Research Article

Preparation and Characterization of Gelatin Nanofiber Film Loaded with the Drug Dolutegravir for Improved Solubility and Controlled Release

Kanchan Chauhan*, Almas Shaikh, Afreen Chougle
Department of Pharmaceutical Quality Assurance, MCE Society's Allana College of Pharmacy, Pune, India.
***Corresponding author's E-mail:** kc7876@gmail.com

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ABSTRACT

The poor aqueous solubility of drugs has been a great challenge to formulation scientists for their effective oral delivery. Poor solubility is often associated with poor dissolution behavior and subsequently, poor bioavailability of drugs. For improvement of dissolution and bioavailability of poorly soluble drugs polymer nanofibers played an important role in pharmaceutical development. Dolutegravir, an antiretroviral drug used to treat HIV, is a BCS class II drug that is poorly soluble in gastric pH, making it difficult to achieve optimal dissolution kinetics. The present work reports preparation of gelatin nanofibers to enhance the solubility of dolutegravir. Centrifugal spinning technique was used to synthesize nanofibers which were then crosslinked with Glutaraldehyde for controlled release of dolutegravir. Dolutegravir loaded nanofibers were characterized using FTIR, DSC, scanning electron microscopy, and drug release studies which confirmed the stability of nanofibers within the film. Dolutegravir loaded gelatin crosslinked nanofibres can be considered as an alternative dosage form in order to improve its biopharmaceutical properties and enhance therapeutic efficacy for anti-HIV therapy which ultimately improves patient compliance and treatment outcomes for individuals living with HIV.

Keywords: Solubility, Dolutegravir, Gelatin, Nanofibers, Controlled Drug Delivery Systems.

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INTRODUCTION

The human immunodeficiency virus (HIV) continues to be a global health challenge, with over 40 million people worldwide living with the virus.[1] Antiretroviral therapy has greatly improved patient outcomes, but the effectiveness of treatment can be limited by poor solubility and low bioavailability of some drugs, such as Dolutegravir (DTG), a BCS class II drug commonly used in HIV treatment regimens. Biopharmaceutics Classification System (BCS) categorizes drugs based on their solubility and permeability characteristics. It classifies the drugs into four classes based on their solubility and permeability characteristics. BCS class I drugs have high solubility and high permeability, while BCS class II drugs have low solubility and high permeability. BCS class III drugs have high solubility and low permeability, and BCS class IV drugs have low solubility and low permeability.[2] Various approaches are being used to enhance the solubility of Dolutegravir but none of these studies report using nanofibrous formulations.[3]

Nanofibers are one-dimensional nanomaterials with diameters ranging from tens to hundreds of nanometers, known for their high surface area-to-volume ratio, nano porosity, and superior mass transport properties. They are used in tissue engineering, textiles, pharmaceuticals, and drug delivery systems.[4,5,6] Nanofibers can be supplied through rapid oral delivery systems, including electro-spun nanofibers, multilayered nanofiber-loaded meshes, and surface-modified or cross-linked nanofibers.[7] Recently, Nanofibers have been investigated for their potential to enhance the solubility and controlled release of BCS Class II drugs. This approach offers numerous advantages, including improved drug absorption, reduced dosing frequency, and minimized adverse effects.[8,9] In this study, we explore the use of nanofibers loaded film for the solubility enhancement and controlled release of Dolutegravir, with the aim of improving drug bioavailability and effectiveness in HIV treatment. We investigate the effect of fiber diameter and crosslinking of gelatin on the release kinetics of dolutegravir and evaluate the dissolution profile of the nanofibers.[10]

MATERIALS AND METHODS

Materials

Dolutegravir drug was obtained as a gift sample from Lupin Pharmaceuticals, Pune. Hydroxy Propyl Methyl Cellulose (HPMC) K15 was purchased from Clariant Chemicals India, Mumbai. Gelatin (Bloom Strength 240) and Sucrose were purchased from Burgoyne Burbidge's and Co., Mumbai. All the polymers and solvents were acquired from Research Lab Fine Chem Industries, Mumbai.

Methodology

Preparation of blank and drug-loaded nanofibers

Nanofibers were prepared by the centrifugal melt spinning method described.[11] The Spinning was carried out using a commercially available small-scale cotton candy machine EMP-EL-CC1 (Emporiumhub, Jaipur, Rajasthan). The heating element was modified for temperature control using a temperature controller to achieve temperatures in the range of 20°C-200°C. A 10 ml aqueous solution containing 50% gelatin and 15% sucrose was blended using the microwave technique for 2 minutes and cooled to room temperature.

Blank gelatin nanofibers (without drug) were prepared by incorporating the cooled solidified solution into the spinneret of the cotton candy machine which was preheated to 40°C and spun at 3000 rpm. The nanofibers were collected on the collector bowl which was 25 cm in diameter. The blank nanofibers were then stored in desiccators for evaluation.

Drug-loaded nanofibers were prepared by adding 200 mg of Dolutegravir into the aqueous solution of gelatin and sucrose prior to microwave blending. The blending of the solution was carried out similarly as described for blank gelatin nanofibers. Further, after cooling, the solution solidified and was introduced into the spinneret and was spun with the same conditions as for blank gelatin nanofibers, and crosslinking of gelatin was done by following the method described.[12,13] The prepared nanofibers were crosslinked using Glutaraldehyde vapors by placing them in a desiccator containing 25% Glutaraldehyde solution for 6 minutes. These cross-linked nanofibers were then stored in a desiccator and were further evaluated.

Characterization of nanofibers

Determination of drug content and drug loading efficiency in drug-loaded nanofibers

Drug-loaded Nanofibers with DTG equivalent to 50 mg weight were dissolved in 50 ml Phosphate buffer pH 6.8 solution at room temperature and the resultant solution was analyzed in UV/Vis spectrophotometer Jasco V-630 at λmax 254 nm. The actual concentration in the fibers was determined through the calibration curve plotted for standard drug concentration versus absorbance. The Drug loading efficiency was determined by using equation (1).

$$Drug\ Loading\ Efficiency = \frac{Practical\ Drug\ Content}{Theorotical\ Drug\ Content} \times 100 \quad \ldots\ldots\ldots (1)$$

Morphological studies

Both blank and drug-loaded nanofibers were analyzed for their size and morphology using optical microscopy and Field Electron- Scanning Electron Microscopy (FE-SEM FEI Nova NanoSEM 450). The optical microscopy studies were done using Binocular Microscope with an in-built camera (Motic Model).

Fourier Transform Infra-Red (FT-IR) studies

The blank and drug-loaded nanofibers were analyzed for molecular interaction during fabrication using Fourier Transform Infra-Red Spectroscopy (FT-IR) studies. The individual drug, excipients, drug excipient mixture, and nanofibers were analyzed in KBr pellets using an FT-IR instrument (FT/IR 4100 Jasco) in transmission mode in the range of 4000-400 cm-1. The FT-IR spectra of all the samples were recorded.

In-vitro dissolution studies

The dissolution rate of DTG was carried out to determine the release pattern of the drug-loaded nanofibers. The dissolution studies were carried out using USP Type I Basket apparatus (Dissolution tester model TDL-08L Electrolab). The dissolution medium was Phosphate Buffer pH 6.8 stirred at 50 rpm at a temperature of 37 ± 0.5°C. 5ml Aliquots were withdrawn at fixed time intervals and were replaced with an equal amount of fresh dissolution medium.[14] The content of released DTG at each time interval was noted using the UV-Vis spectrometry method. The Dissolution study analysis and curve fitting were done using PCP Disso Software version 3.

Stability Studies

The prepared nanofibers were stored in sealable pouches at a temperature of 40 ± 5°C and a relative humidity level of 50 ± 2%, in accordance with ICH guidelines. Following a twelve-week storage period, the fibers were examined for any alterations in their morphology and drug release patterns using Optical Microscopy and Dissolution rate studies.

Preparation of film

An orodispersible film formulation was prepared in order to incorporate the nanofibers.[15] Vanillin, Citric acid, and sucrose were dissolved in ethanol and then diluted with water. The specified quantities of polymers including HPMC K15, Xanthan Gum, PEG 400, and Sodium starch glycolate were dispersed in a mixture of ethanol and then agitated using a lab stirrer (REMI MOTORS). The resulting solution was subjected to degassing via sonication for a duration of 5 minutes. Following degassing, the solution was cast into a petri dish and the nanofibers containing DTG equivalent to 3.15 g were placed in the petri plate. The solution was then allowed to dry for a period of 24 hours, after which the resultant film was cut into 2 × 2 cm2 to get a film with DTG equivalent to 200 mg.

Characterization of the film

The prepared nanofiber-loaded films were evaluated for the following parameters:

Physical properties

The physical appearance was evaluated by simple visual inspection and the surface was evaluated by touching to understand the texture of the film.

Thickness of the film

The thickness of the film was measured using a screw gauge. The thickness was measured for three films of the same dimension to ensure uniformity of thickness.

Folding endurance

The folding endurance of the films, they were repeatedly folded at the same spot without breaking. This process was done for three films from the same batch and the results were recorded.

Disintegration time

The disintegration time was determined by the disintegration testing apparatus (Disintegration Tester Model-ED-2L, Electrolab). The 2×2 cm2 films were introduced into the apparatus and were subjected to a reciprocating motion at the rate of thirty reciprocations per minute. The time taken for the complete removal of the film with no residue on the gauze was noted.

In vitro dissolution

The in vitro dissolution study was carried out for the 2×2 cm^2 film using USP type-II apparatus with pH 6.8 phosphate buffer solution as dissolution medium. The temperature and stirring rate were controlled at 37^{O}C ± 0.5^{O}C and 50 rpm, respectively. The measurement of % drug release was carried out at 254 nm using a UV spectrophotometer and PCP DISSO software version 3.

FTIR Studies

The individual drug, excipients, drug-excipient mixture, and film were analyzed in KBr pellets using an FT-IR instrument (FT/IR 4100 Jasco) in transmission mode in the range of 4000-400 cm^{-1}. The FT-IR spectra of all the samples were recorded.

Thermal Characterization

The thermal characterization was done using Differential Scanning Calorimetry (DSC). The DSC studies were done on Differential Scanning Calorimeter and the thermograms for the pure drug and film were recorded.

Accelerated Stability Studies

The ICH guidelines were followed to conduct accelerated stability studies. Each 2x2 cm2 film was first wrapped in butter paper and then in aluminum foil before being placed in a sealable pouch that was heat-sealed at the end. The stability study was conducted for a period of 3 months at a temperature of 40 ± 2 °C and a relative humidity of 75 ± 5%. Samples were collected monthly and examined for physical appearance and percentage release.

RESULTS AND DISCUSSION

Preparation of blank and drug-loaded nanofibers

The nanofibers were prepared as per the procedure mentioned in the methodology. The prepared nanofibers were found to be stable and are shown in Fig. 1.

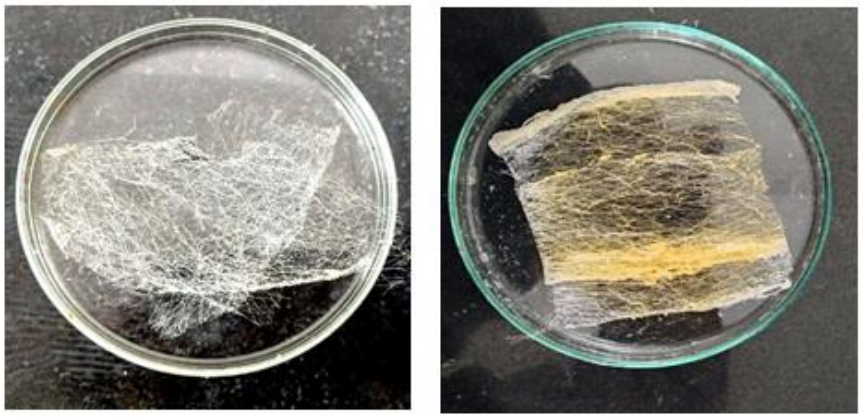

Figure 1: Blank Fibers and Drug Loaded Fibers.

Characterization of nanofibers

Drug Content:

The Drug Content in the nanofibers was calculated by equation (1) as noted in Table 1.

Morphological studies

The FE-SEM studies were conducted at magnifications 30000X, 50000X, and 100000X. The studies revealed that the nanofibers were found to be in the range of 100-220 nm as shown in Fig. 2.

The SEM figures show that the DTG fibers looked smooth and cylindrical. The Optical Microscopy studies revealed the smooth texture of the gelatin fibers. The aged fibers retained their original structure.

FT IR Studies

Based on analysis of the FT-IR spectra, it was determined that the drug and its formulation had comparable peaks with slight variations. This suggests that there was no chemical reaction between the drug and the excipients employed. The IR spectra of Gelatin and Sucrose were also examined, along with dolutegravir, and the following peaks were detected. FT IR Dolutegravir and Nanofibers are shown in Fig. 5. The peaks observed at 3437 cm^{-1}, 2969 cm^{-1} and 968 cm^{-1} correspond to the presence of OH group in the structure of Dolutegravir. The peak at 1361 cm^{-1} and

1025 cm^{-1} correspond to the C-N and C-O groups respectively. The peak at 3382 cm^{-1} shows the presence of the Amine group in Dolutegravir. The structure of gelatin in the nanofiber was confirmed by the presence of peaks in the range of 2879-2930 cm^{-1} which confirms the presence of C-H groups. The peaks observed at 3280 cm^{-1} -3283 cm^{-1} confirm the presence of OH groups present in Gelatin and the peak at 1637 cm^{-1} indicates the presence of carbonyl groups in the structure of Gelatin. The FTIR Spectrum of the nanofibers is shown in Fig. 3.

Table 1: % Drug Content Analysis

Sample No.	Absorbance at 254 nm	Drug Conc.	% Drug Content	Average % Drug Content
	0.4116	49.10066	98.20132	
Sample 1	0.3879	46.402415	92.80483	96.22 %
	0.4093	48.838805	97.67761	
	0.3969	47.427065	94.85413	
Sample 2	0.4019	47.996315	95.99263	96.11 %
	0.4085	48.747725	97.49545	
	0.4083	48.724955	97.44991	
Sample 3	0.3873	46.334105	92.66821	94.76 %
	0.3939	47.085515	94.17103	

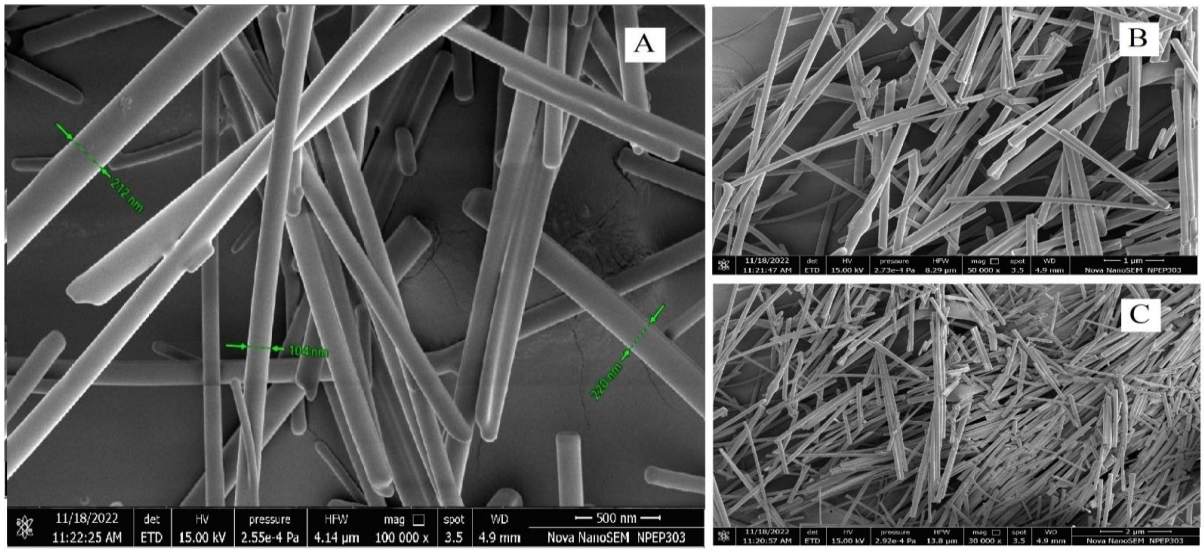

Figure 2: FE SEM Images of Drug Loaded Nanofibers at different magnifications: A. 100000 X B. 50,000 X C. 30,000 X

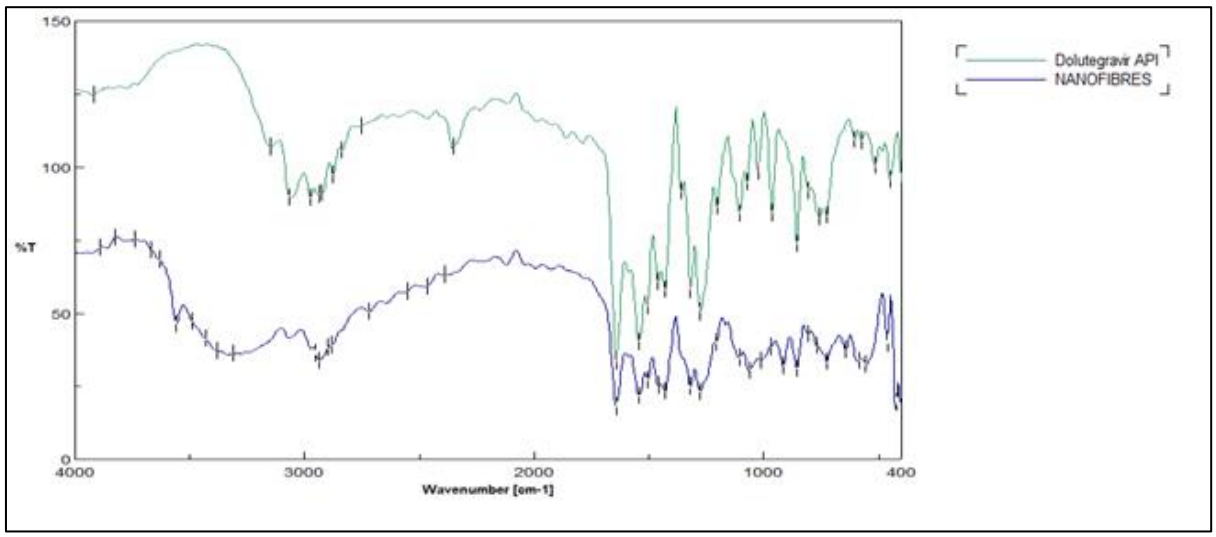

Figure 3: FTIR Spectra Overlay of dolutegravir and Drug Loaded Nanofibers.

In vitro Dissolution Studies

The dissolution test was performed using a USP type I dissolution test apparatus (Basket type) at 50 RPM. A dissolution medium of 900ml of pH 6.8 phosphate buffer was used and kept at a constant temperature of 37±0.5°C. At specific time intervals (1hr, 2hr, 4hr, 6hr, 8hr, 10hr 14hr, 18hr 22hr, 26hr and 30hr), 5mL of the dissolution medium was withdrawn and filtered. The amount of drug dissolved was measured using UV-spectrophotometer by assessing the absorbance of the sample at 254 nm. The Readings were taken in triplicates and the average % release was then noted.

The Drug loaded cross-linked nanofibers showed an average % release of 99.86% at 30 hours. The % release of drug from nanofibers is shown in Table 2.

Table 2: % Drug Release of Nanofibers.

Time	% Release			Avg
In Hours	1	2	3	% Release
0	0.00	0.00	0.00	0.000
1	12.69	13.69	14.40	13.596
2	21.16	21.41	21.79	21.454
4	26.10	26.20	26.78	26.363
6	31.76	32.61	33.81	32.727
8	36.65	36.99	36.82	36.822
10	44.25	44.98	44.64	44.623
14	52.40	52.80	52.73	52.644
18	67.21	65.05	64.69	65.650
22	78.36	76.17	77.76	77.431
26	90.19	89.96	90.42	90.187
30	99.65	100.18	99.77	99.866

For Curve Fitting analysis, different kinetic models were employed to evaluate the drug release kinetics of the Nanofibers. These models included zero-order & first-order for release kinetics, and Matrix, Hixson Crowell and Peppas models for mechanism of release.

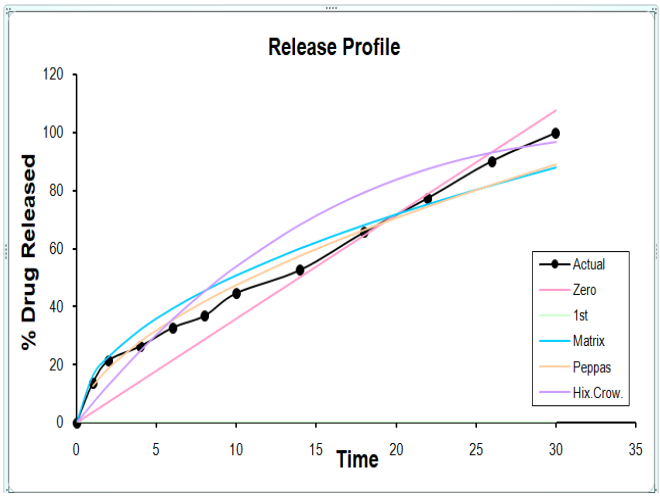

Figure 4: Comparative Dissolution Profile of Nanofibers with Curve Fitting

The comparative dissolution profile was shown in the Figure 4. The Nanofibers exhibited the highest R2 value of 0.9619 for the zero-order plots, which indicates that the drug release follows zero-order kinetics. Furthermore, the mechanism of release was fitted to the Korsmeyer-Peppas equation, with an n value of 0.5708. This indicates non-Fickian diffusion mechanisms and may suggest that the drug release is controlled by more than one process.

Stability studies

Through optical microscopy studies it was confirmed that the aged fibers retained their structure. The dissolution studies revealed that the aged fibers showed dissolution pattern similar to the fresh crosslinked fibers with maximum release of 98.75%.

Preparation of film

The film formulation was prepared by solvent casting method as described in the methodology.

Characterization of the film

Physical properties

The Physical properties of the film evaluated by visual inspection revealed that the film was clear and free from any air bubbles and contamination. The nanofibers appeared to be retained within the film. Fig. 7 shows the visual appearance of the film.

Thickness of the film

The thickness of the film was found to be uniform for each film and was found to be in the range of 0.015-0.021 mm. The average thickness of the film was 0.018 mm.

Folding Endurance

The folding endurance of the films, they were repeatedly folded at the same spot without breaking. The folding endurance of the film was found to be in the range of 166-182.

Disintegration time

The disintegration time taken for the complete removal of the film with no residue on the gauze was found to be 26.16 ± 1.21 seconds.

In vitro dissolution study

The in vitro dissolution study was carried out for the 2×2 cm^2 film using USP type-II apparatus with pH 6.8 phosphate buffer solution as dissolution medium. The time intervals were set at various durations such as 1, 2, 4, 6, 8, 10, 14, 18, 22, 26, and 30 hours similar to the study of nanofibers. At each interval, a 5mL sample of the dissolution medium was withdrawn and filtered. The amount of drug that had dissolved was then measured using a UV-spectrophotometer, which assessed the sample's absorbance at 254 nm. This process was repeated three times, and the average % release was recorded.

Table 3 shows the % release of drug from film, and the film displayed an average % release of 95.13% after 30 hours.

Table 3: % Drug Release from Film Formulation

Time	% Release			Average
In Hours	1	2	3	% Release
0	0	0	0	0
1	7.78	7.38	8.17	7.77
2	11.88	14.58	11.28	12.58
4	22.99	23.23	23.07	23.09
6	30.04	29.78	29.94	29.92
8	36.98	37.33	36.88	37.06
10	46.24	46.57	46.17	46.32
14	52.19	52.03	51.84	52.02
18	69.84	59.28	65.66	64.92
22	80.21	77.77	83.06	80.34
26	91.91	89.86	91.31	91.02
30	95.18	95.22	94.99	95.13

The drug release kinetics of the film were evaluated using various kinetic models such as zero-order, first-order, Matrix, Hixson Crowell, and Peppas models. The results were compared in, and the zero-order model exhibited the highest R2 value of 0.9756, indicating that drug release follows zero-order kinetics and mechanism of release was confirmed as Korsmeyer-Peppas model similar to the mechanism of release from Nanofibers.

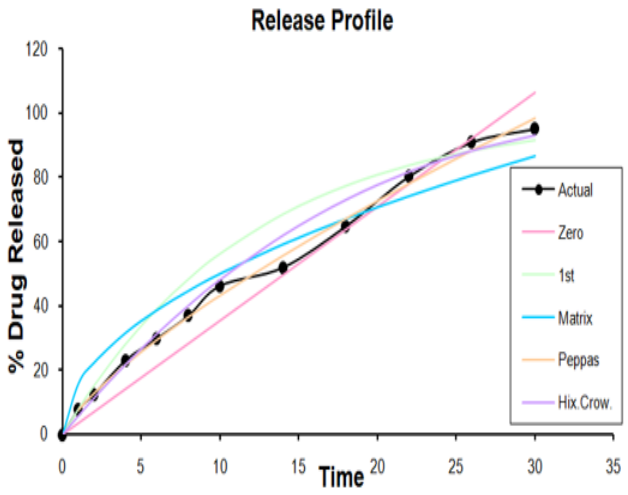

Figure 5: Comparative Dissolution Profile of Film Formulation with Curve Fitting.

FT IR Studies

Figure 6 presents the Fourier-transform infrared (FT-IR) spectra of the individual drug and film. The drug peaks exhibited negligible alterations in the final formulation, indicating that no interaction occurred between the excipients utilized in the film and dolutegravir. The drug peaks observed at 3437 cm^{-1}, 3382 cm^{-1}, 2969 cm^{-1}, 1361 cm^{-1}, 1025 cm^{-1}, and 968 cm^{-1} were maintained. Additionally, peaks corresponding to the presence of gelatin, hydroxypropyl methylcellulose (HPMC), and Xanthan gum were observed. Gelatin's presence was confirmed by the peaks noted at 3860 cm^{-1}, and 3729 cm^{-1} for OH groups, 2749 cm^{-1} for C-H groups, and 1643 cm^{-1} for carbonyl functional groups. The peaks noted at 3279 cm^{-1} and 2884 cm^{-1} corresponded to the OH and C-H groups of Xanthan gum, respectively. The presence of HPMC K15 was confirmed by the peak observed at 3403 cm^{-1} for the OH group and 1643 cm^{-1} for the C=C group.

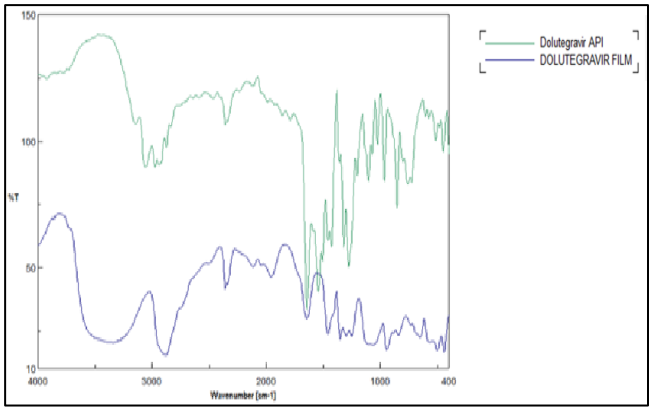

Figure 6: Overlay of FT IR spectra of dolutegravir and Nanofiber loaded film.

Thermal Characterization

The Thermograms of dolutegravir and the film are shown in Figure 11 and Figure 12 respectively. There was no sharp peak observed for Dolutegravir in the range of 50 to 300 ^{O}C owing to the high melting point of Dolutegravir. In the DSC thermogram of Film formulation, 4 sharp peaks are observed at 124.3, 270.4, 276.9 and 334.7 ^{O}C. The dip at 124.3^{O}C may correspond to the denaturation temperature of crosslinked gelatin fibers. The peaks of 270.4 and 276.9 correspond to the melting of Xanthan gum and 334.7^{O}C corresponds to the melting of Dolutegravir.

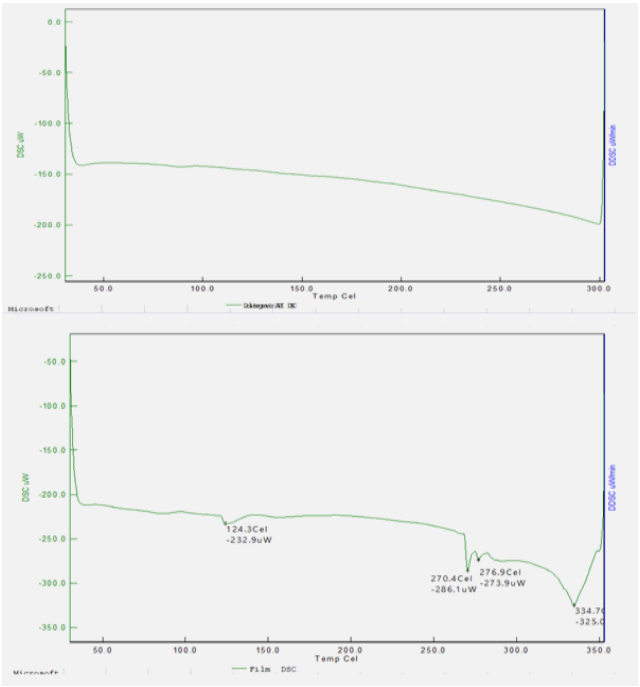

Figure 7: DSC Thermograph of Dolutegravir

Accelerated Stability Studies

To confirm the stability of the film, accelerated stability studies were performed. The samples were kept in controlled temperature and humidity conditions in a stability chamber for 3 months. At the end of each month, Samples were collected from the stability chamber and were evaluated for appearance and Drug release. Each of the collected samples appeared to be stable and retained its physical form and flexibility. No major changes were observed in the dissolution pattern and drug release as well. Therefore, it can be concluded that the formulation is stable.

CONCLUSION

Gelatin based nanofibers of dolutegravir and its controlled release formulation was prepared for enhancing the solubility of an oral antiretroviral drug used to treat HIV, shows promising results. The crosslinked gelatin nanofibers fabricated by centrifugal spinning led to the development of a method for the controlled release of Dolutegravir nanofibers results in improved solubility in buffer solution. In vitro dissolution studies confirmed the drug was released over 30 hours through zero-order release, following the Korsmeyer Peppas model. The nanofibers were also found to be stable within the film, offering a promising approach for ease of oral administration. This innovative approach has the potential to improve patient compliance and treatment outcomes by reducing dosing frequency and enhancing the therapeutic efficacy of Dolutegravir. The use of nanofiber technology could also offer an alternative for poorly soluble drugs, opening up new avenues for drug delivery systems. Overall, this study provides important insights into the potential of nanofiber technology in drug delivery systems and offers a promising approach for the controlled release of Dolutegravir in anti-HIV therapy.

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