Research Article

Designing a Nanofiber Mats as a Targeted Approach of Diltiazem Hydrochloride for Management of Hypertensive Conditions

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ABSTRACT

The goal of this study was to enhance therapeutic effectiveness for a drug with a short half-life and a strong first-pass effect, as well as reduce dose frequency and target drug release. Hence to create and construct diltiazem hydrochloride nanofiber mats for the treatment of hypertension, diltiazem hydrochloride was selected as a model medication. The nanofiber mat was developed utilizing fibres with nanoscale diameters and a higher surface area, resulting in a more successful treatment impact. Scanning electron microscopy has been used to assess the shape and diameter of the mats (SEM). Mats were also studied for their physical properties, total drug content, disintegration time, and *in vitro* drug release. The drug was really in the mats, which had good tensile strength and was also physically stable. The drug dissolved quickly and effort to remove. Mat disintegration time and drug release could be adjusted by varying concentrations of polymers. The bitter taste of diltiazem was masked by using aspartame and menthol. According to the findings, created nanofiber mats might perform better for improving drug loading efficacy, bypassing the first-pass effect, minimising the dose, and improving patient compliance through an effective alternative mode of administration.

Keywords: Nanofiber, Oral disintegration mat, Electrospinning, Diltiazem, Hypertension.

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INTRODUCTION

Because of its simplicity of administration, non-invasiveness, flexibility, patient compliance, and acceptance, the oral route of medication administration is the primary way. Utilizing current innovative technology, many substitutes for the oral route of medication delivery have been given for paediatrics, geriatrics, nauseous, and non-compliance patients. Bio-adhesive mucosal dosage forms such as sticky tablets, gels, and patches have been developed as a consequence of technological breakthroughs. Polymeric films have shown exceptional potential in delivering medication into the buccal cavity for a variety of dose forms.[1]

The Oral Disintegrating Mat (ODM) formulation should be rigid enough to avoid damage during handling and transit, and disintegrate properly in the mouth. However, both characteristics are dependent on the polymeric composition. An excellent oral film should be sturdy while still being flexible, elastic, and soft to sustain the tension in the mouth.[2]

As a result, the goal of this research was to create ODMs out of low-cost polymers and describe them in terms of optical, mechanical, and microstructural features, as well as hygroscopicity, swelling, and disintegration qualities, all of which might affect drug release. The material created might be used for medication delivery, bioactive controlled release *in vivo*, or other applications

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in the future. The specific qualities include no costly lyophilisation, strong mechanical strength, quick disintegration, and minimized choking dangers. Because of their unique features and quick disintegration times ranging from seconds to minutes, ODMs have become extremely important in the pharmaceutical business. The design of ODMs allows for the incorporation of a wide range of pharmaceuticals with different pharmacological effects, such as anti-tussive, anti-epileptic, anti-asthmatic, expectorant, and so on. Due to the high temperature and moisture sensitivity, costly packaging is required.[3] The advantages are oral cavity has a large surface area, allowing the oral dosage form to dissolve and disintegrate fast, with little risk of choking, and ODMs provide for exact dosage since they are solid unit dose forms, Because pre-gastric absorption enhances medicine bioavailability, fewer doses are required, increasing patient compliance. ODMs are more appealing to dysphagic people since they do not require water to swallow. Give your mouth a delightful sensation. Oral mats are less brittle and more flexible than oral disintegrating films, making them simpler to transport, handle, and store.[4] The disadvantages are having extreme temperature and moisture sensitivity reactions, requiring the use of expensive packaging and the bitter taste of most drugs needing the use of a taste-masking agent.[5]

Polymer fibre composites or nanofiber mats of nanometer sizes are now appealing. The nanofiber mats' outstanding properties, such as their enormous surface area to volume ratio and high porosity, make them ideal candidates for ODF formulation. Drawing, template synthesis, phase separation, self-assembly, electrospinning, and other processing techniques were employed to create these nanofiber mats.[6] Electrospinning has been demonstrated to be a feasible technology for producing nanofibers, which may then be evolved into a continuous production of nanofiber mats from polymer solution. As a result, this technology is an excellent alternative for creating nanofiber mats as ODFs. These nanofiber mats for ODFs should have a quick disintegration/dissolution time and a nice flavour in the oral cavity. A suitable water-soluble polymer is required to accomplish fast disintegration, dissolution, and drug release.

PVP (polyvinyl pyrrolidone) is a water-soluble polymer that can give these characteristics. Nonetheless, its hygroscopic characteristic causes water absorption of up to 40% of its weight in ambient circumstances, which may result in unstable nanofiber mats. Hydroxypropyl methyl cellulose (HPMC) is a good film former that may form an inclusion complex by absorbing a whole molecule or a non-polar component into their cavity.[7] The HPMC inclusion complex can be used to improve drug stability. As a result, integrating HPMCs with PVP is of special relevance for improving PVP stability.

Furthermore, by encapsulating the medication molecules at the molecular level, HPMCs may have the ability to reduce the disagreeable taste. Sweeteners and flavours are also added to conceal the taste.

Diltiazem hydrochloride is a Non-Di-hydro pyri dine derivative belonging to the class of Calcium Channel blockers (CCBs), and is an effective therapeutic agent used for myocardial abnormal conditions. It has an extended-release tablet, the initial dose of 30-60mg orally once a day.[8] Calcium antagonists, or CCBs, are another name for them. They prevent calcium from entering certain muscle cells in your heart and blood arteries, making electrical signals more difficult to pass. Some CCBs work by preventing blood vessels from constricting. Others lower your heart rate or reduce the force with which your heart squeezes to push blood through your veins.Calcium channel blockers may be prescribed by a doctor in conjunction with other blood pressure drugs or cholesterol-lowering therapy such as statins.[9]

The main objectives of this present work were to improve the limitations and prepare the fast disintegrating and taste masking mats of the drug. The diltiazem HCl loaded nanofiber mats were developed by an electrospinning process and these formulated nanofiber mats were evaluated for Total drug content, Drug release characteristics, disintegration time and stability.

MATERIALS AND METHODS

Materials used

Diltiazem Hydrochloride received from Brooks laboratories Ltd. Baddi H.P, Polyvinyl pyrrolidone K30, Hydroxypropyl methyl cellulose (HPMC K4M) and aspartame were purchased from Iam pure ingredients, Chennai. Menthol, N, N-Dimethylformamide were used as received.

Determination of Diltiazem HCL solubility

The solubility study of Diltiazem HCl was performed by shaking the flask method with the addition of the drug in distilled water and Phosphate buffer. The samples were analyzed by UV spectroscopy.

UV Spectroscopical Analysis[10]

Scanning for λ_{max} of Diltiazem Hydrochloride

A 100mg of Diltiazem Hydrochloride was accurately weighed and was first dissolved in 35ml methanol

solution. The solution was then diluted using phosphate buffer (pH6.8) to 100mL (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10µg/ml. 10 µg/ml solution was scanned from 200-400nm. From the curve, peaks for the diltiazem hydrochloride were found at 237nm. The results are shown in the Table 1, Figures 1-2.

Standard Calibration Curve of Diltiazem Hydrochloride

Diltiazem hydrochloride, 100 mg, was precisely weighed and dissolved in a 35 mL methanol solution first. The solution was then diluted to 100ml using phosphate buffer (pH 6.8). (stock solution-I). To get 100 g/ml concentrations, create a 10ml solution from stock solution 1 and volume it up to 100ml with phosphate buffer (stock solution II). It was then diluted with phosphate buffer pH–6.8 to provide solutions ranging from 1 to 10 g/ml. At 237nm, the absorbance of these solutions was measured spectrophotometrically. The results are shown in the Table 1 and Figures 1-2.

Table 1: Calibration Curve of Diltiazem HCL in Phosphate buffer.

Sl. No	Concentration (µg/ml)	Absorbance at 237nm
0	0	0
1	1	0.0920
2	2	0.1917
3	3	0.2878
4	4	0.3736
5	5	0.4934
6	6	0.6010
7	7	0.7393
8	8	0.8285
9	9	0.9723
10	10	0.9984

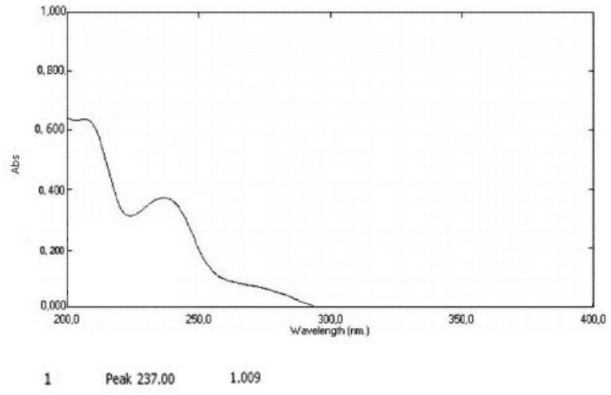

Figure 1: Maximum absorbance of Diltiazem HCL.

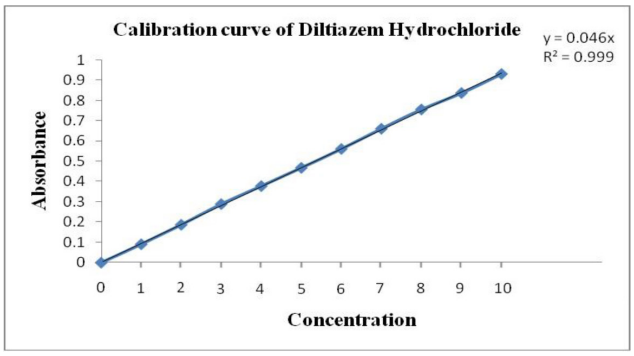

Figure 2: Calibration curve of Diltiazem HCL in phosphate buffer pH 6.8.

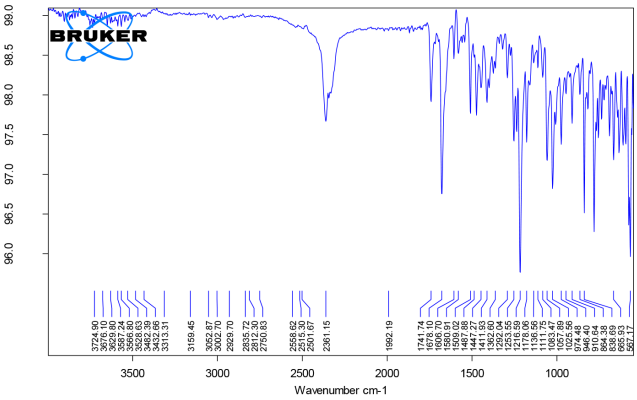

Figure 3: ATR-FTIR Spectrum of Diltiazem HCL Pure Drug.

ATR- FTIR Spectroscopic Studies

The ATR-FTIR spectrum was utilised to identify and verify the medication. The spectrum was captured in the 4000 to 400 cm^{-1} wavelength region. An IR spectrum was acquired using an FTIR-IR spectrophotometer after an evenly mixed sample of the medication was poured into the die cavity of the sample holder. The results are shown in the Figure 3-6.

Preparation of Diltiazem HCl loaded Nanofiber mats by Electrospinning Method[11-12]

- Polyvinyl pyrrolidone (PVP K30) / Hydroxy Propyl Methyl Cellulose (HPMC K4M) powder was weighed and thoroughly dissolved in Dimethylformamide at 80°C. The PVP solution was made at a constant concentration of 10% w/v.
- Diltiazem HCL was added to the PVP solution after bringing it to room temperature (37°C), followed by

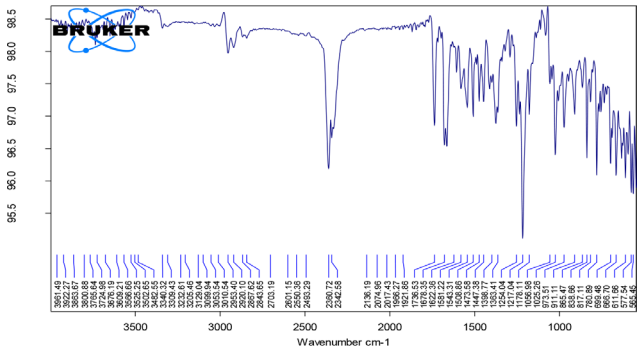

Figure 4: ATR-FTIR Spectrum of Diltiazem HCL + PVP + HPMC + Aspartame + Menthol.

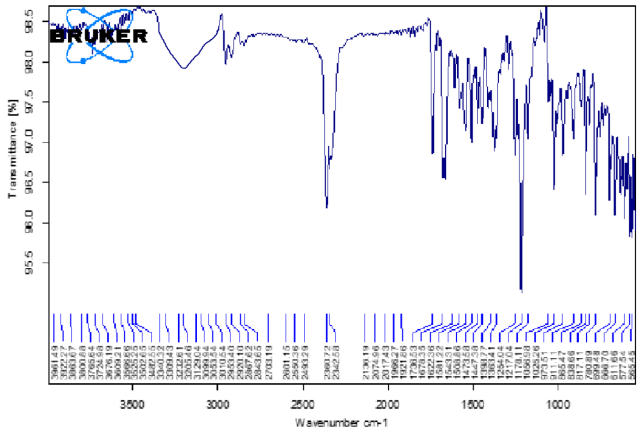

Figure 5: ATR-FTIR Spectrum of Nanofiber MAT (F5) Formulation.

Evaluation of Nanofiber Mats

All the formulations prepared were evaluated for different parameters such as SEM study, Tensile strength, Drug content and drug loading efficacy, *in vitro* disintegration time, *in vitro* drug release, and Stability studies and their reports are discussed below.

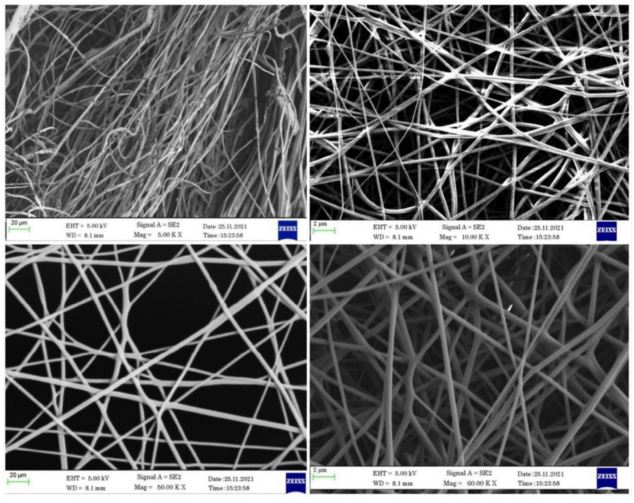

Figure 6: SEM images of nanofiber mat formulation.

aspartame and menthol in a specified ratio, all while stirring constantly for 4 hr. Add up to 100ml of DMF to the mix.

- Before electrospinning, the viscosities (250 mPas) and conductivities (2 S/cm) of the as-prepared solutions were measured using a viscometer and a conductivity metre, respectively.
- By connecting the emitting electrode from the High-Voltage DC power source to the solutions in a 50-mL syringe, the Electrospinning technique was conducted on the prepared solutions.
- The shear rate was set to 10 s-1, and the spindle rotation rate was set to 20 cycles per minute, with the open end of the syringe serving as both a delivery nozzle and a grounding electrode for a manufactured revolving metal drum. Applying a set electrical potential of 15 kV over a fixed distance of 15 cm between the tip of the nozzle and the drum's outer surface produced a 15 kV/15 cm electrostatic field intensity. The spinning drum went through 50–60 revolutions per minute.

Ingredients (in mg)	F1	F2	F3	F4	F5	F6
Diltiazem	20	20	20	20	20	20
PVP K30	10	15	20	25	30	35
HPMC K4M	20	40	60	80	100	120
Aspartame	50	50	50	50	50	50
Menthol	25	25	25	25	25	25
Dimethyl formamide	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation of nanofiber mats[13-14]

Morphology analysis (SEM study)

A Hitachi S-4700 scanning electron microscope has been used to examine the morphology of Diltiazem HCL-loaded electrospun nanofiber (Hitachi Company, Japan). Before even being considered, samples were mounted to metal ends using double-sided adhesive tape and vacuum-coated with a gold sputter layer. The average diameter of the fibres was then calculated using the SEM images. The results are shown in the Table 6.

Tensile Strength and Swelling Index

A texture analyzer with a 5 kg load cell as well as a tensile grab holder was used to test the nanofiber mats' tensile strength.[15] The resulting nanofiber formulation was cut into a rectangular shape of strips (6 × 35 mm). These samples varied in thickness from 20 to 30 µm.

Polymer swelling is required for the relaxation and interpretation of polymer chains. The % hydration

Table 2: Tensile strength and swelling index of the various formulation.

Formulations	Tensile strength (MPa)	Swelling index (nm)
F1	2.0±1.7	19.3±1.5
F2	2.2±1.5	18.8±2.0
F3	2.1±0.9	18.4±2.5
F4	1.6±0.5	17.8±3.0
F5	1.9±0.4	17.2±3.2
F6	1.8±0.3	17.4±2.7

(Mean ± SD, *n*=3)

Table 3: Drug content and drug entrapment efficiency of various formulations.

Formulations	Total drug content (mg)	Entrapment efficiency (%)
F1	18.90±0.07	81.28±1.83
F2	18.87±0.07	81.43±1.68
F3	18.88±0.04	81.40±2.72
F4	18.91±0.06	81.79±3.64
F5	18.95±0.04	81.79±3.64
F6	18.93±0.04	81.67±2.85

(Mean ± SD, *n*=3)

of nanofiber mats was used to assess their swelling properties. The results are shown in the Table 2.

$$\text{Percent swelling [\% S]} = [X_t\text{-}X_0/X_0] \times 100$$

Where Xt is the swollen film's weight at time t.
X_0 is the starting weight of the film at zero time.

Drug Content and Drug Entrapment Efficacy[16]

Dissolving a nanofiber mat (150 mg) in 50 ml of phosphate buffer at pH 6.8 for 24hrs determined the amount of Diltiazem HCL in the mat. 2.38 g Na2HPO4, 0.19 g KH2PO4, and 8 g NaCl per litre of deionized water were used to make the phosphate buffer, which was adjusted to pH 6.8 using phosphoric acid. Under such conditions, the solubility of Diltiazem HCL was lower than its saturation solubility. The level of Diltiazem HCL in the nanofiber mats (as determined by the feeding condition) was 10% w/w. The concentration of theoretical Diltiazem HCL (13.5 mg) in the 150 mg nanofiber mat was 0.27 mg/ml following dissolving it in 50 ml of phosphate buffer pH 6.8. The concentration was less than 50 mg/ml, which is the saturation solubility. The solution was then analyzed using a UV-visible spectrophotometer calibrated at 362 nm. The following formulae were used to calculate the total drug content (mg) and loading capacity (%) of Diltiazem HCL. The results are shown in the Table 3.

Table 4: *In vitro* disintegration time.

Formulations	*In vitro* disintegration time (in seconds)
F1	33.0±3.2
F2	35.0±2.7
F3	36.0±2.1
F4	32.0±1.8
F5	30.0±0.3
F6	34.0±2.2

(Mean ± SD, *n*=3)

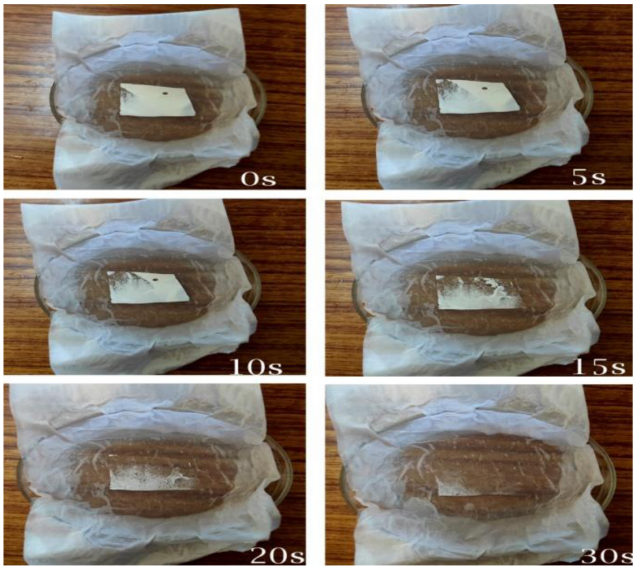

Figure 7: Images of diltiazem loaded nanofiber mats (F5) during the disintegration test at several time points.

Drug content (mg) = Concentration × Dilution factor

% Drug content = Drug content (mg) / Label claim (-mg)

% Loading efficiency = Actual drug content (AC) / Theoretical drug content (TC)

In vitro Disintegration Time[17]

A piece of paper tissue was folded twice and placed in a 10 cm diameter plastic dish containing 10 ml of phosphate buffer pH 6.8 to check the disintegration time of the nanofiber mats. The disintegration time is calculated by inserting a nanofiber mat into the folded paper's central axis and monitoring the time it took for the water to spread over the mat from the absorbent paper. Images were taken at various intervals until the mats had totally dissolved. The results are shown in the Table 4, and Figure 7.

In vitro Drug Release[18]

In phosphate buffer (Artificial saliva pH 6.8), the release properties of Diltiazem HCL from nanofiber

Table 5: *In vitro* drug release profile of formulation F1 to F6.

Sl. No	Time (in min)	F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0
2	10	21.32	31.04	20.04	13.15	24.63	19.76
3	20	28.53	38.56	29.56	16.41	30.63	22.89
4	30	39.90	46.35	37.35	21.98	42.52	26.24
5	40	45.96	52.52	45.52	26.09	50.31	35.32
6	50	57.14	56.75	52.75	29.54	58.25	39.75
7	60	63.85	62.53	56.53	34.36	65.78	43.09
8	70	68.25	68.84	59.84	41.69	68.17	48.16
9	80	70.83	70.93	60.93	47.95	73.57	53.36
10	90	73.46	77.52	62.52	52.77	78.27	57.12
11	100	75.77	82.25	67.25	58.42	86.64	62.78
12	110	78.15	85.92	69.72	67.02	89.87	73.79
13	120	81.63	85.06	73.46	74.46	94.89	87.31

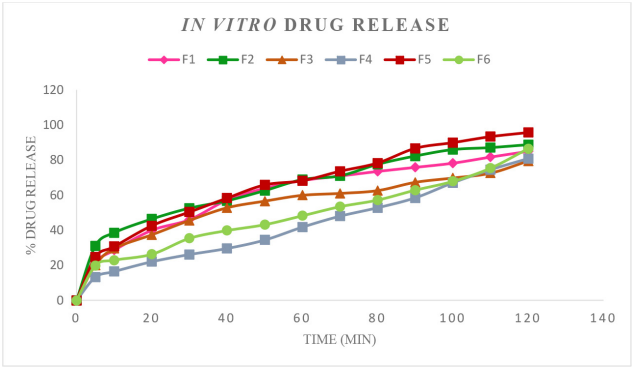

Figure 8: *In vitro* drug release profile of mat formulations (F1 to F6).

mats containing Diltiazem HCL were examined. The nanofiber mats were precisely weighed and put in the dissolving equipment with 900 mL of release media. Throughout the test, the medium was kept at 37 ± 0.5°C at 50 rpm at a speed of 50 rpm. At each time point, 1ml of sample solution was removed and replaced with an equal quantity of fresh medium. A UV visible spectrophotometer set to 237 nm was used to measure the quantity of Diltiazem HCL in the sample solutions. The collected data was carefully examined to calculate the total quantity of Diltiazem HCL released from the specimens at each immersion time point. The results are shown in the Table 5 and Figure 8.

Stability Studies

The optimised diltiazem-loaded nanofiber formulation for stability determination accelerated stability conditions at (40°C/75 percent RH). Over three months, the Swelling index, Tensile strength, and *in vitro* drug release

Table 6: Stability studies of the optimized formulation.

Time	Swelling index (nm)	Tensile strength (Mpa)	*In vitro* drug release
Initial	17.2±3.2	1.9±0.4	94.89
15 days	18.3±2.8	1.9±0.4	94.82
30 days	19.8±2.1	1.8±0.5	94.79
60days	22.7±2.4	1.6±0.6	94.63
90 days	25.2±3.1	1.3±0.8	94.50

(Mean ± SD, *n*=3)

nanofiber formulations were evaluated. All of these features are compared to the initial sample, which is then analysed to see whether it meets the requirements. If this is the case, the batch has passed the test. The results are shown in the Table 6.

RESULTS AND DISCUSSION

Diltiazem Solubility

The solubility of Diltiazem HCL was evaluated using a shaking flask technique with the addition of the medication in distilled water and phosphate buffer. The goal was to discover the solvent with the maximum Diltiazem solubility that could be employed in the electrospinning process. DTZ was soluble in water (46.5 mg/100ml), phosphate buffer (0.80 mg/ml), and DMF (10 mg/ml). As a result, DMF was chosen as the electrospinning solvent for the Diltiazem HCL polymeric nanofiber mats.

DISCUSSION[19]

Diltiazem Solubility

Solubility test results show diltiazem solubility range in distilled water and phosphate buffer pH 6.8. The melting point of the diltiazem pure drug was found to be 214°C, which was similar to reference standards.

Scanning for λ_{max} of Diltiazem Hydrochloride and standard calibration curve

The sample diltiazem hydrochloride was scanned in the UV-vis spectrophotometer in the range of 200- 400 nm using a blank and the wavelength corresponding to maximum absorbance (max) was recorded. At a wavelength of 237nm, the highest absorption was obtained. The absorbance V/S concentration of Diltiazem Hydrochloride was plotted at 237nm to produce the standard calibration curve. and good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Drug-excipients Interaction studies by ATR-FTIR spectroscopy

Compatibility studies were performed using ATR-FTIR spectrophotometer. The ATR-FTIR spectrum of pure drug, polymers, excipients and physical mixture were studied by using a Bruker, ATR FTIR facility by using direct sample technique. Here, there is no physical interaction occurs. The optimized drug-loaded nanofiber mat formulation (F5) was studied and the results showed no chemical interaction between drug and excipients.

Evaluation of nanofiber mats[15]

Morphology analysis (SEM study)

SEM analysis was used to assess the surface morphology of the optimal drug-loaded formulations at magnifications of X5 K, X10 K, X50 K, and X60 K, as shown in Figure. The fibre-shaped particles are within the stipulated size range and were fibre-shaped. SEM analysis studied for the optimized nanofiber formulation mat (F5) was evaluated for the surface morphology of the formulation at magnification X5 K, X10 K, X50 K and X60 K are shown in Figure 6, this image shows that the prepared nanofiber was diameter ranging about 300 nm.

Tensile Strength and Swelling Index

Formulations of prepared mats indicate the study result of tensile strength and swelling index ranging from 1.6 to 2.2 and 17.2 to 19.3. Among this studied formulation F1 – F6 formulation F5 showed tensile strength and swelling index values of 1.9 and 17.2 which was the optimal range compared to other formulations.

Drug Content and Drug Entrapment Efficiency

Formulations containing selected polymer total drug content ranging from 18.87±0.07 to 18.95±0.04 mg and entrapment efficiency 81.28±1.83 to 81.79±3.64% respectively. The results show optimized nanofiber mat formulation (F5) has higher drug content of 18.95±0.04 mg and best entrapment efficiency of 81.79±3.64% compared to other formulations.

In-vitro Disintegration Time

Within 60 sec, the Diltiazem-loaded nanofiber mats were soaked, dissolved, and lost their original structure. The disintegration time ranges from 30 to 36 sec, as shown by the manufactured nanofiber mats. In comparison to the other formulations investigated, formulation F5 was wetted, decomposed, and lost its original shape within 30 sec.

In vitro Drug Release

Dissolution apparatus was used to explore *in vitro* drug release. Diltiazem HCL *in vitro* release rate was measured using 900 ml of phosphate buffer (i.e. artificial saliva pH 6.8) at 37 ± 0.5°C and 50 rpm. A sample of the solution (1 ml) was taken at regular intervals for up to 120 min. A UV visible spectrophotometer with a wavelength of 237 nm was used to evaluate the gathered sample solutions. When compared to other formulations, the improved formulation (F5) had a superior release (94.89) within 120 min, according to the *in vitro* drug release data. It was shown that increasing the surface area of diltiazem and the polymer carrier with a nanofiber mat enhanced the dissolving rate. Based on these findings, the best mats with the quickest disintegration and diltiazem release were identified as F5.

Stability Studies as per ICH Guidelines

The stability of the optimised diltiazem nanofiber mat formulation was assessed for three months in a short-term environment (25°C and 60% RH) vs an accelerated condition (40°C and 75% RH) according to ICH recommendations. Stability studies were conducted for finally optimized formulation (F5) at the accelerated condition for three months. Mild variations were noticed in tensile strength and swelling property, and *in-vitro* drug release, but were statistically insignificant. As a result, it may be inferred that the ideal storage condition for nanofiber mats.

SUMMARY AND CONCLUSION

As a result, the diltiazem-loaded nanofiber mats were effectively manufactured using an electrospinning method. These nanofiber mats were smooth and had a diameter specification in the nanometer range. It has a tensile strength and swelling index that are appropriate. Within 30 sec, the diltiazem-loaded nanofiber mat formulation (F5) dissolved. The mat disintegration time and drug release could be adjusted by varying concentrations of polymers. The results were concluded that developed nanofiber mats could perform better for leading to improve drug loading efficacy, bypassing first-pass effect, minimising the dose, and improving the patient compliance by an effective alternate route of administration.

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College of Pharmacy, Salem, Tamil Nadu for extending their support and facilities for this research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ATR-FTIR: Attenated Total Reflectance- Fourier Transform Infrared; **DSC:** Differential Scanning Calorimetry; **F1:** Formulation 1; **Mins:** Minutes; **Ml:** Milli Litter; **NaCl:** Sodium Chloride; **ODMs:** Oral Disintegrating Mats.

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