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Traversing the Profile of Biomimetically Nanoengineered Iron Substituted Hydroxyapatite: Synthesis, Characterization, Property Evaluation and Drug Release Modeling

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Section S1

Mathematical Model for determining diffusivity through Drug release profile analysis

The basic intent of this section was to obtain a mathematical model in order to determine drug's diffusion coefficient, which is homogeneously distributed in a matrix of dimension (a * a * a/5). Further, the model has been applied to the release kinetics of drug in order to obtain the value of diffusion coefficient. And, the other intent was to compare the calculated diffusivity values of the drug in matrix of different samples, so as to understand the drug release mechanism.

Mathematical Model

The mathematical model was developed based on the concept that the amount of mass transferred in all the respective directions is equal to the change in the residual drug concentration. The model was derived considering pseudo-steady state condition (using Fick's first law of diffusion) at each instant, while other assumptions are as follows: (a) perfect sink conditions were maintained throughout the experiment, (b) uniform diffusivities in respective directions, (c) drug aligned in accordance with the Cartesian system and (d) there is no swelling tendency of pellets in the medium. The schematic of the drug loaded homogeneously in the matrix (a * a * a/5) is shown in Fig. 2, here M is considered as the amount of drug release at time t, $D_{x,d}$, $D_{y,d}$ and $D_{z,d}$ represents the diffusion coefficients of the drug (d) in the permeating fluid in x , y and z direction respectively, A is the total amount of the drug present in the matrix per unit volume and C_S is the solubility of drug in the permeating fluid. Here, we assumed that for A>>Cs, a pseudo steady state condition would exist during the leaching process. Equation describing the unidirectional flux at isobaric and isothermal condition for a steady state condition given by Fick's first Law of diffusion:

$$Nx,d = -Dx,d\frac{dC}{dx} \quad \ldots (1)$$

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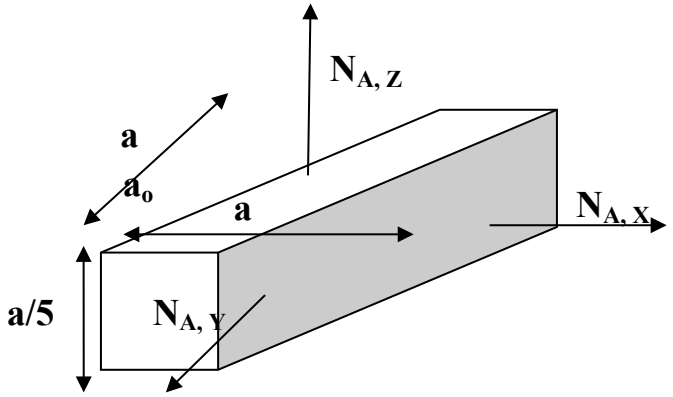

Fig. S1 Schematic representation of the drug in the Cartesian Co-ordinate System

Here, $N_{X,A}$ represents the amount of mass transported per unit area per unit time i.e. flux of A in x direction, and dC/dx represents the concentration gradient. Similarly, the fluxes corresponding to y and z direction are illustrated in equation 2 and 3 respectively.

$$Ny,d = -Dy,d\frac{dC}{dy} \quad \ldots (2)$$

$$Nz,d = -Dz,d\frac{dC}{dz} \quad \ldots (3)$$

So, net mass transferred per unit time, considering all the direction is given by equation 4,

$$\left(\frac{dM}{dt}\right)_{net} = \left(\frac{dM}{dt}\right)_x + \left(\frac{dM}{dt}\right)_y + \left(\frac{dM}{dt}\right)_z \quad \ldots (4)$$

Since the rate of change of mass in the x direction is given by the product of Flux and the area in the x direction i.e. ($N_{x,d}$. A_{yz}). So, modifying equation 4 with the above stated concept results in equation 5 and putting the values from equation 1, 2 and 3 in equation 5 gives equation 6

$$\left(\frac{dM}{dt}\right)_{net} = N_{x,d}.A_{yz} + N_{y,d}.A_{xz} + N_{z,d}.A_{xy} \quad \ldots (5)$$

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$$\left(\frac{dM}{dt}\right)_{net} = \left(-Dx,d\,\frac{dC}{dx}\right).A_{yz} + \left(-Dy,d\,\frac{dC}{dy}\right).A_{xz} + \left(-Dz,d\,\frac{dC}{dz}\right).A_{xy} \quad \ldots (6)$$

Since, we assumed that the uniform diffusion coefficient in all respective direction, therefore,

$$D_{x,d} = D_{y,d} = D_{z,d} = D_d \quad \ldots (7)$$

This results equation 6 to be in the form:

$$\left(\frac{dM}{dt}\right)_{net} = \left(-Dd\,\frac{dC}{dx}\right).A_{yz} + \left(-Dd\,\frac{dC}{dy}\right).A_{xz} + \left(-Dd\,\frac{dC}{dz}\right).A_{xy} \quad \ldots (8)$$

As during the leaching of drug from the matrix, a sharp front will be formed between the partially leached and the un leached portion, and in between these portions a pseudo steady state is assumed, as shown in Fig. 3, where b'(a'/2) the length scale where the portion is un-leached and $b^o(a^o/2)$ is the length scale for the whole. The area A_{xy}, A_{yz} and A_{zx} of the matrix is equal a^2, $a^2/5$, $a^2/5$, putting the values in equation 8 it turns out to be:

$$\left(\frac{dM}{dt}\right)_{net} = \left(-Dd\,\frac{dC}{dx}\right).\frac{a^2}{5} + \left(-Dd\,\frac{dC}{dy}\right).\frac{a^2}{5} + \left(-Dd\,\frac{dC}{dz}\right).a^2 \quad \ldots (9)$$

Since, it is steady state condition, we have

$$\frac{dC}{dx} = \frac{dC}{dy} = \frac{dC}{da} \quad \ldots (10)$$

$$\frac{dC}{dz} = 5.\frac{dC}{da} \quad \ldots (11)$$

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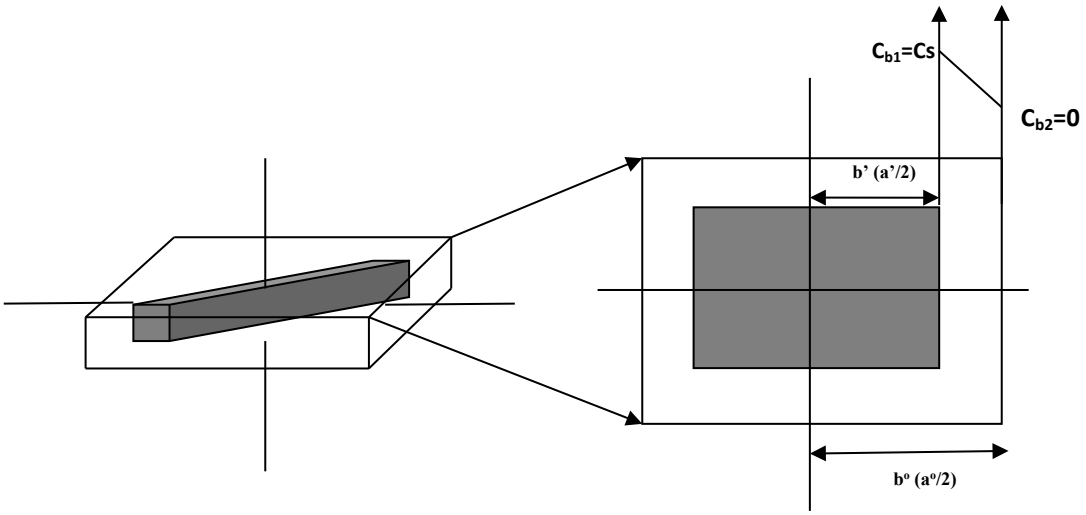

Fig. S2 Crossectional view of drug loaded m-HA at intermediate time period of leaching

Putting equation 10 and 11 back to the equation 9, which can be recast as:

$$\left(\frac{dM}{dt}\right)_{net} = \left(-Dd\frac{dC}{da}\right).\frac{a^2}{5} + \left(-Dd\frac{dC}{da}\right).\frac{a^2}{5} + \left(-Dd\frac{dC}{da}\right).5a^2 \quad \ldots (12)$$

Therefore,

$$\left(\frac{dM}{dt}\right)_{net} = \left(-Dd\frac{dC}{da}\right).\frac{27a^2}{5} \quad \ldots (13)$$

$$\left(\frac{dM}{dt}\right)_{net}\int\frac{1}{a^2}da = \frac{27}{5}Dd\int dc \quad \ldots (14)$$

$$\left(\frac{dM}{dt}\right)_{net}\left(-\frac{1}{a}\right)_{b}^{b^o} = \frac{27}{5}Dd.C_b \quad \ldots (15)$$

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$$\left(\frac{dM}{dt}\right)_{net}\left(\frac{1}{b}-\frac{1}{b^{o}}\right) = \frac{27}{5} Dd.C_b \quad \ldots (16)$$

Since, b = a/2 so putting this value in equation 16 the equation modified to

$$\left(\frac{dM}{dt}\right)_{net}\left(\frac{1}{a}-\frac{1}{a^{o}}\right) = \frac{27}{10} Dd.C_a \quad \ldots (17)$$

It is quite relevant in such case that the product doesn't stay at the surface it immediately get soluble in the medium, so the concentration of drug at surface turns out be zero, however, the concentration at the front separating leached and un-leached portion is Cs, which is also illustrated in Fig. S2.

$$\left(\frac{dM}{dt}\right)_{net} = \frac{\frac{27}{10} Dd.C_a}{\left(\frac{1}{a^{o}}-\frac{1}{a'}\right)} = \frac{\frac{27}{10} Dd.C_s}{\left(\frac{1}{a^{o}}-\frac{1}{a'}\right)} \quad \ldots . (18)$$

Since C = C_s at a=a' and Ca =0 at a = a^o and hence

$$C_a = C_s.\frac{a'}{a}.\left(\frac{a^{o}-a}{a^{o}-a'}\right) \quad \ldots . (19)$$

It is persuading that the amount of drug left un-leached is the sum of the amount remained in un-leached portion (a < a') and that the region which is no longer saturated with Cs (a' < a < a^o). So, the residual concentration left can be calculated as:

$$\text{Residual Concentration} = \frac{8.(a')^3}{5} + 2\int_{a'}^{a^{o}} C_a.\frac{a^2}{5}.da + 2\int_{a'}^{a^{o}} C_a.\frac{a^2}{5}.da + 2\int_{\frac{a'}{5}}^{\frac{a^{o}}{5}} C_a.\frac{a^2}{5}.da \quad \ldots (20)$$

Putting the value of Ca from equation 19 to 20, it can be recast as:

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$$\frac{8.(a')^3}{5}.A + 4\int_{a'}^{a^o} C_s.\frac{a'}{a}.\left(\frac{a^o - a}{a^o - a'}\right).\frac{a^2}{5}.da$$

$$= \quad \Rightarrow$$

$$+\frac{2}{5}\int_{\frac{a'}{5}}^{\frac{a^o}{5}} C_s.\frac{a'}{a}.\left(\frac{a^o - a}{a^o - a'}\right)\frac{a^2}{5}.da$$

$$\frac{8.(a')^3}{5}.A + \frac{C_s.a'}{(a^o - a')}.\left[\frac{487a^{o3}}{6750} - \frac{101a'^2.a^o}{6750} + \frac{1002a'^3}{1875}\right] \quad \ldots (21)$$

So, the change in the residual drug concentration corresponding to the change da' would be then

$$= \frac{8.(a')^2}{5}.A + \frac{C_S}{(a^o - a')}.\left[\frac{487a^{o3}}{6750} - \frac{101a'^2.a^o}{6750} + \frac{1002a'^3}{1875}\right](da') \quad \ldots (22)$$

And, initially what we have considered that the rate of mass transported can be equalized to the residual change in the concentration, which can be written as by equating 18 and 22 i.e.

$$\left(\frac{dM}{dt}\right)_{net}.dt = \frac{\frac{27}{10}Dd.C_S}{\left(\frac{1}{a'} - \frac{1}{a^o}\right)}.dt = \frac{8.(a')^2}{5}.A + \frac{C_S}{(a^o - a')}.\left[\frac{487a^{o3}}{6750} - \frac{101a'^2.a^o}{6750} + \frac{1002a'^3}{1875}\right](da') \quad \ldots (23)$$

As earlier, we assumed Cs << A, therefore Cs term can be neglected and

$$\frac{27}{10}D_d.C_S.a^o \int dt = \int_{a'}^{a^o} \frac{8.(a')}{5}.A.(a^o - a')da \quad \ldots (24)$$

$$\frac{81.C_S.D_d.t}{8.a^{o2}} = A.\left[1 - 3\left(\frac{a'}{a^o}\right)^2 + 2\left(\frac{a'}{a^o}\right)^3\right] \quad \ldots (25)$$

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Residual fraction of the drug in pellet $= \left(\frac{a'}{a^o}\right)^3$, Here, we are taking release fraction as $\frac{M_t}{M_\infty}$, where M_t represent % drug leached at time t and M_∞ is the % drug leached at infinite time (taken as 100). So putting $\left(\frac{a'}{a^o}\right) = \left[1 - \frac{M_t}{M_\infty}\right]^{1/3}$ in equation 25 gives

$$\frac{81.C_s.D_d.t}{8.a^{o2}} = A.\left[1 - 3\left[1 - \frac{M_t}{M_\infty}\right]^{2/3} + 2\left[1 - \frac{M_t}{M_\infty}\right]^{3/3}\right] \quad \ldots (26)$$

Well, we have considered this solution for steady state conditions, in which Taylor series turns to be valid, so using Taylor series expansion, Equation 26 can be reformulated as:

$$\left[\frac{M_t}{M_\infty}\right] = \sqrt{\frac{243.C_s.D_d.t}{40.a^{o2}.A}} \quad \ldots (27)$$

Which is the equation for the % of drug release from the matrix at any time t in our case.

3.1.1 Determination of Diffusion coefficient using mathematical model

The diffusion coefficients of the different HA samples (i.e. undoped and doped) were calculated by using the release profile data of the different samples up to 8 hours as a function of square root of time. This is because the release is governed by Fickian transport up to initial 8 hours. From the linear fitting of this plot the value of slope *i.e.* $\sqrt{243.C_s.D_d / 40.a^{o2}.A}$ can be obtained. Therefore, the diffusion coefficient can be calculated from D = slope^2/0.0121.

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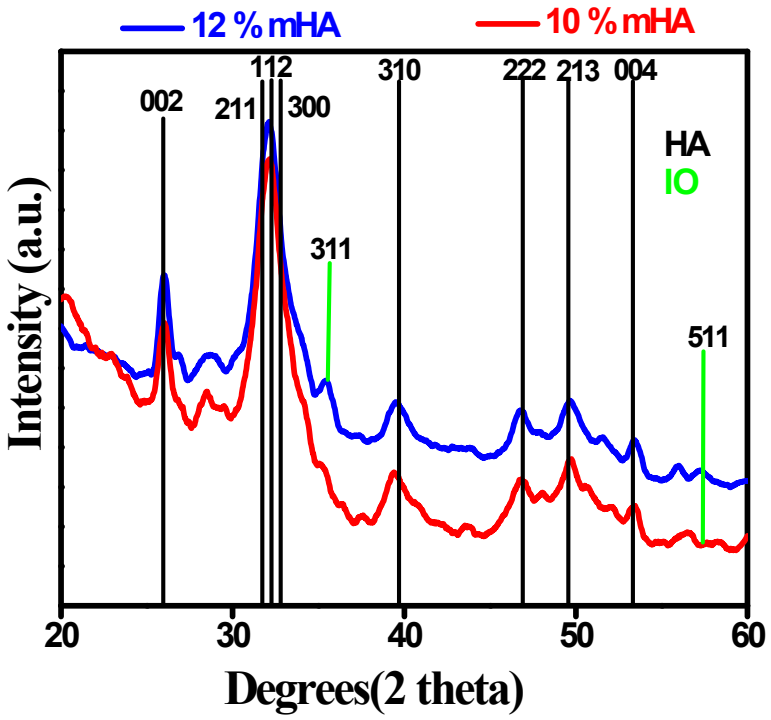

Fig. S3 XRD pattern showing formation of composite after increasing iron concentration beyond 10% indicating the optimum doping concentration by the adapted protocol is 10%.

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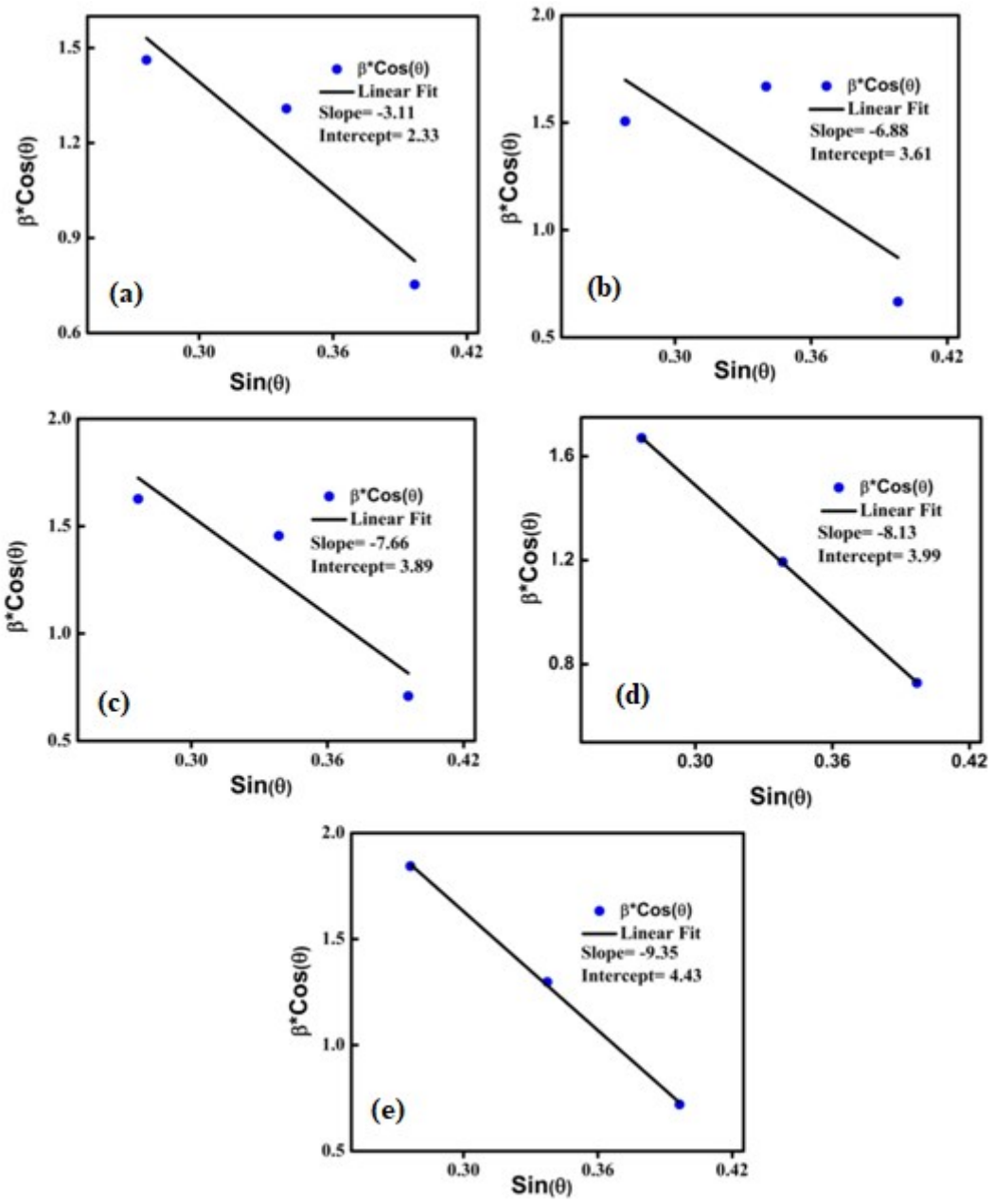

Fig. S4 (a), (b), (c), (d) and (e) shows the William-Hall plot for strain calculations for 2%, 4%, 6%, 8%, and 10% m-HA respectively

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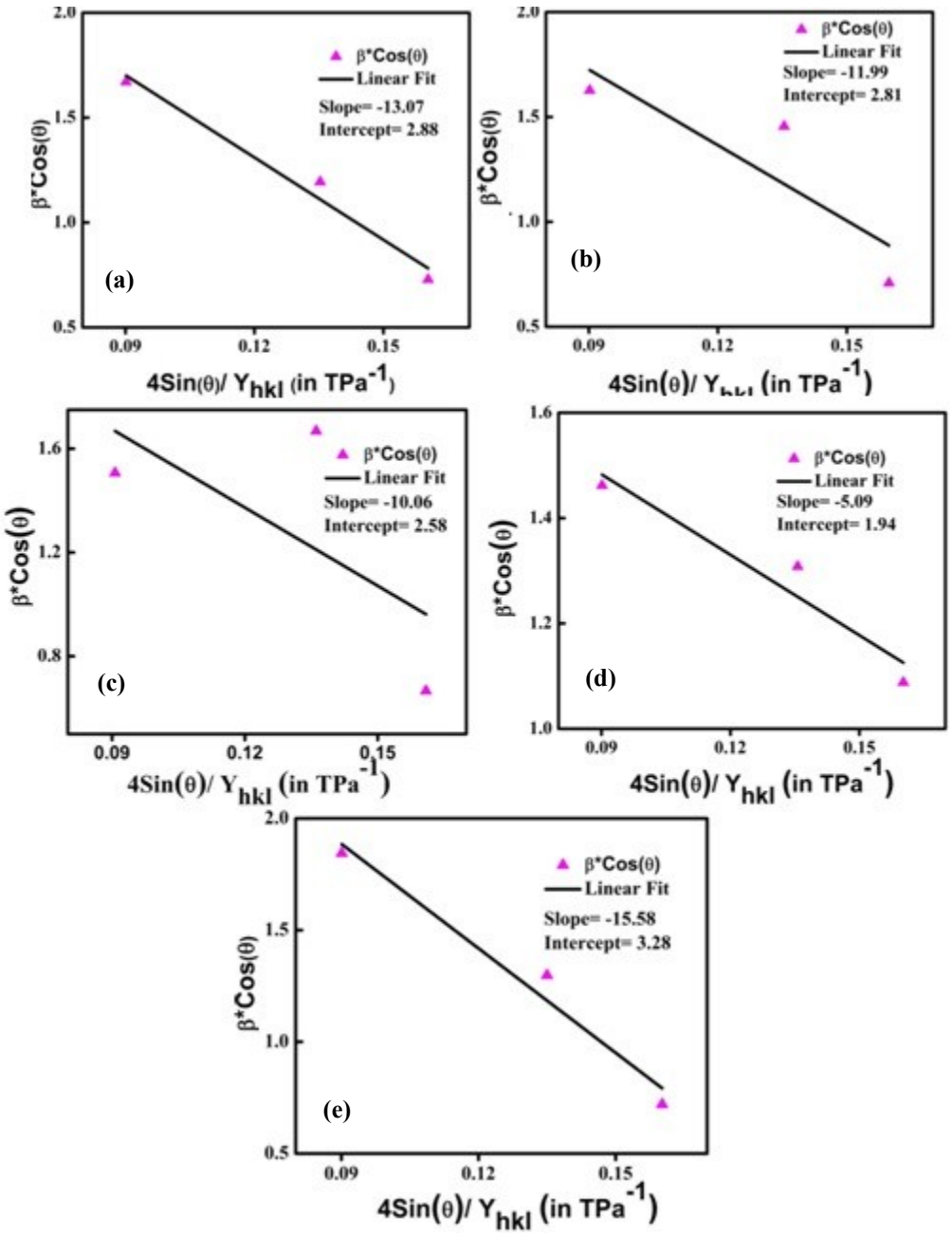

Fig. S5 (a), (b), (c), (d) and (e) shows the William-Hall plot for stress calculation for 2%, 4%, 6%, 8%, and 10% m-HA respectively.

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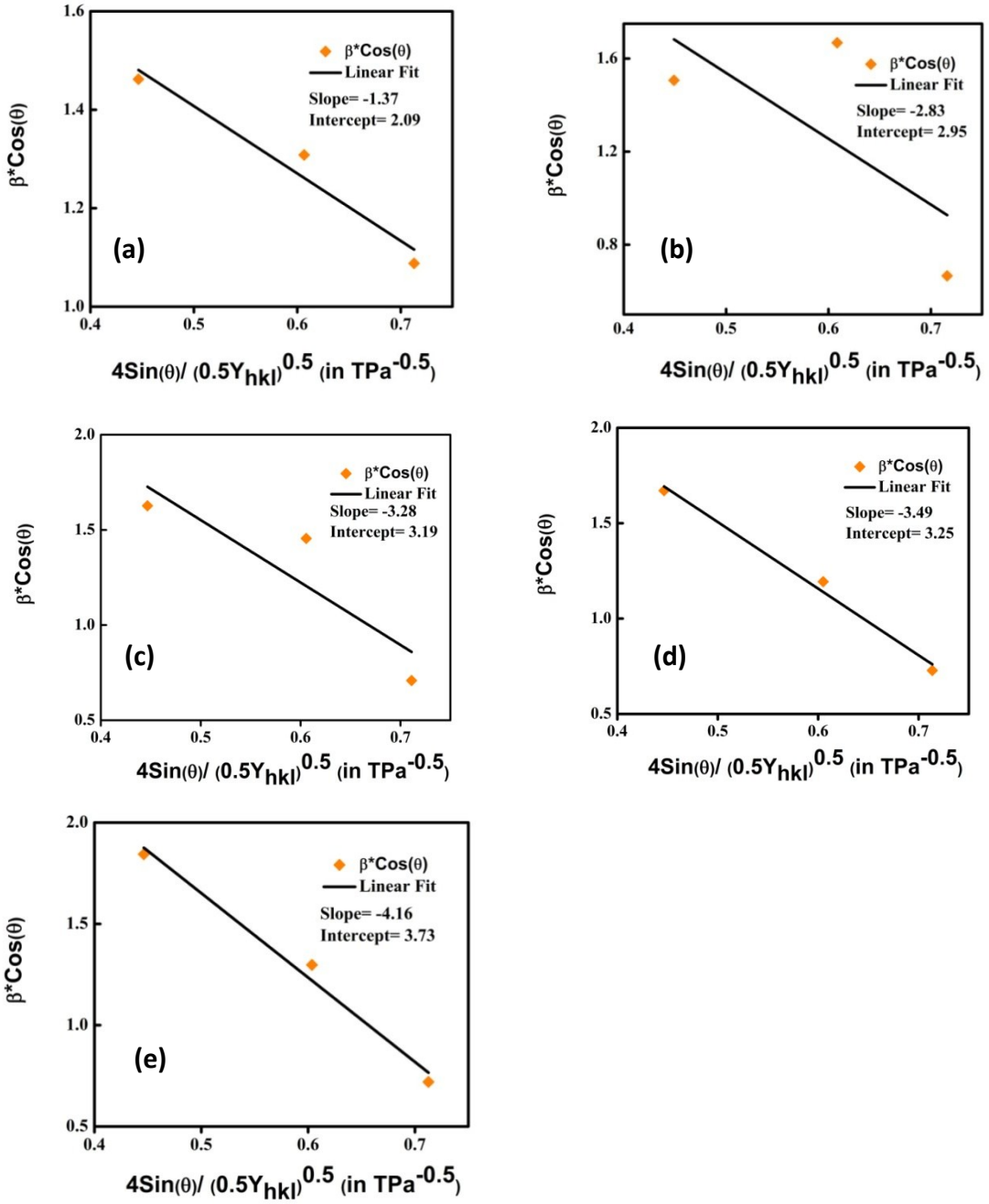

Fig. S6 (a), (b), (c), (d) and (e) shows the William-Hall plot for energy density calculation for 2%, 4%, 6%, 8%, and 10% m-HA respectively

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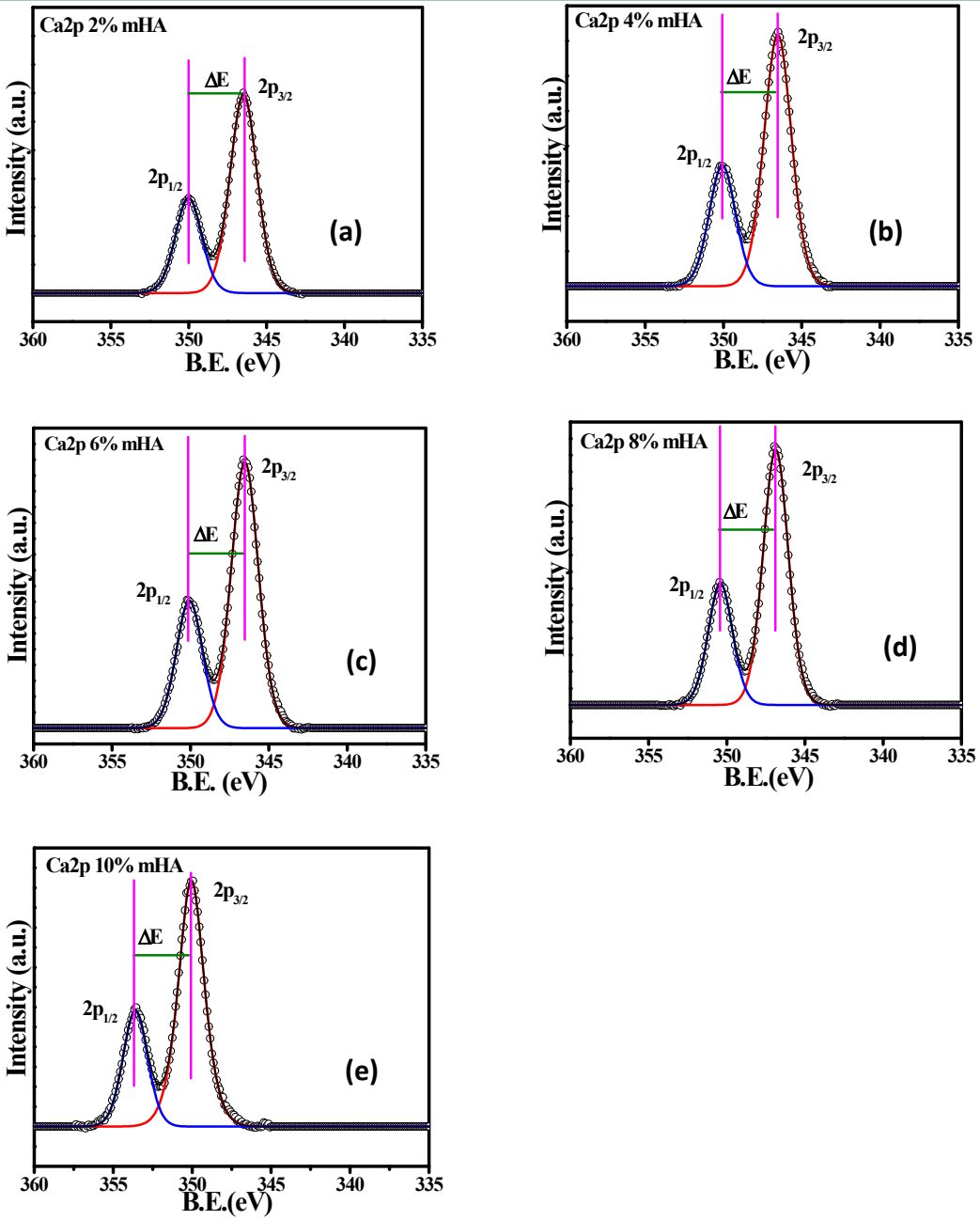

Fig. S7 (a), (b), (c), (d) and (e) shows deconvulated Ca2p peak of 2%, 4%, 6%, 8%, and 10% m-HA respectively. The peak position and peak energy separation matches with the Ca^{+2} oxidation state.

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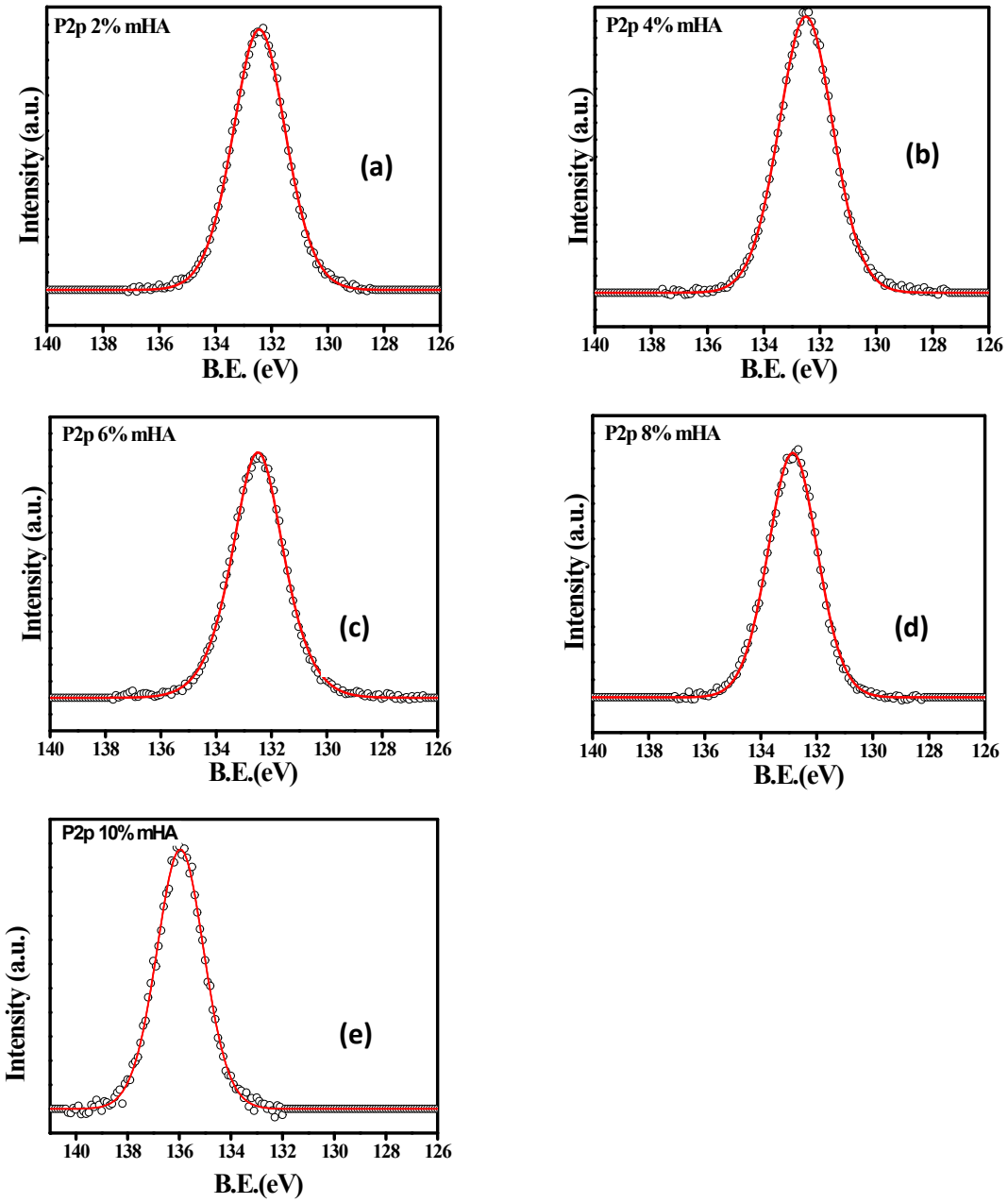

Fig. S8 (a), (b), (c), (d) and (e) shows deconvulated P 2p peak of 2%, 4%, 6%, 8%, and 10% m-HA respectively