6). ASF6 achieved 99.86 ± 0.11% drug release within 16 mins., followed by ASF5 (99.19 ± 0.56% at 20 mins.), whereas ASF1 and ASF2 required 22 mins. and ASF3 and ASF4 required 26 mins. to achieve near-complete release. The superior performance of ASF6 was attributed to enhanced hydration, wettability, matrix erosion, and rapid diffusion of Apixaban from the mesoporous silica network. Based on these findings, ASF6 was selected as the optimized trial formulation, while the concentration ratio of HPMC E5:Pullulan (X_1), and the concentration of Kollidon® CL-SF (X_2), were identified as the critical formulation variables and selected as independent factors for subsequent optimization using a 3^2 full factorial design.

Results of Apixaban MSN loaded ODFs formulated by using 3^2 Factorial design

Physical Appearance: The prepared Apixaban-loaded oral disintegrating films were evaluated for film clarity, stickiness, and surface appearance to assess their overall quality and patient acceptability. All formulations exhibited satisfactory film formation without visible drug crystallization, phase separation, or cracks, indicating good compatibility between the drug and excipients. Transparent to semi-transparent films with smooth and uniform surfaces were obtained for most formulations, while slight opacity and minor surface irregularities observed in a few batches were attributed to variations in polymer concentration and superdisintegrant content. Most films were non-sticky and could be easily handled and peeled from the casting surface, whereas a few formulations exhibited slight tackiness due to the plasticizing effect of PG. Among all the formulations, ASMF5 demonstrated the most desirable physical characteristics, exhibiting a transparent appearance, smooth and elegant surface, and non-sticky nature, making it suitable for further optimization and evaluation.

The results for physicochemical parameters are shown in table 3 and 4.

Table 3: Thickness, Weight variation, Surface pH and Folding Endurance data

Batch	Thickness (mm± SD) (n=3)	Weight variation (mg± SD) (n=10)	Surface pH ± SD (n=3)	Folding Endurance ± SD (n=3)
ASMF 1	0.223 ± 0.06	25.56 ± 0.19	6.83 ± 0.20	237.33 ± 0.58
ASMF 2	0.110 ± 0.06	25.71 ± 0.17	6.67 ± 0.30	241.67 ± 0.58
ASMF 3	0.193 ± 0.07	25.89 ± 0.20	6.83 ± 0.04	248.00 ± 1.00
ASMF 4	0.170 ± 0.04	30.28 ± 0.12	7.07 ± 0.05	336.67 ± 0.58
ASMF 5	0.207 ± 0.06	30.63 ± 0.20	6.77 ± 0.20	379.67 ± 1.53
ASMF 6	0.180 ± 0.12	30.98 ± 0.18	7.03 ± 0.07	365.67 ± 1.53

ASMF 7	0.250 ± 0.04	35.36 ± 0.22	6.93 ± 0.11	287.33 ± 2.08
ASMF 8	0.300 ± 0.06	35.53 ± 0.23	6.90 ± 0.00	309.00 ± 1.00
ASMF 9	0.287 ± 0.06	35.89 ± 0.21	7.13 ± 0.25	294.33 ± 0.58

Thickness: The thickness of the prepared oral disintegrating films ranged from 0.110 ± 0.06 to 0.300 ± 0.06 mm, indicating successful fabrication of thin and flexible films. The variation in thickness was mainly influenced by the polymer concentration, with higher polymer content producing thicker films. All formulations exhibited acceptable thickness suitable for oral administration, while ASMF5 showed an optimum thickness (0.207 ± 0.06 mm) that provided a balance between mechanical strength and rapid disintegration.

Weight Variation: The films exhibited uniform weight ranging from 25.56 ± 0.19 to 35.89 ± 0.21 mg, demonstrating reproducibility of the solvent casting process. The low standard deviation values indicated homogeneous distribution of drug and excipients throughout the polymeric matrix. ASMF5 showed uniform weight (30.63 ± 0.20 mg), confirming good formulation consistency.

Surface pH: The surface pH of all formulations ranged between 6.67 ± 0.30 and 7.13 ± 0.25, which is close to the physiological pH of saliva. These values indicate that the films are unlikely to cause irritation to the oral mucosa. ASMF5 exhibited a near-neutral surface pH (6.77 ± 0.20), suggesting good compatibility for oral administration.

Folding Endurance: Folding endurance values ranged from 237.33 ± 0.58 to 379.67 ± 1.53, demonstrating adequate flexibility and mechanical integrity of all formulations. The high folding endurance of ASMF5 (379.67 ± 1.53) indicated excellent flexibility without brittleness, which can be attributed to the optimized HPMC–Pullulan ratio and plasticizer concentration.

Table 4: % Drug content, *In vitro* Disintegration time, % Moisture Loss, % Moisture uptake data

Batch	% Drug Content (% ± SD) (n=3)	*In vitro* Disintegration time (sec. ± SD) (n=3)	% Moisture Loss (% ± SD) (n=3)	% Moisture Uptake (% ± SD) (n=3)
ASMF 1	99.56 ± 0.87	28.72 ± 0.51	4.73 ± 0.06	3.17 ± 0.52
ASMF 2	98.93 ± 0.65	26.53 ± 0.35	4.57 ± 0.21	3.18 ± 0.54
ASMF 3	99.07 ± 0.52	25.31 ± 0.28	4.42 ± 0.24	3.48 ± 0.57
ASMF 4	99.57 ± 0.87	17.28 ± 0.65	3.83 ± 0.12	4.39 ± 0.53
ASMF 5	99.73 ± 0.25	09.18 ± 0.91	3.62 ± 0.04	4.46 ± 0.56
ASMF 6	99.16 ± 0.11	13.58 ± 0.96	3.75 ± 0.09	4.42 ± 0.56
ASMF 7	98.86 ± 0.02	23.81 ± 0.41	4.29 ± 0.19	3.52 ± 0.57
ASMF 8	97.79 ± 0.88	20.24 ± 0.57	4.01 ± 0.28	4.15 ± 0.57
ASMF 9	98.45 ± 0.75	21.38 ± 0.64	4.17 ± 0.30	3.73 ± 0.91

Drug Content: Drug content was found to be within 97.79 ± 0.88% to 99.73 ± 0.25%, indicating uniform distribution of Apixaban throughout the films. All formulations complied with acceptable pharmaceutical limits, while ASMF5 exhibited the highest drug content (99.73 ± 0.25%), confirming efficient drug incorporation and excellent content uniformity.

***In vitro* Disintegration Time:** The films disintegrated rapidly within 9.18 ± 0.91 to 28.72 ± 0.51 s, demonstrating their suitability as oral disintegrating films. The rapid disintegration was attributed to the hydrophilic polymer matrix and the presence of Kollidon® CL-SF. Among all formulations, ASMF5 showed the shortest disintegration time (9.18 ± 0.91 s), indicating rapid hydration and film dispersion.

% Moisture Loss: The moisture loss ranged from 3.62 ± 0.04% to 4.73 ± 0.06%, indicating acceptable residual moisture in all formulations. Controlled moisture loss contributes to film stability while maintaining flexibility. ASMF5 exhibited the lowest moisture loss (3.62 ± 0.04%), suggesting efficient drying and improved physical stability.

% Moisture Uptake: Moisture uptake varied between 3.17 ± 0.52% and 4.46 ± 0.56%, reflecting acceptable hygroscopic behaviour of the films. Moderate moisture uptake promotes rapid hydration and disintegration without compromising stability. ASMF5 showed the highest moisture uptake (4.46 ± 0.56%), which correlated with its rapid

disintegration.

***In vitro* Cumulative Drug Release:** All formulations exhibited rapid drug release, with cumulative release increasing progressively over time. ASMF5 demonstrated the fastest release profile, achieving 62.41% drug release within 2 mins. and 99.75% within 14 mins., whereas other formulations required a longer time to achieve complete release as depicted in figure 3. The enhanced release from ASMF5 can be attributed to the optimized HPMC–Pullulan polymer ratio, appropriate Kollidon® CL-SF concentration, rapid film disintegration, and improved hydration, resulting in efficient diffusion of Apixaban from the MSN.

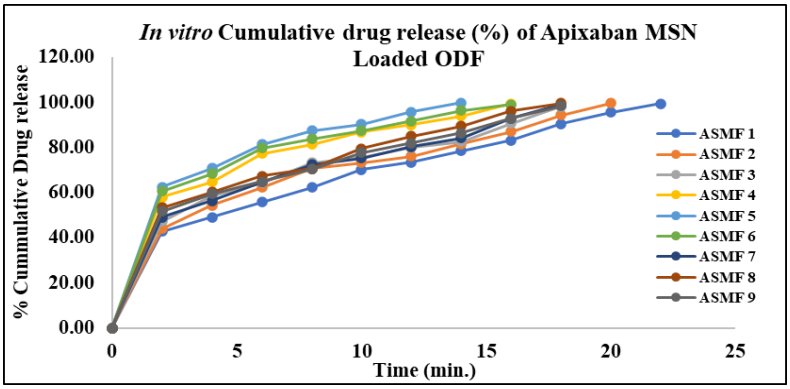

Figure 3: *In vitro* Cumulative Drug release (%) profile of batch ASMF1 to ASMF9

Drug Release Kinetics: The release kinetics were evaluated using zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Although the Korsmeyer–Peppas model showed the highest statistical fit (R^2 = 0.9916), its applicability was limited because more than 60% of the drug was released within the first 2 mins. Therefore, the Higuchi model (R^2 = 0.9911) was considered the most appropriate model, indicating that drug release was predominantly governed by diffusion from the mesoporous silica matrix following rapid dissolution of the oral film.

Statistical Analysis

The optimized formulation, ASMF5, exhibited the highest folding endurance (379.67 ± 1.53), the shortest disintegration time (9.18 ± 0.91 s), and the maximum drug release at 2 mins. (62.41 ± 0.78%) and 14 mins. (99.75 ± 0.85%), demonstrating an ideal balance between mechanical strength and rapid drug release. ANOVA confirmed that all developed models were statistically significant ($p < 0.05$) with high model F-values and excellent goodness-of-fit (R^2 = 0.9637–0.9868), indicating a strong correlation between the formulation variables and the measured responses. The high adjusted and predicted R^2 values, together with adequate precision values greater than 4, further confirmed the robustness and predictive capability of the developed models. The factorial design effectively optimized the formulation variables, and ASMF5 was identified as the optimized oral disintegrating film for further characterization and evaluation.

Effect of Formulation Variables on Folding Endurance (Y_1)

The polynomial equation generated in terms of coded factors was $Y_1 = 370.81 + 7.78\ X_1 + 27.28\ X_2 - 0.9167\ X_{12} - 15.22\ X_1^2 - 91.06\ X_2^2$. The response surface analysis demonstrated that the quadratic model for folding endurance was statistically significant (Model F = 30.22, p = 0.0091) with an excellent coefficient of determination (R^2 = 0.9805), indicating that the model reliably described the effect of formulation variables on film flexibility. The polynomial equation revealed that both the HPMC:Pullulan Concentration (X_1) and Kollidon® CL-SF concentration (X_2) positively influenced folding endurance at lower and intermediate levels, with Kollidon® CL-SF exerting a greater effect than the polymer blend. However, the negative quadratic coefficients indicated that excessive concentrations of either variable reduced film flexibility, suggesting the existence of an optimum concentration range. The contour (figure 4A) and three-dimensional (figure 4B) response surface plots further confirmed that maximum folding endurance was achieved at intermediate levels of both formulation factors, whereas extreme concentrations resulted in reduced mechanical strength. Additionally, the close agreement between the predicted and experimental values (figure 4C) demonstrated the excellent predictive capability and robustness of the developed

model, confirming its suitability for optimization of the Apixaban MSN-loaded ODFs.

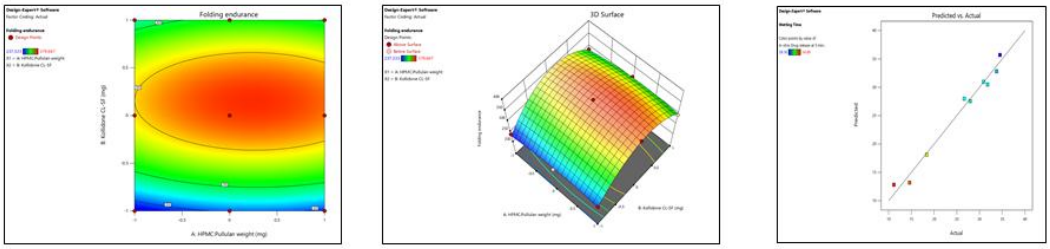

Figure 4: A. 2D Contour plot for Y_1, B: 3D surface graph for Y_1, C: Actual value vs predicted comparison graph for Y_1

Effect of Formulation Variables on *In vitro* Disintegration Time (Y_2)

The fitted quadratic model generated the following polynomial equation in coded factors, representing the influence of the formulation variables on *In vitro* Disintegration Time was $Y_2 = 11.33 - 1.59\ X_1 - 2.52\ X_2 + 0.2433\ X_{12} + 3.03\ X_1^2 + 10.98\ X_2^2$. The response surface analysis demonstrated that the quadratic model for *In vitro* disintegration time was statistically significant (Model F = 15.94, p = 0.0227) with a high coefficient of determination ($R^2 = 0.9637$), confirming the reliability of the developed model. Both the HPMC:Pullulan Concentration (X_1) and Kollidon® CL-SF concentration (X_2) reduced the disintegration time at lower and intermediate levels, with Kollidon® CL-SF exhibiting a greater influence owing to its rapid swelling and water uptake properties. However, the positive quadratic terms indicated that excessive concentrations of either variable increased the disintegration time due to the formation of a denser polymeric matrix and reduced water penetration. The contour (figure 5A) and three-dimensional response surface plots (figure 5B) identified an optimum region at intermediate levels of both formulation variables, where the minimum disintegration time of approximately 9.18 s was achieved. Furthermore, the close agreement between the predicted and experimental values (figure 5C) confirmed the excellent predictive accuracy and robustness of the quadratic model, demonstrating its suitability for optimizing the disintegration behavior of Apixaban MSN-loaded ODFs.

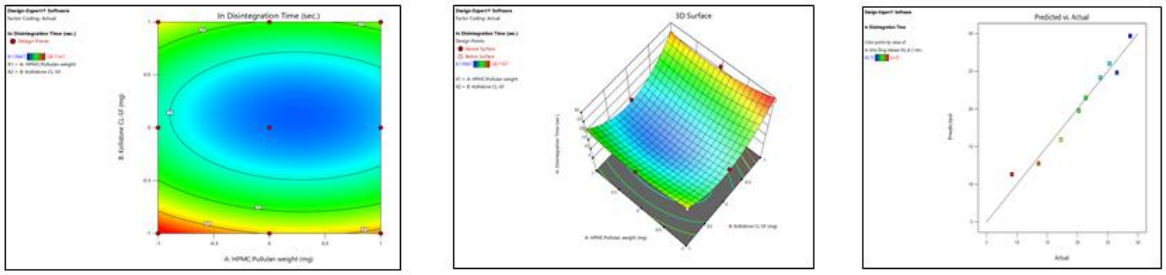

Figure 5: A. 2D Contour plot for Y_2, B: 3D surface graph for Y_2, C: Actual value vs predicted comparison graph for Y_2

Effect of Formulation Variables on *In vitro* Cumulative Drug Release at 2 mins. (Y_3)

The relationship between the independent variables and *In vitro* Cumulative Drug Release at 2 mins. was described in terms of coded factors by the polynomial equation $Y_3 = 61.48 + 1.62\ X_1 + 3.38\ X_2 - 0.4975\ X_{12} - 1.66\ X_1^2 - 12.28\ X_2^2$. The response surface analysis demonstrated that the quadratic model for drug release at 2 mins. was statistically significant (Model F = 31.28, p = 0.0086) with an excellent coefficient of determination ($R^2 = 0.9812$), indicating that the model accurately described the influence of the formulation variables on the initial drug release. Both the HPMC:Pullulan Concentration (X_1) and Kollidon® CL-SF concentration (X_2) positively influenced the early drug release, with Kollidon® CL-SF exerting a greater effect due to its rapid swelling and superdisintegrating properties. However, the negative quadratic coefficients indicated that excessive concentrations of either variable reduced the release rate by increasing matrix compactness and limiting efficient hydration. The contour (figure 6A) and three-dimensional response surface plots (figure 6B) identified an optimum region at intermediate levels of both variables,

where the maximum drug release of approximately 62.41% within 2 mins. was achieved. Furthermore, the close agreement between the predicted and experimental values (figure 6C) confirmed the high predictive accuracy and robustness of the developed quadratic model, demonstrating its suitability for optimizing the rapid drug release characteristics of Apixaban MSN-loaded ODFs.

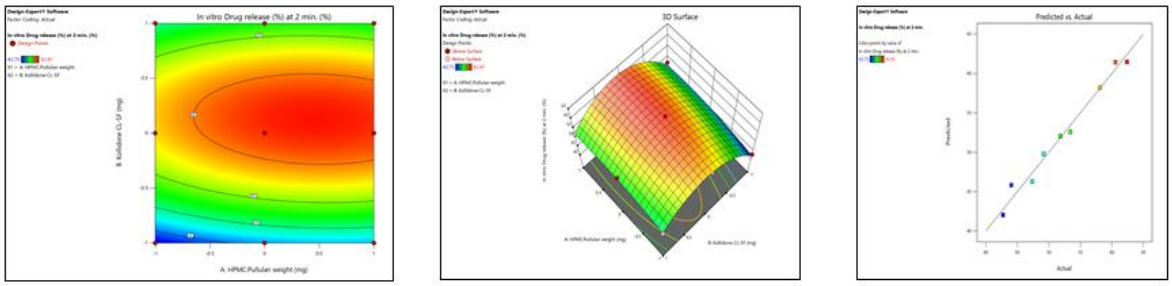

Figure 6: A. 2D Contour plot for Y_3, B: 3D surface graph for Y_3, C: Actual value vs predicted comparison graph for Y_3

Effect of Formulation Variables on *In vitro* Cumulative Drug Release at 14 mins. (Y_4)

The response surface analysis yielded the quadratic polynomial equation $Y_4 = 98.84 + 1.49\ X_1 + 2.90\ X_2 - 0.4400\ X_{12} - 3.17\ X_1^2 - 12.93\ X_2^2$ in coded variables to predict the *In vitro* Cumulative Drug Release at 14 mins. of the oral disintegrating films. The response surface analysis demonstrated that the quadratic model for drug release at 14 mins. was highly significant (Model F = 44.73, p = 0.0051) with an excellent coefficient of determination (R^2 = 0.9868), indicating that the model accurately predicted the influence of formulation variables on cumulative drug release. Both the HPMC:Pullulan Concentration (X_1) and Kollidon® CL-SF concentration (X_2) positively affected drug release, with Kollidon® CL-SF showing a more pronounced effect owing to its rapid swelling and matrix-disintegrating properties. However, the negative quadratic coefficients indicated that excessive concentrations of either variable reduced drug release due to increased matrix density and structural heterogeneity. The contour (figure 7A) and three-dimensional response surface plots (figure 7B) identified an optimum formulation region at intermediate levels of both variables, where the cumulative drug release reached approximately 99.75% within 14 mins. Furthermore, the close agreement between the predicted and experimental values (figure 7C) confirmed the suitability for optimizing the dissolution performance of Apixaban MSN-loaded ODFs.

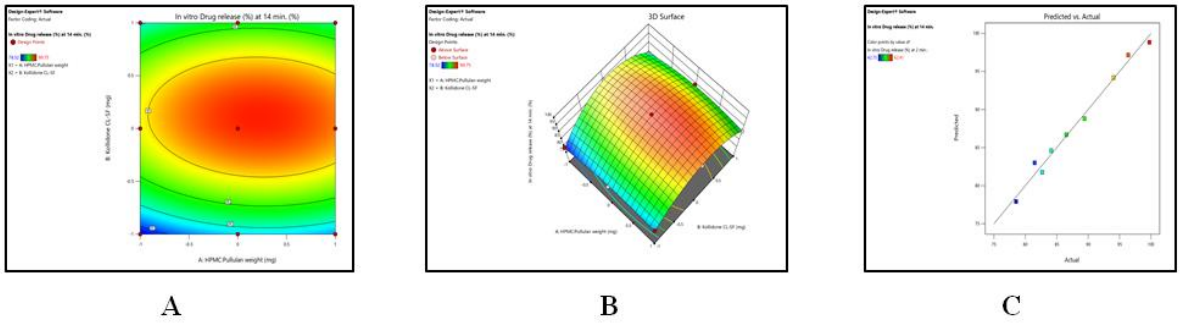

Figure 7: A. 2D Contour plot for Y_4, B: 3D surface graph for Y_4, C: Actual value vs predicted comparison graph for Y_4

Checkpoint Analysis and Validation of the Optimized Formulation

The predictive capability of the developed 3^2 full factorial design was validated through checkpoint analysis by preparing two formulations within the optimized design space and comparing the experimentally observed responses with the predicted values and the overlay plot is shown in figure 8 and table 5.

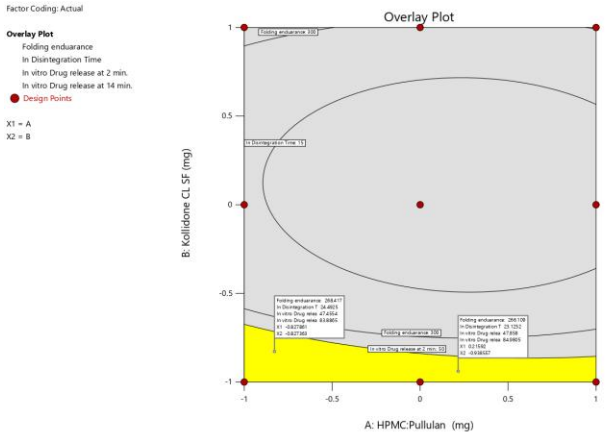

Figure 8: Overlay Plot showing the optimized design space for Apixaban MSN Loaded ODF

Table 5: Checkpoint Analysis of Optimized Apixaban MSN Loaded ODFs

Parameters	Check point 1			Check point 2		
	Actual	predict	% error	Actual	predict	% error
Folding endurance	271.33	268.42	-1.09	269.00	266.11	-1.09
DT	23.64	24.49	3.47	22.28	23.13	3.67
CDR 2 mins.	48.61	47.46	-2.43	46.26	47.86	3.34
CDR 14 mins.	85.63	83.89	-2.08	83.26	84.98	2.02

The overlay plot identified a feasible design space where all desired formulation criteria, including high folding endurance, minimum disintegration time, maximum drug release at 2 mins., and near-complete drug release at 14 mins., were simultaneously achieved. Both checkpoint formulations showed excellent agreement between the predicted and experimental results, with prediction errors ranging from −2.43% to 3.67%, well within the acceptable limit of ±5%. The low prediction errors and the absence of systematic over- or under-prediction confirmed the robustness, reliability, and excellent predictive capability of the quadratic models. These findings validate the Quality-by-Design (QbD) optimization approach and demonstrate that the developed response surface models can reliably predict the performance of Apixaban MSN-loaded ODFs within the established design space.

Stability Studies

The stability of the optimized Apixaban-loaded MSN incorporated into oral disintegrating film (ASMF5) was evaluated under ICH Q1A(R2) intermediate storage conditions (30 ± 2 °C/65 ± 5% RH) for 6 months. Throughout the study, the formulation maintained satisfactory physicochemical and functional properties with only minor variations. The surface pH remained within the physiological range (6.60 – 6.77), indicating suitability for oral administration without the risk of mucosal irritation. Drug content showed only a slight reduction from 99.73% to 98.36%, confirming excellent chemical stability. Although folding endurance decreased marginally (379.67 to 355.83 folds) and disintegration time increased slightly (9.40 to 12.49 s), both parameters remained within acceptable limits, demonstrating preservation of mechanical integrity and rapid disintegration. A gradual increase in moisture uptake was observed during storage, while moisture loss remained relatively constant, indicating good moisture stability of the polymeric matrix. Results are depicted in table 6. The *In vitro* drug release profile exhibited only a slight reduction in the initial release rate; however, cumulative drug release remained above 97% at 14 mins. As shown in figure 9 below, after 6 months, confirming that the dissolution performance was not significantly affected.

Table 6: Result of the Stability Study

Evaluation parameter	Initial 0 Day	After 1 month	After 2 months	After 3 months	After 6 months
Surface pH (pH ± S.D.) (n=3)	6.77 ± 0.23	6.67 ± 0.06	6.63 ± 0.12	6.67 ± 0.06	6.60 ± 0.01
Drug Content (% ± S.D.)	99.73 ± 0.25	98.80 ± 0.42	98.73 ± 0.31	98.86 ± 0.52	98.36 ± 0.71

(n=3)					
Folding Endurance (± S.D.) (n=3)	379.67 ± 1.53	371.67 ± 0.58	368.00 ± 1.00	361.67 ± 0.58	355.83 ± 0.76
***In Vitro* Disintegration Time (sec. ± S.D.) (n=3)**	9.40 ± 0.60	10.86 ± 0.61	11.48 ± 0.18	11.84 ± 0.23	12.49 ± 0.20
% Moisture Uptake (% ± S.D.) (n=3)	3.17 ± 0.52	3.50 ± 0.58	3.82 ± 1.68	4.46 ± 1.51	4.78 ± 2.57
% Moisture Content (% ± S.D.) (n=3)	3.62 ± 0.04	3.30 ± 0.74	4.32 ± 0.17	3.12 ± 0.85	3.47 ± 0.81

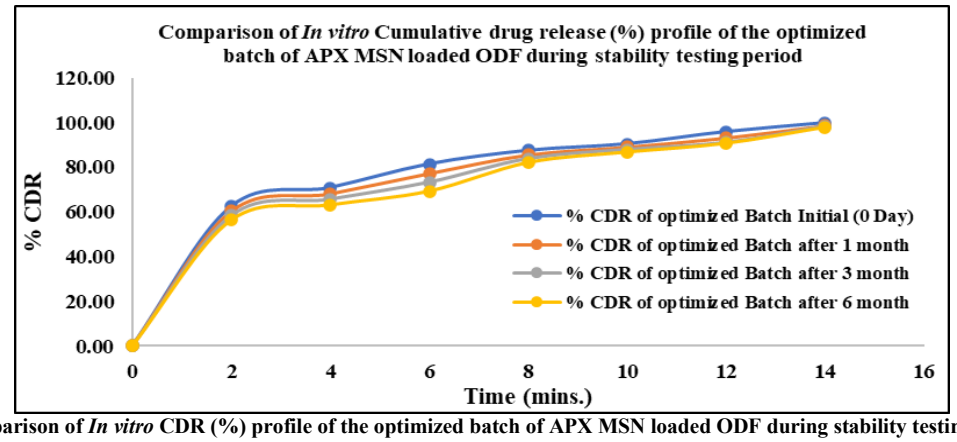

Figure 9: Comparison of *In vitro* CDR (%) profile of the optimized batch of APX MSN loaded ODF during stability testing period

SUMMARY & CONCLUSION:

This study was developed to overcome the drug's poor aqueous solubility while providing a patient-friendly dosage form. MSNs were synthesized using a surfactant-templated sol-gel method and optimized to achieve desirable particle size, high entrapment efficiency, and enhanced saturation solubility. The optimized nanoparticles were subsequently incorporated into ODFs prepared by solvent casting. A QbD framework employing a 3^2 full factorial design was used to evaluate the influence of the HPMC E5:Pullulan Concentration and Kollidon® CL-SF concentration on folding endurance, disintegration time, and *In vitro* drug release. Response surface methodology and statistical analyses established the significance of both variables in governing film performance and enabled the identification of a reliable design space. The optimized formulation (ASMF5) demonstrated robust mechanical flexibility, rapid disintegration, uniform drug content, and markedly enhanced dissolution—releasing approximately 62.41% of Apixaban within 2 mins. and 99.75% within 14 mins. Kinetic analysis indicated diffusion from the mesoporous matrix as the predominant release mechanism. Six-month stability testing under ICH conditions confirmed that the formulation retained its physicochemical, mechanical, and dissolution attributes. From a clinical standpoint, this MSN-loaded ODF platform offers a promising patient-centric alternative for pediatric, geriatric, dysphagic, and anticoagulant-dependent populations who face difficulty swallowing conventional tablets. The integration of nanotechnology with oral film technology presents a scalable approach that may be extended to other BCS Class II drugs requiring rapid onset. Future in vivo pharmacokinetic, bioavailability, and clinical studies are warranted to establish the translational potential of this delivery system.

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