Supporting Information

Futuristic Alzheimer's Therapy: Acoustic-Stimulated Piezoelectric Nanospheres for Amyloid Reduction

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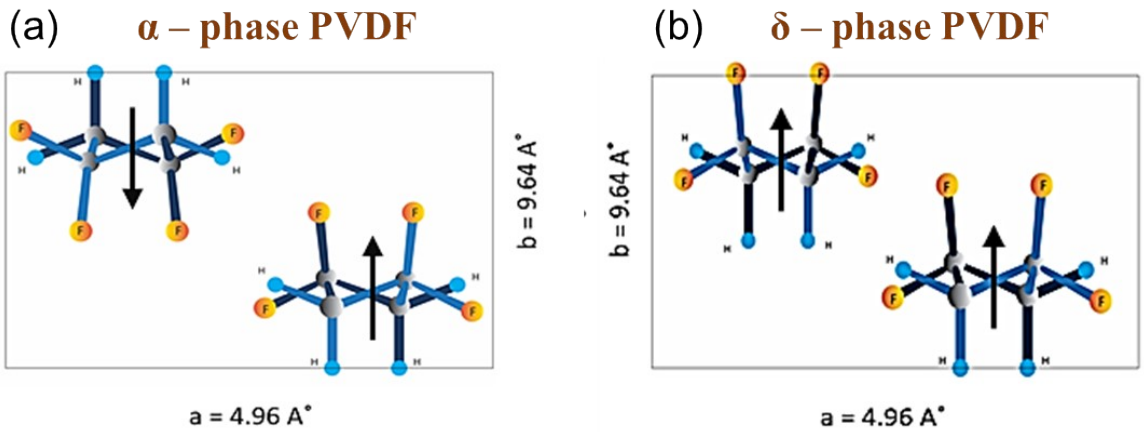

Fig.S1: Unit cell chemical structure of (a) α-phase and (b) δ-phase PVDF.

PVDF has an electro-active phase, so it can respond to external mechanical stimuli. In addition, as compared to other piezoelectric classes of polymers, PVDF has been found to exhibit very high piezoelectric coefficient, which helps to get higher efficacy over the other polymers.

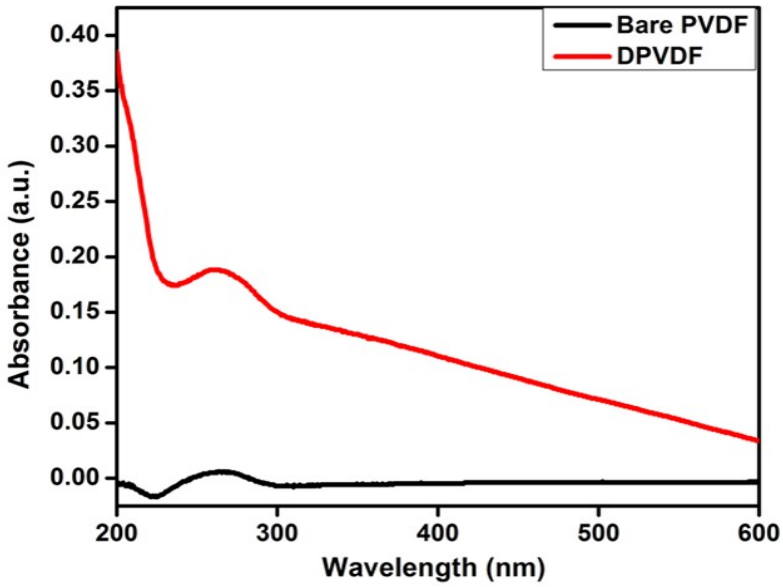

Fig. S2: UV-Visible absorbance spectra of DPVDF and PVDF nanospheres.

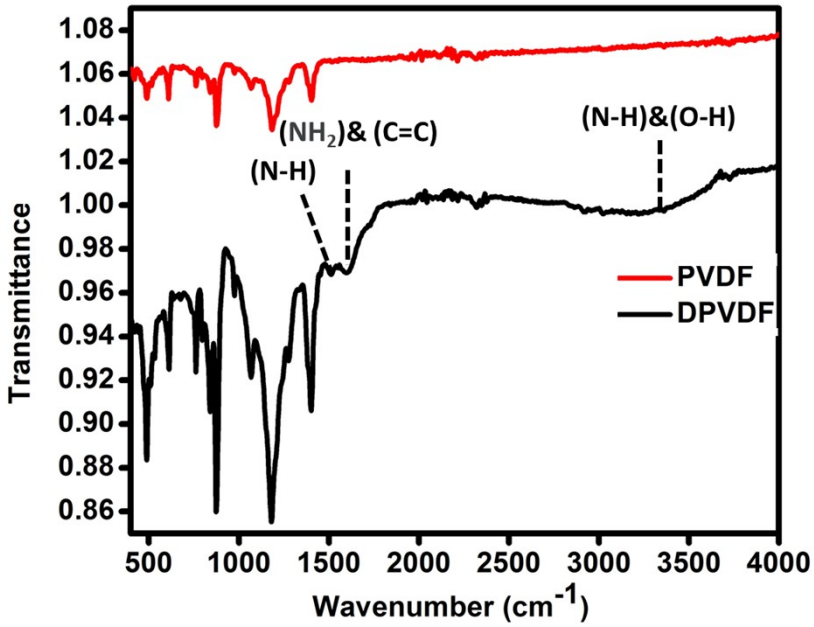

Fig. S3: ATR-FTIR spectra of DPVDF and PVDF nanospheres.

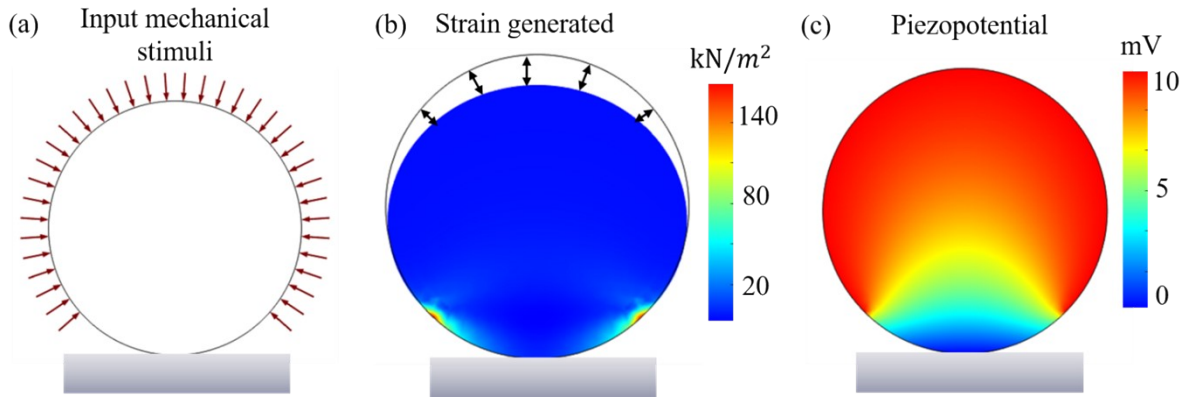

Fig. S4. (a) Scheme demonstrating the input mechanical stimuli (shown by arrows) of 100 kN/m^2 provided to the PVDF nanosphere. (b) Strain generation within the nanosphere (as per FEA analysis) due to the input mechanical agitation (double headed arrows indicate the

mechanical deformation caused due to the stimuli). (c) Piezoelectric potential generated in PVDF nanospheres due to strain generation under the mechanical stimuli.

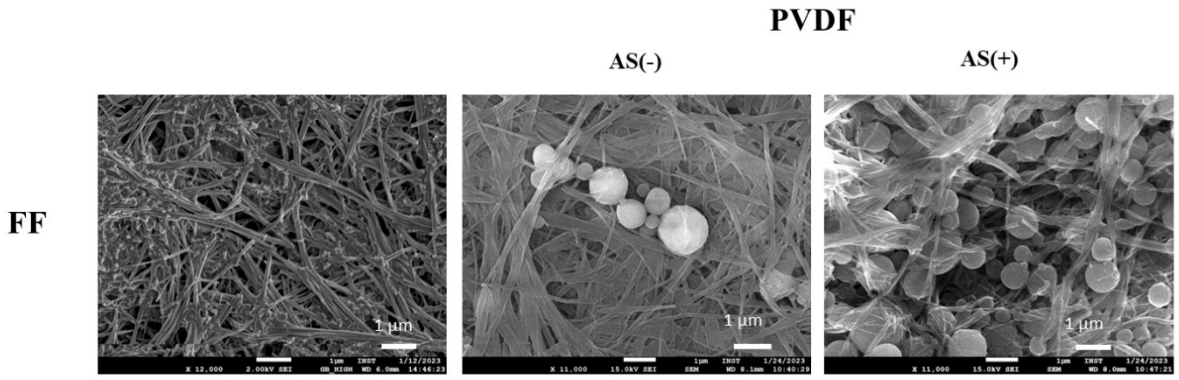

Fig. S5: FESEM images showing no significant structural and morphological transitions of FF fibrils after being treated with acoustic stimulus activated and non-activated PVDF nanospheres (Scale bars are 1 µm).

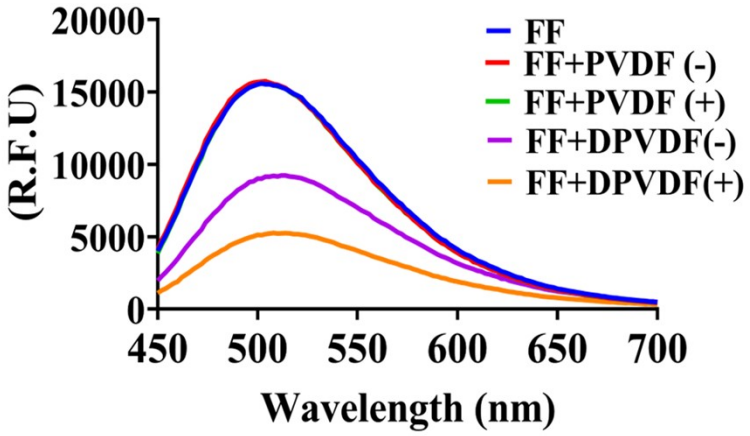

Fig. S6: Bis-ANS assay showing disaggregation of FF fibrils in the presence of acoustically activated and non-activated PVDF and DPVDF nanospheres.

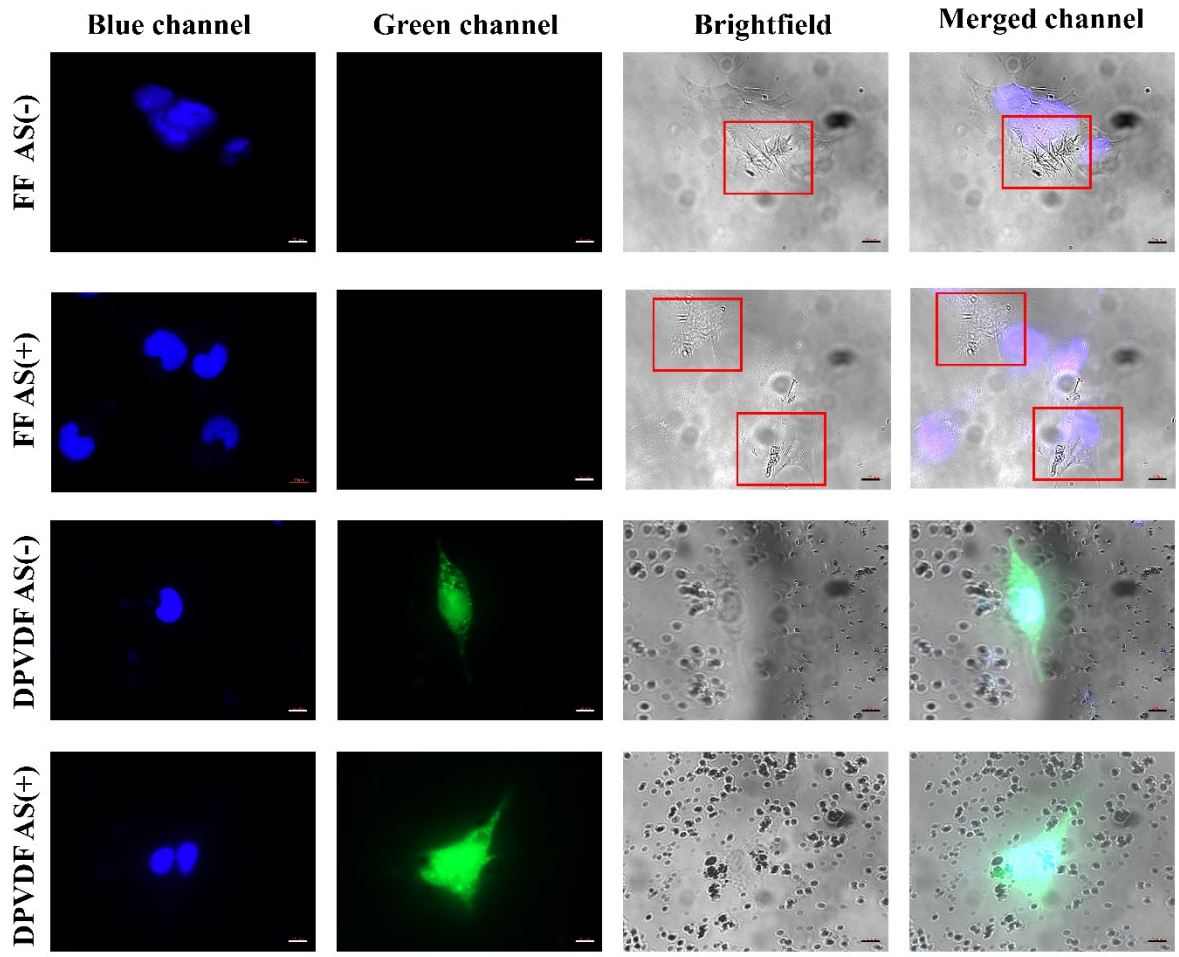

Fig. S7: Confocal microscopic images depicting in situ disaggregation behaviour of FF fibrils by the DPVDF nanospheres in SH-SY5Y cells in presence and absence of acoustic stimulus (scale bar~10 µm). Green fluorescence of the cells is due to the autofluorescence of the spheres.

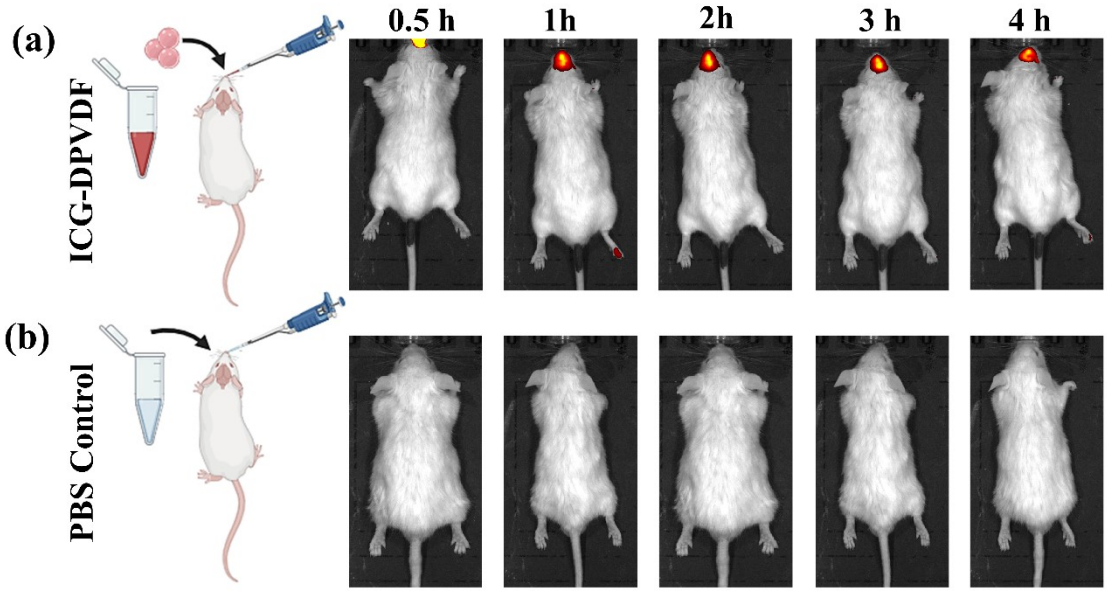

Fig. S8: Fluorescent images of ICG-labelled DPVDF nanospheres obtained in Balb/c mice in (In vivo imaging system) IVIS. (a) Fluorescent images of ICG- DPVDF nanospheres-treated mice demonstrated that the particles can reach and stay in the brain tissues from the nasal cavity after 1,2, 3, and 4 h of nanospheres administration. (b) Fluorescence images of PBS treated mice.

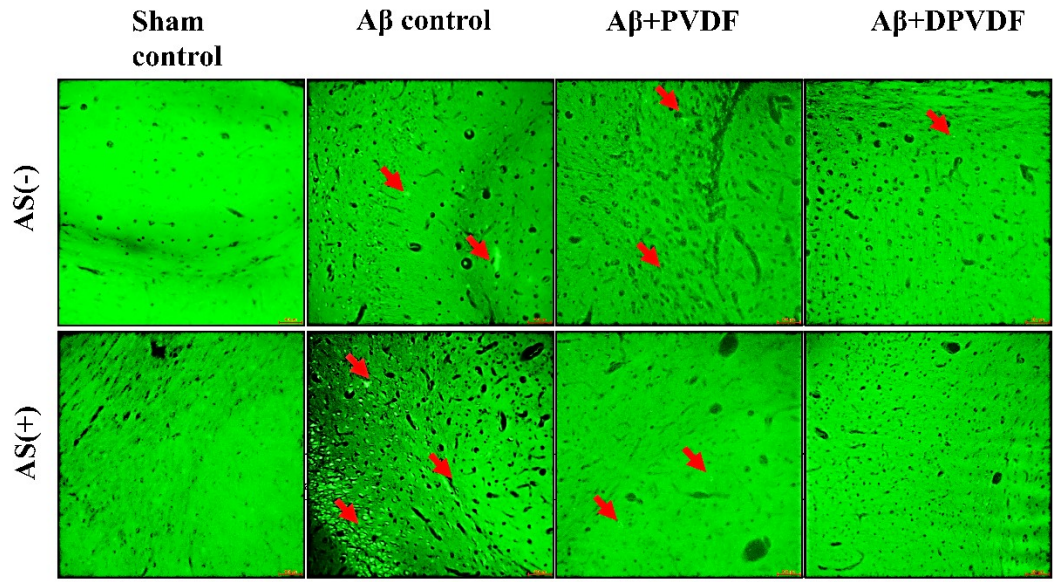

Fig. S9: Fluorescent images of brain tissue of mice (n=3) stained with Thioflavin-T. The deposition of amyloid beta plaques is indicated with arrows (red color).

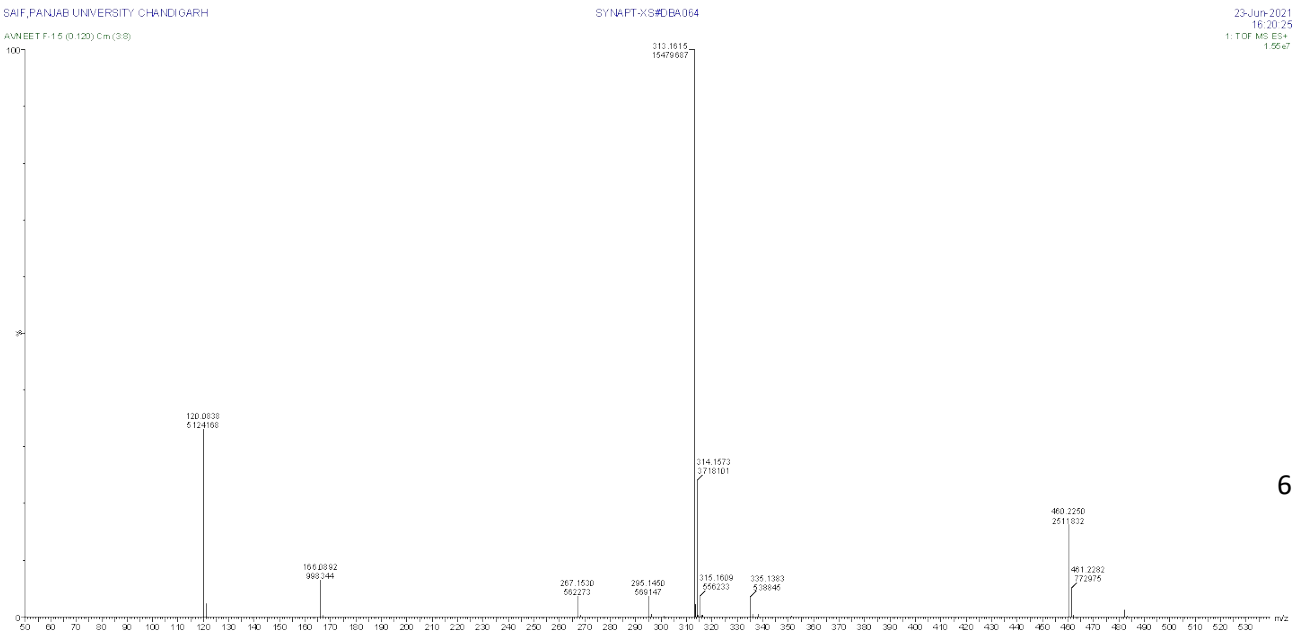

Fig. S10: Mass spectrum of FF. Expected mass, 312 Da; Observed mass, 313.16 Da.

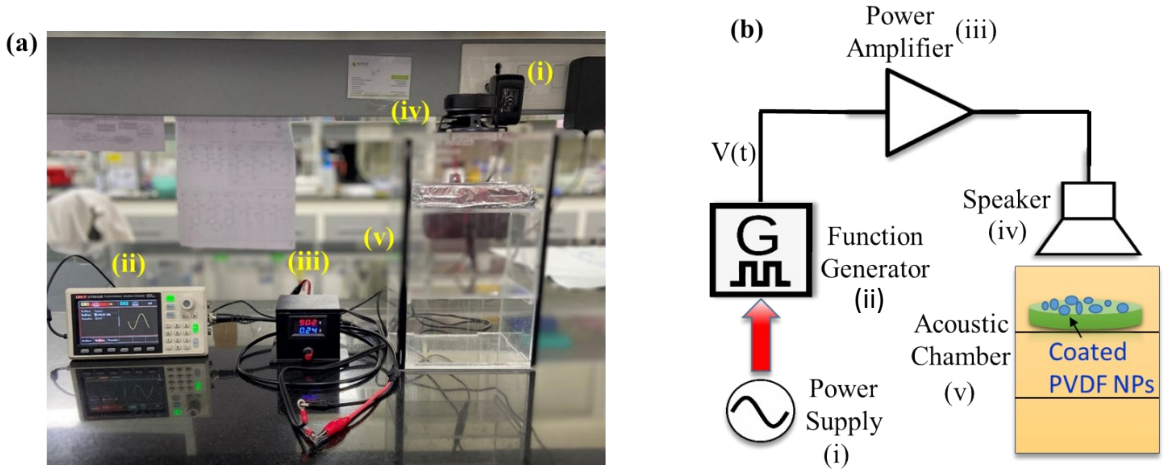

Fig. S11. (a) Image showing the acoustic chamber used in the study for achieving acoustic stimulation-based activation of the nanospheres. (b) Equivalent circuit diagram comprising of (i) power supply, (ii) function generator, (iii) power amplifier and (iv) speaker for the mechanical stimulation in the acoustic chamber (iv) where the 'specimen of study' was placed.

Fig. S11a shows an acoustic chamber, which is a sealed container made up of acrylic, used to generate and control sound waves. The chamber of dimension 16 × 27 × 24 cm^3, is capable of delivering 2 watts of acoustic power at a frequency of 40 kHz. This specific frequency aligns with the cellular studies conducted. A targeted approach was used to achieve optimal interaction between the sound waves and the nanospheres. The chamber's design involves potential acoustic tuning elements, such as dampening or waveguides, to ensure resonance and to focus the sound energy within the chamber. This controlled acoustic environment enabled

the investigation of nanosphere activation by sound waves in a precise and reproducible manner.

The corresponding electrical circuit depicted in Fig. S11b powers the acoustic chamber, which includes a power supply, function generator, power amplifier, and speaker. The power supply provides ample current to drive the speaker, while the function generator creates sound waves to stimulate the specimen (Nature Communications, 12, (2021), 1; Adv Mater., 33 (2021) 1). The power amplifier amplifies these waves, and the speaker emits the resulting sound waves into the acoustic chamber to activate the piezoelectric nanospheres (ACS Nano, 16 (2022), 1; Advanced Materials, 35, (2023), 1).