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Original Article

Preparation and Evaluation of PLGA-Safinamide Mesylate Nano Particles for the Management of Parkinson's Disease

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ABSTRACT

Aim/Background: Parkinson's Disease (PD) is second most common chronic ongoing neurodegenerative disease recorded in ageing population, which is primarily treated with medications that either replace dopamine or mimic its effects in the brain. In this study, safinamide mesylate popular for its use during "off" episodes in PD was used. PLGA Nanoparticles of Safinamide mesylate (PNS) was prepared and evaluated to improve the bioavailability and targeted delivery of the drug. **Materials and Methods:** PNS prepared by emulsion solvent evaporation method. Various trials were carried out to obtain particles in nano range with optimum drug entrapment. Three different batches of PNS were prepared by varying polymer concentrations. The prepared formulations were evaluated for particle size, zeta potential, drug loading, entrapment efficiency, XRD, TEM etc. and the *In vitro* release studies of the formulations were recorded. **Results:** Batch PF1(1:1) had particle size of 606 nm, zeta potential of -30 mv, PDI of 0.224, entrapment efficiency of 22.69% and 11.35% of drug loading. Zeta potential was in the range of -24.2 to 30 mV, and zeta potential -30mV of PF1(1:1) ensuring stability. PXRD studies of PF1(1:1) showed amorphous state when scanned at 2θ and coated PNS was clearly identified from TEM images. The results of *in vitro* drug profiles studies were subjected to curve fitting, where PF1(1:1), followed Korsmeyer-Peppas model and value was 1.963 when compared to other batches. Accelerated studies showed no significant changes in drug content and *in vitro* release profile. **Conclusion:** Hence it could be predicted that the prepared PNS, due to its inherent nano size will increase permeability of the drug and has the potential to decrease the T_{max} and further improve bioavailability in management of Parkinson's disease.

Keywords: Drug Loading, Entrapment Efficiency, Particle Size, PLGA Nanoparticle, PXRD.

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INTRODUCTION

Parkinson's Disease (PD) known as 'shaking palsy' is a chronic, degenerative disorder of the brain, associated with motor symptoms and non-motor complications (DeMaagd and Philip, 2015; Jankovic and Tan, 2020). According to the estimation around 9.4 million PD global population in 2020 is higher than the previously reported 6 million PD in 2016 (World Health Organization [WHO], 2020). Parkinson's disease is treated with medications that raise dopamine levels in the brain, influence other chemicals in the brain, and assist manage nonmotor symptoms (Senturk, 2020). One of the popular drugs used in the management of Parkinson's disease is safinamide mesylate, a Monoamine Oxidase B Inhibitor (MAO-B). It acts centrally, by blocking the oxidation of dopamine in the synapse (Ema, 2016). SAF is approximately 5000 times more selective for MAO-B than MAO-A (1000 times more selective in humans), compared with selegiline (127 times) or (203 times) (Baker and Kim, 2017) rasagiline (Lecht *et al.*, 2007). SAF is a potent drug, which is responsible for a distinct and reversible inhibition of MAO-B with blockade of voltage-dependent NA^+ and CA^{2+} channels and inhibition of glutamate release (National Library of Medicine, 2021). In several controlled release products, poly DL (lactide-coglycolide) 50:50 (PLGA), a copolymer of Poly (Lactic Acid) (PLA) and Poly (Glycolic Acid) (PGA), has been employed as a drug delivery vehicle due to its good biocompatibility and degradability in physiological conditions. A variety of popular solvents, such as tetrahydrofuran, acetone, ethyl acetate, and chlorinated solvents, can dissolve PLGA (Xu and Kim, 2017). Safinamide mesylate (SAF), an inhibitor of monoamine oxidase-B is used as adjunctive therapy, in combination with levodopa and carbidopa (Drug Bank, 2015). SAF, belongs to the BCS class II, whose solubility is highly pH dependent, high solubility at low pH 2 and pH 4, low solubility at pH 6.8 and when orally administered

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its absolute bioavailability is high (95%) (U.S. Food and Drug Administration, 2017). Thus, in this present work SAF and PLGA was selected. In order to achieve rapid drug absorption, quick onset of action and to improve the bioavailability, we intend to convert this drug into nano (Yetisgin *et al.*, 2020; Ezike *et al.*, 2023; Pratap Singh *et al.*, 2019), delivery systems.

By developing this novel delivery system, we could reduce the dosing demand and avoid gastrointestinal irritation, improve patient compliance and improve the effective delivery of the drug in the treatment of Parkinson's disease.

MATERIALS AND METHODS

SAF drug, a gift sample from Jubilant Generics, Mysore, PLGA50:50 purchased from Nomisma health care private Ltd., Dichloromethane (DCM) from central drug house Private. Ltd., Polyvinyl Alcohol (PVA) was purchased from Fisher Scientific India Private. Ltd., Mumbai. Distilled water and all other reagents of analytical grade were used with no further purification and dissolution data modelling using DD Solver 1.0 software.

Preparation of PLGA-Nanoparticles of Safinamide mesylate (PNS)

The emulsion solvent evaporation (Alghareeb *et al.*, 2024; Ahadian *et al.*, 2020; Shailender *et al.*, 2017; Operti *et al.*, 2021) technique was used to prepare the nanoparticles (Herdiana *et al.*, 2022). Three different formulations were prepared. The Drug: polymer ratio was 1:1, 1:2 and 1:5. Formulation $PF_{1(1:1)}$ was prepared by mixing the aqueous phase and organic phase. The aqueous phase A containing 0.4%w/v (80 mg) of PVA solution and SAF 25 mg (equivalent to 18.97 mg of safinamide) was mixed thoroughly. The organic phase B contained PLGA (25 mg) dissolved in 10 mL DCM. The organic phase B was added dropwise to the aqueous phase A followed by homogenisation for 30 min and sonicated for 15 min (using PCI Analytics probe sonicator, power 40%, son 30's, gap 5's, temp 27°C) to form oil in water type of emulsion. After sonication, 0.5% w/v (100 mg) PVA solution was added, stirred for 2 hr using magnetic stirrer till organic solvent was evaporated. Then, the emulsion was centrifuged (using Remi centrifuge) at 10,000 rpm for 30 min. The supernatant was separated from the pellet (Figure 1) and the amount of free drug and entrapped drug was carried by measuring the absorbance at 226.5 nm utilizing a UV-visible spectrophotometer (UV-1700 Shimadzu 1700 Japan). The same procedure was followed for all the formulations $PF_{2(1:2)}$, $PF_{3(1:5)}$ prepared by varying the concentration of PLGA and by keeping the drug concentration constant. Formulation (PF_0) was without drug (Al-Nemrawi *et al.*, 2018; Chatterjee and Chanda, 2022) shown in Table 1.

Determination of absorption maxima (λ_{max}) and calibration curve of SAF

Prepared 15 µg/mL solution of SAF in distilled water and scanned in the range of 200 to 350 nm using UV-visible spectrophotometer (UV-1700, Shimadzu, Japan). Calibration curve was prepared by transferring 25 mg of the SAF drug (equivalent to 18.97 mg of safinamide) in 10 mL distilled water. Further dilutions were made then, aliquots 5, 10, 15, 20 and 25 µg/mL solutions (0.5, 1.0, 1.5, 2.0 and 2.5 mL) was prepared using distilled water in 10 mL volumetric flask (EMA/CHMP/393951/2014; Gao *et al.*, 2020) and absorbance was noted using UV-visible spectrophotometer.

Drug and polymer compatibility study by FTIR spectroscopy

The study was carried out by using FTIR Spectrophotometer (Shimadzu IR Spirit) to find out the possible interactions of functional groups between the SAF (Ledesma *et al.*, 2020), polymer PLGA (Gurpreet *et al.*, 2014), physical mixture of SAF with PLGA (Ahmad *et al.*, 2017), and optimized formulation. The samples were compressed into pellets after being finely crushed with IR-grade potassium bromide. Transmissions of infrared spectra were made at room temperature spanning the 4000-500 cm^{-1} range and its data interpretation was recorded.

Characterization of PNS formulations PF_0, $PF_{1\,(1:1)}$ $PF_{2\,(1:2)}$ and $PF_{3\,(1:5)}$

Utilizing Dynamic Light Scattering (DLS) at 25°C Zeta sizer nano ZS90 instrument (Malvern Instruments, Malvern, UK) is used to measure the PNS formulations' PF_0, $PF_{1(1:1)}$ $PF_{2(1:2)}$ and $PF_{3(1:5)}$ mean Particle Size (PS), Polydispersity Index (PDI), and Zeta Potential (ZP). In clear disposable zeta cells, diluted samples of the PNS in deionized water were placed at 25°C to evaluate the zeta potentials. Using the Smoluchowski equation, a zeta potential was created using the electrophoretic mobility between the electrodes (Tripathi *et al.*, 2021; Karavelidis *et al.*, 2011) respectively.

Percentage drug Entrapment Efficiency (EE%) and Drug Loading capacity (%DL) of PNS

Drug Loading capacity (%DL) and percentage drug Entrapment Efficiency (EE%) for PNS were calculated. In order to calculate entrapment efficiency, the free quantity of SAF that was not encased inside the NPs was compared to the total amount of SAF used in each formulation of $PF_{1(1:1)}$ $PF_{2(1:2)}$ and $PF_{3(1:5)}$. While formulating PNS, the supernatant that remained over after centrifuging all of the formulations was examined for free SAF using a UV-visible spectrophotometer set to 226.5 nm. The absorbance of this supernatant was then interpolated using a standard calibration curve (Raj *et al.*, 2018; Rukmangathen *et al.*, 2019; Gulati *et al.*, 2014). A total of three measurements was made (n=3).

The drug entrapment efficiency and loading capacity were calculated by using formula given below.

EE% = (total amount of the drug−free drug)/ total amount of the drug x100

%DL = (total amount of the drug-free drug)/ nanoparticles weight x 100

Powder X-ray Diffraction (PXRD)

PXRD is analytical method for characterizing materials, helps in studying the particles in a powdery form in single crystalline material. PXRD (Tabletop XRD Rigaku Mini flex 600 6G) helps to identify the peak positions, intensities, width and shape of the material. Sample $PF_{1(1:1)}$ formulation with 1D scan mode, was scanned within the 3° to 90° with speed of 2.00° per minute with step width of 0.01° respectively. The diffractometer was calibrated with Standard Reference Material 640d. Samples of about 500 mg were used (Pawlak *et al*., 2021; Lemercier *et al*., 2023; Nanubolu, 2020) Same procedure was followed for the formulations PF2 (1:2) and PF3 (1:5).

Transmission Electron Microscopy (TEM)

TEM is an analytical technique where an electron beam passes through a sample in which electrons are transmitted or diffracted. Transmitted electrons provide brightfield images which reveal structure with higher contrast. To study morphology of the nanoparticles, sample preparation for TEM analysis (Thermo Fisher Scientific instrument) was carried out.

Sample Preparation for TEM analysis

Approximately 3.5 to 4 µL of sample $PF_{1(1:1)}$ formulation was withdrawn using 10 µL micropipette and placed on the copper coated grid which contained 300 mesh and labelled respectively. Sample $PF_{1(1:1)}$ was fixated on the grid for 10 sec, then the samples were stained first using 3.5 µL uranyl acetate and strained out. Again, the same stain was added to the samples and was rubbed for 5 sec. Allowed the stained sample to dry for 5-8 min. The grid was placed inside the sample cavity, adjusted and closed by tightening the screws in the sample holder. When the instrument indicates the signal (air was replaced by vacuum) then the sample holder was inserted completely. Now the instrument was focussed for general settings and then image on the grid was properly focussed by adjusting the magnification and intensity, once the image focussed was done, the image was captured (Zumaya *et al*., 2022; Gustafson *et al*., 2022; Solorzano *et al*., 2016; Hu *et al*., 2021). Same procedure was followed for the formulations $PF_{2(1:2)}$ and $PF_{3(1:5)}$.

In vitro release studies

Transferred the sample, 2 mL of formulation $PF_{1(1:1)}$ containing 1.35 mg into a glass tube with lower part of the tube covered with dialysis membrane (cellulose acetate membrane) (Mekjaruskul *et al*., 2021). The glass tube with dialysis membrane containing sample was placed into 100 mL of aqueous recipient PBS medium (pH 6.8) with continuous stirring at 100 rpm and 37±2°C, for the complete separation of drug in PBS. At various time intervals (15, 30, 60, 120, 180, 240, 300, 360, 420 and 480 min) the sample was withdrawn and same volume of fresh PBS (pH 6.8) was added and samples were analyzed using UV-visible spectrophotometer (Wolska and Szymanska, 2023; Garg *et al*., 2014; Weng *et al*., 2020). Same procedure was followed for formulations$PF_{2(1:2)}$ and $PF_{3(1:5)}$ and their data were statistically calculated by different models like zero order kinetics (Dash *et al*., 2010; Laracuente *et al*., 2020), first order kinetics (Bhattacharyya and Prabhakar, 2015), Higuchi model (Borandeh *et al*., 2021) and Korsmeyer's-Peppas model (Jahromi *et al*., 2020; Sun *et al*., 2015; Pavaloiu *et al*., 2021; Jain *et al*., 2022; Azadi *et al*., 2017; Jain *et al*., 2015; Bruschi *et al*., 2015) study was carried out using DD Solver 1.0 software. All measurements were done in triplicate.

In vitro Statistical release kinetics

Kinetic analysis in drug delivery involves time-dependent experimental evaluations of the release rate of a drug from its formulation. This information is usually acquired from *in vitro* drug release experiments, where the total amount or percentage of drug released is plotted over time. These data enable the modeling and analysis of release mechanisms and rates through mathematical kinetic models.

Stability study

Stability studies aim to assess and monitor the quality of Active Pharmaceutical Ingredients (API) and Finished Pharmaceutical Products (FPP) affected by various factors including environmental conditions (temperature, humidity, light), interactions between API and excipients, packaging materials, shelf life, or container-closure systems over a specific duration. As per ICH guidelines, the accelerated stability studies were conducted at a temperature of 40°C±2°C and 75% RH±5% relative humidity for both the drug and formulations using Temperature and humidity chamber (106 model) (Bajaj *et al*., 2012). All measurements are done in triplicate.

RESULTS

Drug content estimation

Samples containing pellets and supernatant of all formulations $PF_{1(1:1)}$ $PF_{2(1:2)}$ and $PF_{3(1:5)}$ were analysed for drug content using UV-visible spectrophotometer and the values are 0.527±0.002, 1.651±0.01, 2.109±0.013 mg/mL and 19.325±0.015, 19.51±0.13, 19.95±0.14 mg/mL respectively.

Determination of λ_{max} and calibration curve of SAF using UV-visible spectrophotometer

Prepared SAF (15 µg/mL) solution was scanned by using UV-visible spectrophotometer, and the λ_{max} was found to be 226.5 nm. Then prepared aliquots 5, 10, 15, 20 and 25 µg/mL (0.5, 1.0, 1.5, 2.0 and 2.5 mL) of SAF was analysed at λ_{max} 226.5 nm, absorbance was recorded in Table 2. By plotting concentration versus absorbance, calibration curve of SAF was drawn as depicted in Figure 2.

Drug and polymer compatibility study using FTIR spectroscopy

The study was carried out to find out the possible interactions of functional groups between the SAF and PLGA and optimized formulation of $PF_{1(1:1)}$.

FTIR spectroscopy study of the SAF, PLGA, SAF-PLGA and optimised PNS $PF_{1(1:1)}$

SAF shows characteristics absorptions at 3385.38, 2827.81, 1696.97, 1250.62. and 1183.60 cm^{-1} for the N-H amide, C-H stretching, C=O carbonyl group, ether C-O-C, and C-F stretching modes were observed.

PLGA exhibits molecular vibrations of functional bands at 3500-3450cm^{-1} which shows stretching vibrations of OH group, 2956.15 with C-H stretching intense bands at 1770 and 1750 cm^{-1} shows stretching vibration of carbonyl groups. Medium intensity bands between 1300 and 1150 cm^{-1} are attributed to asymmetric and symmetric-C(=O)-O stretches were observed.

SAF and PLGA showed bands at 3513.7 and 3386.81 with NH-OH molecular bonding, 3197 stretching vibrations of secondary amine N-H, and at 3385 bending vibrations were observed, 2883.42 with C-H stretching 1696-1756.86 and also at 1250 stretching vibrations of C=O, 1390.37 stretching vibrations of S=O, 1182.17 shows stretch of C-F. Results of FTIR spectroscopy of SAF and PLGA showed that they are compatible with each other.

Optimized formulation $PF_{1(1:1)}$ showed that drug-polymer are compatible. No shift in the drug peaks was recorded. The spectra reveal strong OH-NH molecular bonding at bands 3386.81 and 3513.73 depicted in Figure 3.

Table 1: Formulations PF_0, $PF_{1(1:1)}$, $PF_{2(1:2)}$, $PF_{3(1:5)}$.

Sl. No.	Particulars	PF_0	PF1 (1:1)	PF2 (1:2)	PF3 (1:5)
1.	Safinamide mesylate	-	25 mg	25 mg	25 mg
2.	Poly DL (lactide-co- glycolide) 50:50	25 mg	25 mg	50 mg	125 mg
3.	Poly Vinyl Alcohol	180 mg	180 mg	180 mg	180 mg
4.	Dichloromethane	10 mL	10 mL	10 mL	10 mL
5.	Distilled water	40 mL	40 mL	40 mL	40 mL

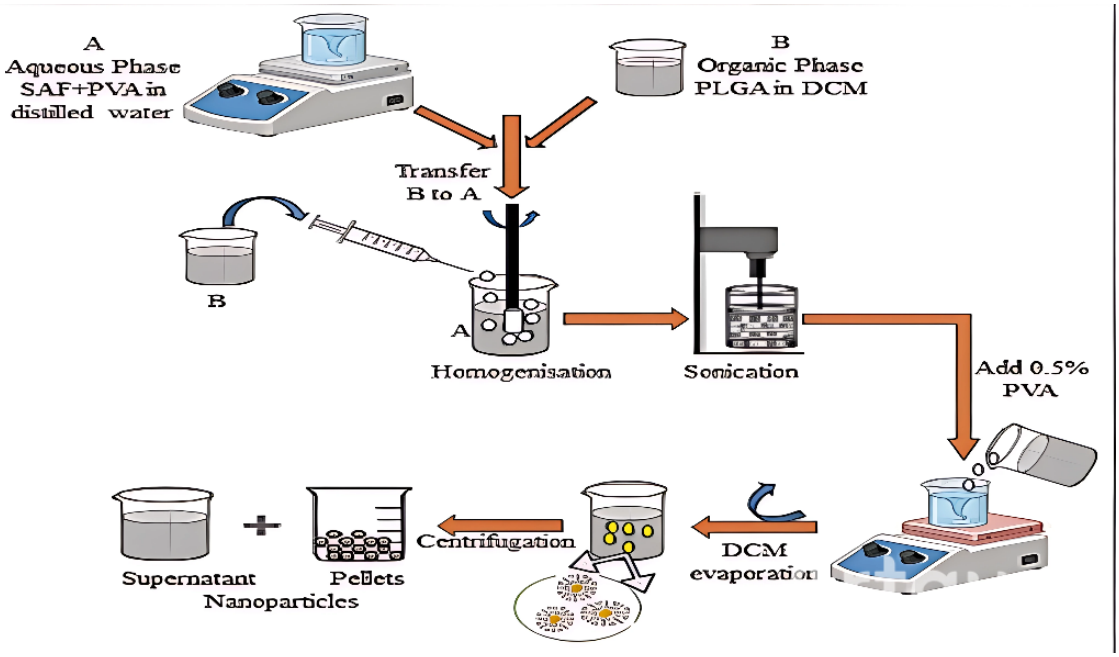

Figure 1: Preparation of PNS.

Characterisation of PNS formulations PF_0, $PF_{1(1:1)}$ $PF_{2(1:2)}$ and $PF_{3(1:5)}$

The mean Particles Size (PS), Polydispersity Index (PDI) and Zeta Potential (ZP) of all formulations PF_0, $PF_{1(1:1)}$ $PF_{2(1:2)}$ and $PF_{3(1:5)}$ were analysed using Zetasizer ultra/ advanced instrument and readings of PS are 392.4, 606, 613, 629 nm; PDI are 0.639, 0.224, 0.217, 0.12 (less than 2) and ZP are -4.64, -30, -24.2, -29mV (±30Mv) respectively and optimized $PF_{1(1:1)}$ with PS and ZP as depicted in Figure 4.

Percentage drug Entrapment Efficiency (EE%) and loading capacity (%DL) of PNS

Formulations $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$ and $PF_{3\ (1:5)}$ were analysed for Drug Entrapment Efficiency (EE%) and Drug Loading capacity (%DL) using formula and readings are 22.697±0.01%, 21.953±0.52, 20.186±0.36 and 11.348±0.25, 7.317±0.56 and 3.364±0.65 respectively. All measurements were conducted thrice.

Results of all Formulations PF_0, $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$ and $PF_{3(1:5)}$ showed that the formulation $PF_{1(1:1)}$ was chosen as optimized formulation when compared to formulations $PF_{2\ (1:2)}$ and $PF_{3\ (1:5)}$ with respect to PS, PDI, ZP, %EE and %DL.

Table 2: Calibration curve data of SAF with different concentrations using distilled water.

Concentration (µg/mL)	Absorbance*
5.0	0.2141±0.009
10.0	0.4342±0.0043
15.0	0.6237±0.001
20.0	0.8204±0.003
25.0	0.9994±0.001

*Values expressed as Mean± SD, *n*=3 SD= Standard deviation

Powder X-ray diffraction of PNS optimised formulation $PF_{1\ (1:1)}$

The X-ray diffraction pattern of formulation $PF_{1(1:1)}$ which was selected as optimized formulation showed characteristic peak thereby indicating that the amorphous state as shown in Figure 5. Powder X-ray Diffractometry (PXRD) diffraction pattern of SAF was characteristic of an amorphous state with intensity maxima appearing at 4.27° with d A 20.68° and the diffraction pattern obtained for PLGA showed no maximum which confirms its amorphous state indicating that the encapsulation technique used had no effect on the polymer characteristics.

Transmission Electron Microscopic (TEM) images of PNS optimised formulations $PF_{1\ (1:1)}$

Selecting formulation $PF_{1(1:1)}$ as optimized formulation, encapsulation of PNS was observed by adjusting magnification of images in TEM (Thermo Fisher Scientific instrument) and the images shown were spherical in shape. This conforms the encapsulation of drug with polymer matrix and images from 30 to 700nm were captured as shown in Figure 5. *In vitro* studies of PNS formulations $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$ and $PF_{3(1:5)}$

All formulations $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$ and $PF_{3(1:5)}$ (each 2 mL) were taken and performed *in vitro* studies using dialysis membrane and pH 6.8 buffer solutions as medium. Formulations PF_{1} (1:1) $PF_{2\ (1:2)}$ and $PF_{3(1:5)}$ showed drug release kinetics using different drug models like zero order, first order, Higuchi and Korsmeyer-Peppas model and their values with zero order kinetics are 91.86±0.52%, 87.84±0.14%, 61.46±0.80%, with first order kinetics 0.91±0.34, 1.08±0.4, 1.58±0.58, with Higuchi model 91.86±0.52%, 87.84±0.14%, 61.46±0.80% and finally with Korsmeyer-Peppas model 1.96±0.3, 1.94±0.37 and 1.78±0.86 respectively. This significant increase ($p<0.05$) of SAF release from the formulation could be explained by the drug properties itself. The results explained that $PF_{1\ (1:1)}$ followed Korsmeyer-Peppas model as depicted in Figure 6, and statistical kinetics data of all formulations $PF_{1(1:1)}$, $PF_{2\ (1:2)}$, $PF_{3\ (1:5)}$ their slope (n) was found

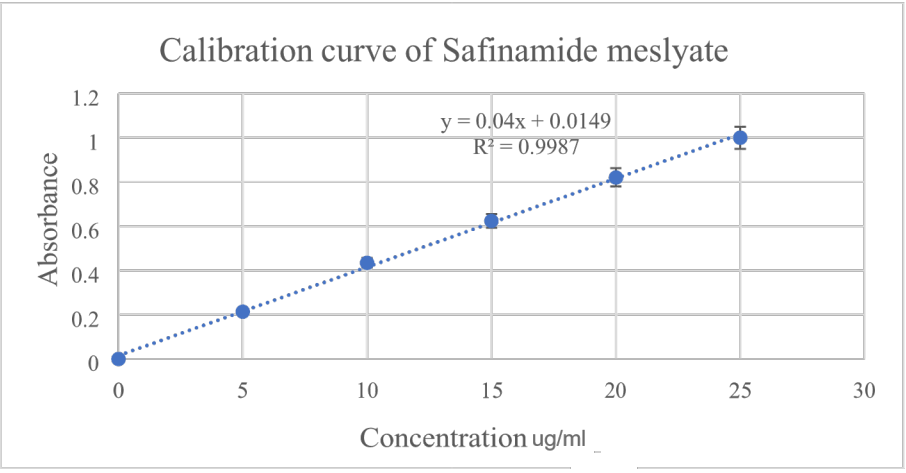

Figure 2: Graphical representation of calibration curve of SAF using distilled water at 226.5 nm.

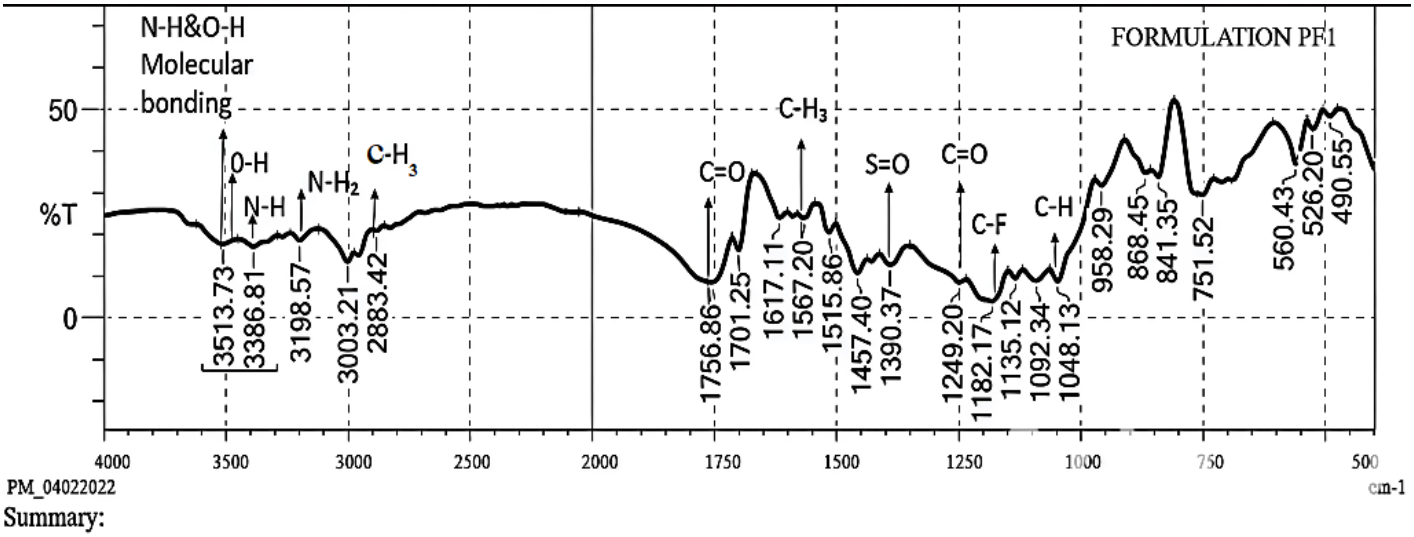

Figure 3: FTIR Spectra of optimised formulation $PF_{1(1:1)}$.

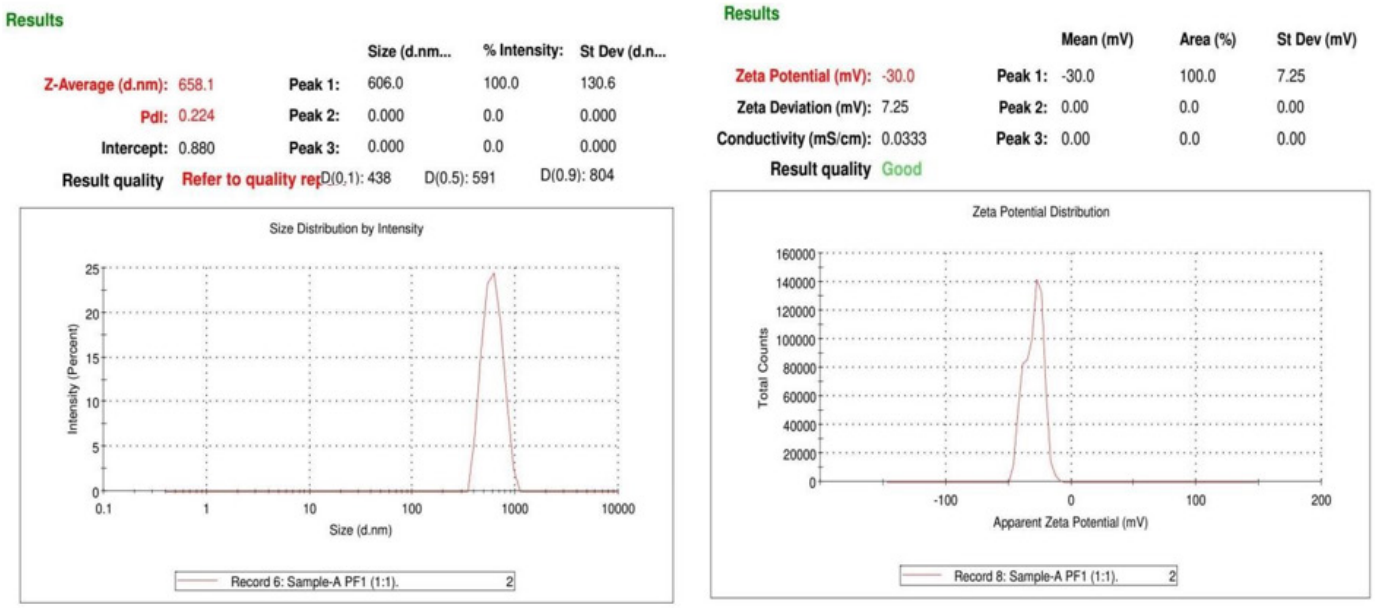

Figure 4: Formulation $PF_{1\ (1:1)}$ showing a) PS 606.0 and PDI 0.224 b) ZP -30mV.

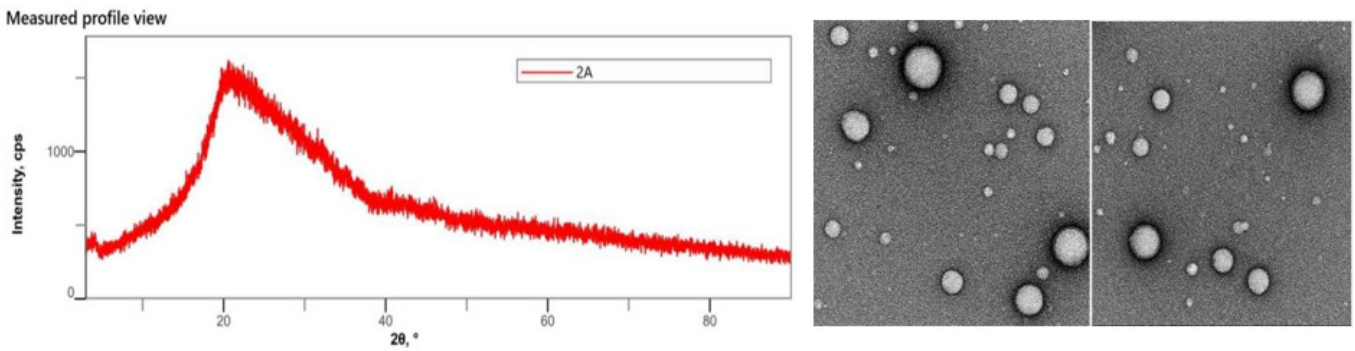

Figure 5: a) PXRD diffraction pattern, b) TEM images from 30 to 700 nm of optimised formulation PF1 (1:1).

Table 3: Data on kinetic models with regression values of formulation $PF_{1\ (1:1)}$, $PF_{2\ (1:2)}$, $PF_{3\ (1:5)}$.

Formulations	Zero order		First order		Higuchi	Korsmeyer-Peppas model			
	k_0	R^2	k_1	R^2	k_H	R^2	K_{KP}	n	R^2
$PF_{1\ (1:1)}$	0.261	0.7172	0.026	0.8237	5.201	0.8608	34.557	0.163	0.9800
$PF_{2\ (1:2)}$	0.245	0.7104	0.017	0.7960	4.859	0.8553	24.598	0.213	0.9378
$PF_{3\ (1:5)}$	0.191	0.4736	0.006	0.8053	3.911	0.6669	44.247	0.068	0.9537

Where, k_0, k_1, k_H and k_{KP} are release rate constant of zero, first, Higuchi and Korsmeyer-Peppas model release kinetics, n is slope.

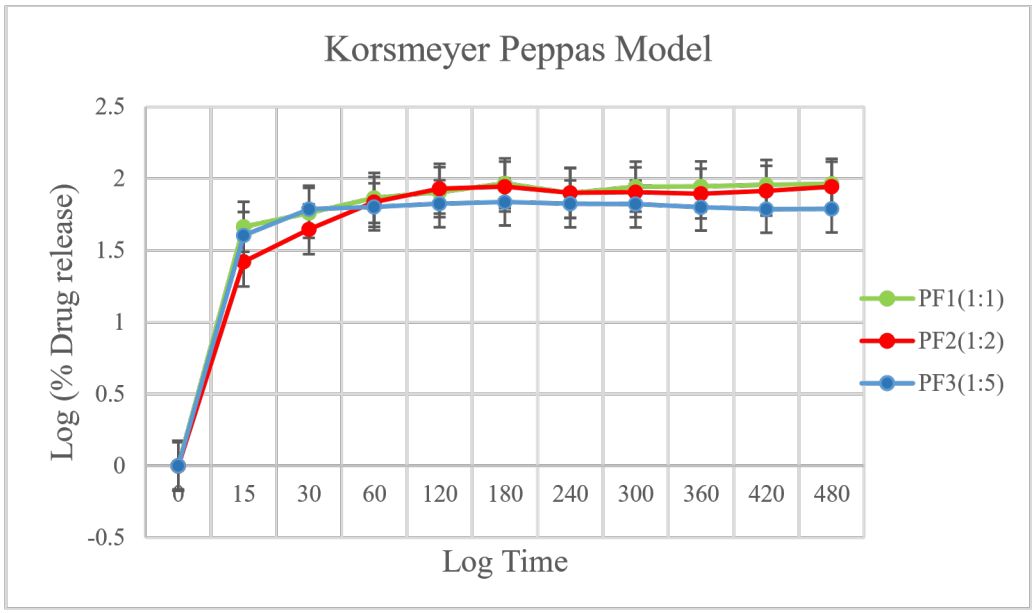

Figure 6: Korsmeyer model study of formulation $PF_{1\ (1:1)}$, $PF_{2\ (1:2)}$, $PF_{3\ (1:5)}$.

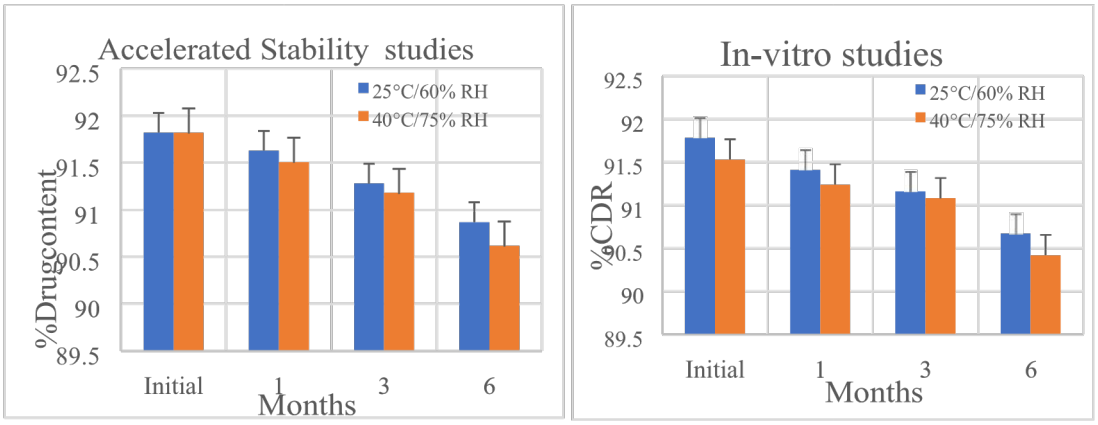

Figure 7: Schematic representation of %drug content and *in vitro* drug release of $PF_{1(1:1)}$ at room temperature versus accelerated temperature.

to be 0.163, 0.213 and 0.068, R^2 values were 0.9800, 0.9378 and 0.9537 (Table 3), Akaike Information Criteria (AIC) values are 67.1516, 80.3223 and 69.0446 and Model Selection Criteria (MSC) was found to be 1.8043, 1.0472 and 0.5394 respectively which represented a Fickian type of diffusion of the drug.

Accelerated Stability Study

Stability of nanoparticles is a crucial factor regarding their size and effectiveness. The formulation $PF_{1\ (1:1)}$ was placed in securely sealed glass vials and underwent stability testing. The optimized formulation $PF_{1\ (1:1)}$ were maintained at room temperature (25°C±2°C/60% RH) and under accelerated conditions (40°C±2°C/75%±5% RH) and were assessed for drug content and *in vitro* drug diffusion studies over six months. Results of drug content and *in vitro* drug release profile over six months at room temperature 25°C±2°C/60% RH and accelerated rate are 40°C±2°C/75%±5%RH are 90.87%±0.20%, 90.62%±0.21%and

90.67%±0.58%, 90.42%± 0.25% respectively as depicted in Figure 7.

DISCUSSION

Three different batches of PNS were prepared by emulsion solvent evaporation method, by varying the ratios of polymer and one batch without drug, Batch $PF_{1\ (1:1)}$ had particle size of 606 nm, zeta potential of -30 mV, PDI of 0.224, entrapment efficiency of 22.69% and 11.35% of drug loading. 'PDI is less than 0.25 hence 99% of the particles are uniform size. Prepared $PF_{1\ (1:1)}$ exists in amorphous state when scanned at 2θ using PXRD. TEM images of $PF_{1\ (1:1)}$ showed that drug was entrapped by PLGA. Nanoparticles of SAF by emulsion solvent evaporation method with PLGA was successfully developed with particle size in nano range with optimum entrapment. Zeta potential of PNS was in the range of -30 mV ensuring stability. Entrapment efficiency and drug loading were optimum with minimum loss of drug. Invitro drug release models like Zero order, first order, Higuchi and Korsmeyer-Peppas model were applied to the formulations $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$ and $PF_{3(1:5)}$. The data indicates that the percentage release of SAF was 91.86±0.52% for $PF_{1\ (1:1)}$, 87.84±0.14% for $PF_{2\ (1:2)}$, and 61.46±0.80% for $PF_{3(1:5)}$, all measured over an 8-hr period. This notable rise ($p<0.05$) in SAF release from the formulations may be attributed to the drug's inherent characteristics. SAF, categorized as a BCS class-II drug, exhibits lower solubility in a pH 6.8 buffer solution. Therefore, the enhanced drug release observed from the $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$ and $PF_{3(1:5)}$ formulations may result from the drug's incorporation into the nanoparticles, which can readily diffuse through the dialysis membrane in the dissolution medium. A small reduction in the release profile from the $PF_{3(1:5)}$ compared to the $PF_{1\ (1:1)}$ and $PF_{2\ (1:2)}$ formulations may be attributed to the creation of a PLGA network around the nano drug particles, which served as an obstacle for the drug and consequently slowed its diffusion from the formulation. Upon analyzing the release kinetics data, including zero, first-order, Higuchi, and Korsmeyer-Peppas models, the release profile of SAF from $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$ and $PF_{3(1:5)}$ was determined to follow the Korsmeyer-Peppas model, exhibiting the best correlation coefficients (R^2) of 0.9800, 0.9378 and 0.9537, correspondingly. This suggests that the release of SAF from the created formulations was not influenced by the drug concentration in the formulation. Upon additional assessment, the kinetics of drug release from the formulations adhere to the Korsmeyer-Peppas model, suggesting that the release is based on diffusion processes from the formulations. To verify the diffusion mechanism from the formulation, the data were additionally analyzed using the Korsmeyer-Peppas equation, where the slope value revealed the release mechanism. Consequently, the drug's release mechanism from the formulations was observed to align with the Korsmeyer-Peppas model, which is due to a mix of diffusion and erosion processes, indicating that this model is the most appropriate, slope value indicated the release mechanism. The slope (n) was determined to be 0.163, 0.213, and 0.068 for the $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$ and $PF_{3(1:5)}$ formulations, respectively, indicating a Fickian diffusion type of the drug. The accelerated stability study of optimized formulation $PF_{1\ (1:1)}$ was conducted at 25°C±2°C/60% RH for drug content, at initial month, 3rd month and 6th month are 91.63±0.1%, 91.28±0.1%, 90.87±0.20% and at 40°C±2°C/75% RH showed 91.51±0.06%, 91.18±0.085%, 90.62±0.21% respectively and *in vitro* drug release at 25±2°C/60% RH was 91.78±0.035%, 91.16±0.072%, 90.67±0.58% and 40±2°C/75% RH was 91.53±0.21%, 91.08±0.06%, 90.42±0.25% respectively, hence there was no significant changes in drug content and *in vitro* drug diffusion studies.

CONCLUSION

PLGA nanoparticles of SAF were prepared by emulsion solvent evaporation method. Three formulations $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$, $PF_{3(1:5)}$ (drug with varying concentration) and one formulation PF_0(without drug) were developed. Prepared PNS formulations $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$, $PF_{3(1:5)}$, choosing $PF_{1\ (1:1)}$ with optimum range entrapment using PLGA having particle size 606, polydispersity index 0.224, Zeta potential was in the range of -30 mv ensuring stability. 'PDI is less than 0.25 hence 99% of the particles are uniform size. Drug Entrapment efficiency was 22.69 and drug loading of 11.35 were optimum with minimum loss of drug. Selected PF_1 (1:1) as optimum formulation having maximum drug release when compared to other batches. PXRD revealed that $PF_{1\ (1:1)}$ exists in amorphous state, TEM images captured showing encapsulation of SAF with PLGA. *In vitro* drug profiles of $PF_{1\ (1:1)}$ $PF_{2\ (1:2)}$ and $PF_{3(1:5)}$, using Korsmeyer Peppas model was 1.963,1.94 and 1.78, R^2 values are 0.9800, 0.9378 and 0.9537 respectively. $PF_{1\ (1:1)} > PF_{2\ (1:2)} > PF_{3\ (1:5)}$ followed Korsmeyer Peppas model and considered to be suitable model for this study as it was clearly showed that drug release was not time dependent but it was dependent on diffusion of drug through polymer matrixes. The accelerated stability studies showed no significant changes over 6months in drug content and drug diffusion profile. PNS due to its inherent nano size will increase solubility of the drug and has the potential to decreasing the t_{max}, cross Blood Brain Barrier (BBB) and further improve bioavailability in treatment of Parkinson's disease. Thus, taking into account of the PNS results, study was further used for development of intranasal drug delivery system which helps in the management of PD.

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ABBREVIATIONS

PD: Parkinson's disease; **SAF:** Safinamide mesylate; **PNS:** PLGA Nanoparticles Safinamide mesylate; **SD:** Standard deviation; **PS:** Particle size; **PDI:** Poly dispersity index; **ZP:** Zetapotential; **EE%:** Drug entrapment efficiency; **%DL:** Drug loading; **DCM:** Di chloro methane; **PVA:** Poly vinyl alcohol; **DLS:** Dynamic light scattering; **NPs:** Nanoparticles; **PBS:** Phosphate buffered saline; **API:** Active pharmaceutical ingredients; **FPP:** Finished pharmaceutical products; **RH:** Relative humidity; **T_{max}:** Time to reach maximum plasma concentration; **CDR:** Cumulative drug release, k-constant; **TEM:** Transmission electron microscope; **PXRD:** Powder X-ray diffraction; **FTIR:** Fourier Transform Infar Red; **AIC:** Akaike Information Criteria; **MSC:** Model Selection Criteria; **BBB:** Blood brain barrier.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

Veena Kalyani S, Dr. Vedamurthy Joshi and Anoop M conceived, designed the experiments, analyzed the data and drafted the article. Veena Kalyani and Anoop performed the research work.

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