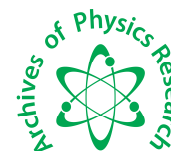




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Study of 2-acetoxybenzoic acid (aspirin) nanoparticles containing w/o microemulsion

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ABSTRACT

Due to large surface to volume ratio, the nano-scale structures have unique properties and dissolution behaviors which are expected to avoid the unwanted side effects and the higher conventional dosage levels in case of Active Pharmaceutical Ingredients (APIs). The suitable micro-emulsion is an interesting and potentially powerful alternative carrier for the targeted drug delivery. In the present study, well known API, 2-acetoxybenzoic acid or acetyl salicylic acid or Aspirin, nano-particles were obtained by W/O micro-emulsion technique, where AOT, n-heptane and chloroform were taken as surfactant, oil phase and solvent, respectively. The micro-emulsion with synthesized Aspirin nano-particles was characterized by the Dynamic Light Scattering (DLS) for obtaining distribution of particle size, Transmission Electron Microscopy (TEM) for estimation of particle size and particle morphology and UV-Vis spectroscopy for the estimation of particle size and energy band gap. The particle size was found to be within 5 to 9 nm and the energy band gap was estimated to be 3.60 eV. The results are discussed.

Keywords: Nano-particles; Aspirin; Phase-diagram; W/O micro-emulsion

INTRODUCTION

Aspirin (acetyl salicylic acid; IUPAC name: 2-acetoxybenzoic acid) is chemically identical to the salicylic acid; which is a well known analgesic, anti-inflammatory and antipyretic drug. It is one of the popular Non steroidal Anti-inflammatory Drugs (NASIDs) and prescribed widely all over the world. It has attracted the attention due to its efficiency in the anti-platelet therapy for maintaining vessel potency in patients after undergoing coronary artery bypass grafting or angioplasty [1]. A wide spectrum of literature is available on Aspirin [2-4]. The first satisfactory mechanism for the action of this drug was proposed by Vane [5]. The most common adverse effect of this drug is gastrointestinal disturbances such as, nausea, dyspersia and vomiting [6].

Various properties of bulk and crystalline Aspirin samples have been studied rigorously. The monoclinic crystal structure was reported [7-8] and several spectroscopic studies were carried out, for example, NMR [9] fluorescence and phosphorescence spectroscopy [10-11]. Moreover, Vachhani et al [12] have grown Aspirin single crystals and characterized them by FTIR, TGA, Powder XRD studies. Notwithstanding, the studies on nano-particles of Aspirin are not well reported. Aspirin is involved along with chitosan [13] and albumin [14] nano-particles for drug delivery.

Micro-emulsion has large number of applications in various fields, which is reviewed by Gupta et al [15]. Micro-emulsion has been used for the targeted drug delivery to avoid the side effects [16]. Some chemicals or therapeutic agents exhibit success *in vitro* but fail to produce the same effect in the human body or *in vivo* because of the limitation to target the designated area. As a result, the high concentrations are administered to patients and the consequences are more intense side effects [17].

It has been already known that the particle size of an Active Pharmaceutical Ingredient (API) is an important parameter in drug formulation and processing. In micrometer range, the size effect of particles on compaction and tablet formation is reported [18]. When the particle size decreases to nano meters, the effects are quite different [19]. The large surface to volume ratio present in nano-particles is expected to bring different physical properties. The physical properties of nano and micro particles processed with solid dosage forms of drugs have been discussed by Lee [20]. As Aspirin being widely used API, in the present study, Aspirin nano-particles were synthesized by W/O micro-emulsion technique and characterized by Dynamic Light Scattering (DLS), Transmission Electron Microscopy (TEM) and UV-Vis spectroscopy along with the micro-emulsion form.

MATERIALS AND METHODS

For any micro-emulsion it is first required to construct the phase diagram. At room temperature, a phase diagram for the AOT/n-heptane/water system was constructed by varying their concentrations in a step wise manner and a single phase region was determined. A lipid solution was obtained for the single phase region. The single phase region was used to obtain the micro-emulsion of Aspirin nano-particles.

The surfactant AOT was dissolved into the oil phase of n-heptane and then the desired amount of water was added to maintain [water] / [surfactant] molar ratio within the single phase region [21]. After the addition of water, the mixture was treated with continuous magnetic stirring until a lipid solution was obtained and, thereafter, the solution of Aspirin in chloroform was added in a drop-wise manner. Finally, the system was again treated with magnetic stirrer for 15 - 20 minutes. Treatments with stirring were necessary to give the energy to the system to speed up the formation of the reverse micelles. The micro-emulsion with Aspirin nano-particles was used for further characterization.

The DLS study was performed on BROOKHAVEN 90 PLUS particle size analyzer. TEM analysis was conducted on PHILIPS-TECNAI using EHT potential 200 kV. UV-Vis spectroscopic analysis of micro-emulsion containing nano-particles was carried out on UV-1601 SHIMADZU spectrophotometer with 190 nm to 400 nm scanning range.

RESULTS AND DISCUSSION

Reducing the particle size of API is found to be an efficient and reliable method of improving the bioavailability of relatively insoluble drugs, which is many times limited by poor dissolution [22]. As per the Noyes-Whitney equation, the dissolution rate is linearly dependent on surface area and hence the large surface to volume ratio of nano-particles increases the dissolution rate [23]. Organic nano-particles such as cholesterol, rhovanil and rhodiarome were synthesized by using micro-emulsion technique by Destree and Nagy [21]. Recently, cholesterol nano-particles have been synthesized by W/O micro-emulsion by Vyas et al [24]. The usual preparation of organic nano-particles is by direct precipitation of the active compound in aqueous cores of micro-emulsion. Generally, this occurs through several stages. The solution of the active compound, here, Aspirin, in chloroform penetrates inside the aqueous cores by crossing the interfacial film. The solvent plays the role of transporting the active compound inside the water cores. This active compound precipitates in water cores due to its insolubility in water and thus nuclei formed. These nuclei grow further because of the exchange of the active compound between the water cores. Ultimately, the nano-particles are stabilized by the surfactant present in the solution.

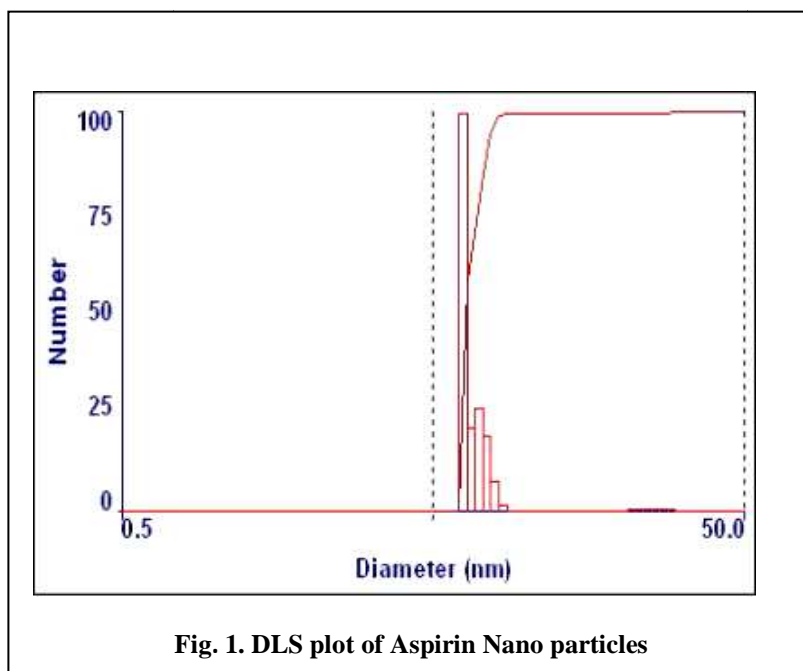
The micro emulsion technique is a versatile technique finding applications in the numerous fields [25]. Because of the ease of micro-emulsion preparation, the drugs that are thermo-labile are easily incorporated without the risk of degradation [26]. In drug delivery, micro-emulsions ultimately increase the surface area of drugs, which improves their solubilization and permeation behavior. They are shown to increase solubility and bioavailability of Class II and IV drugs according to the biopharmaceutical drug classification system. Class II drugs have high solubility but low permeability and Class IV drugs have low solubility and low permeability [26]. Plasma concentration profiles and drug bioavailability have been shown to be more reproducible in micro-emulsion formulations [27, 28]. The rate of penetration of drug is much faster from micro-emulsion systems than from other drug delivery vehicles, while having controlled drug release rates, slow degradation, and target specificity [26]. Micro-emulsions have a higher solubilization capacity for both hydrophilic and hydrophobic compounds than simple micellar solutions. Because of their thermodynamic stability, they are more favorable than regular emulsions or suspensions since micro-emulsions can be established or manufactured with very little energy input and have a long shelf life [27].

Micro-emulsions have some disadvantages as well. Formation of micro-emulsions generally requires large amounts of surfactants and/or co-surfactants. All of these at high concentrations are, generally, irritating, if not slightly toxic,

to the biological system [29, 30]. Many outside factors, such as temperature and pH, influence the stability of micro-emulsions as well. Considering the large applications of micro-emulsions the present authors used water/oil micro-emulsion of Aspirin for study.

DLS Analysis

Figure-1 shows DLS plot of Aspirin nano-particles containing micro-emulsion indicating the maximum number of particles within the size distribution of 5-7 nm range. The mean diameter of Aspirin nano-articles was obtained around 6.6 nm.



TEM Analysis

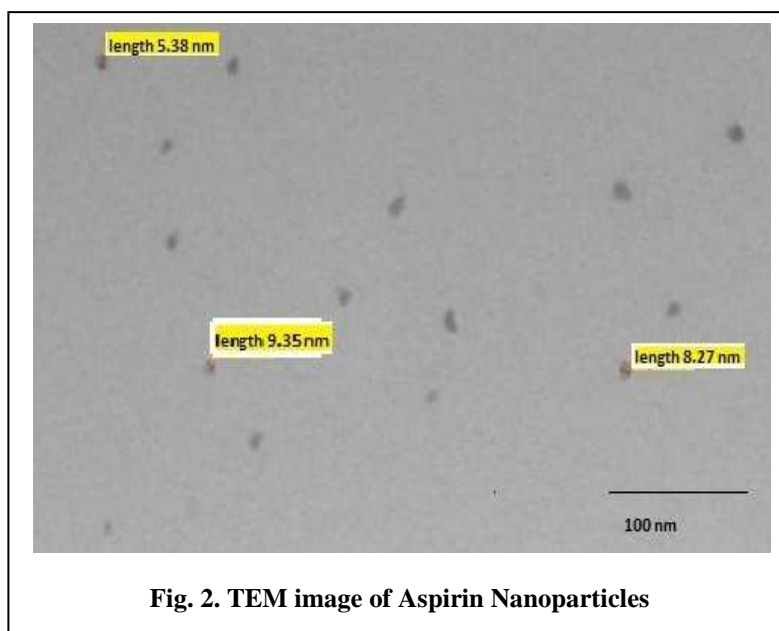


Figure-2 shows the TEM image of Aspirin nano-particles indicating the nearly spherical morphology with size range of 6 to 9 nm. This result is in good agreement with the results obtained from DLS analysis.

UV-Vis Analysis

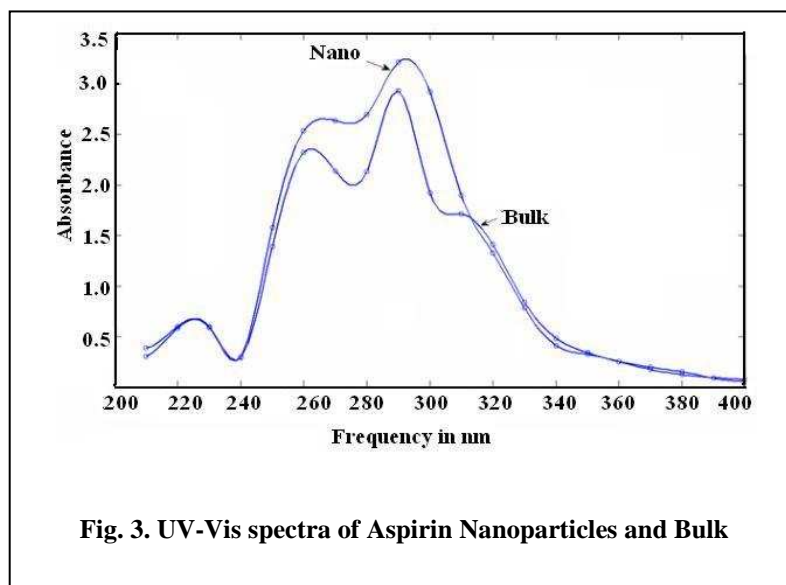


Fig. 3. UV-Vis spectra of Aspirin Nanoparticles and Bulk

The nano-materials have discrete quantized energy levels due to quantum confinement effect and consequently a larger band gap is observed compared to bulk studies. These quantum size effects on the band gap absorption energy can be measured by UV-Vis absorption spectroscopy. UV-Vis study of quantum dots and the theoretical aspects are well known [31]. The particle size measurements have been carried out using UV-Vis absorption spectra for metal and semiconductor nano particles [32]. The size dependence of band gap energy of semiconductor nanocrystals is considered by using Brus equation for several compounds [33]. For example, the band gap energy is 3.6 eV for bulk ZnS sample, while it is 4.03 eV for nano-particles of ZnS [34]. There are several organic compounds behave as semiconductor materials, which are discussed in detail by Coropceanu et al [35]. The organic semiconductors incorporate critically the efficiency with which charge carriers (electron and/or holes) move within the π -conjugated bonds of materials.

The nanostructured organic semiconductors have been obtained via direct supra-molecular assembly by Rancatore et al [36]. Moreover, the self assemblies of 1-D organic semiconductor nanostructures were derived by Nguyen et al [37]. The preparation of high quality organic semiconductor nano-particle films by solvent evaporation induced by self assembly is reported by Zheng et al.[38]. Apart from this, the opportunities for organic nano-particles in science and technology has been reviewed by Rannard [39].

Figure-3 shows UV-Vis absorption spectra of Aspirin nano-particles in micro-emulsion and the bulk Aspirin materials. The well-defined surface-plasmon band is observed at 290 nm.

By using the standard equations, the cut off wave length λ_c was calculated as 344.46 nm and the energy band gap was found to be 3.56 eV for the bulk crystalline Aspirin. This indicates that Aspirin is wide band gap semiconductor material like ZnS [33]. In the present study, the effective mass model is considered to calculate the particle size of the Aspirin nano-particles in the micro-emulsion from the UV-Vis absorption spectrum. The effective mass model is discussed by several authors [32, 40].

The Average particle size was calculated by using following equation [40],

$$E_g^* = E_g^{bulk} + \frac{\hbar^2 \pi^2}{2r^2} \left(\frac{1}{m_e^*} + \frac{1}{m_h^*} \right) - \frac{1.8e^2}{4\pi\epsilon\epsilon_0 r} - \frac{0.124 e^4}{\hbar^2 (4\pi\epsilon\epsilon_0)^2} \left(\frac{1}{m_e^*} + \frac{1}{m_h^*} \right)^{-1} \dots\dots (1)$$

Where,

E_g^* = Band gap energy of the nano-particle (eV)

E_g^{bulk} = Band gap energy of the bulk sample in (eV)

h = Planck's constant (6.625×10^{34} J · s)

r = Particle radius (m)

m_e = Mass of a free electron (9.11×10^{-31} kg)

m_e^* = Effective mass of a conduction band electron ($0.19 m_e$)

m_h^* = Effective mass of a valence band hole
($0.80 m_e$)

e = Elementary charge (1.602×10^{-19} C)

ϵ_o = Permittivity of free space (8.854×10^{-12} F / m)

ϵ = Relative permittivity of the sample ~ 2

In this equation, the first term is known as the quantum localization term, which shifts E_g to the higher energy proportionally to r^{-2} , the second term is due to the screened Coulomb interaction between hole and electron and shifts E_g to lower energy as r^{-1} and the third term is size independent term indicating the salvation energy loss [32]. The average particle-size was found to be 13.60 nm. The variation found in the values of particle size, compared to the same obtained from DLS and TEM studies, was due to various assumptions made in the formulation. The energy band gap values for the nano-particles and the bulk were found to be 3.60 eV and 3.56 eV, respectively. Higher energy band-gap value for nano-particles could be explained as it varies with diameter as r^{-2} [41] and predominance of the first term of equation (1) over the second term. The energy band gap values of Aspirin bulk and nano-particles are at par with that of ZnS and can find various applications as organic quantum dot alike the ZnS quantum dots.

CONCLUSION

Aspirin nano-particles containing W/O micro-emulsion was successfully established. The average particle size of Aspirin was obtained by DLS analysis and TEM, which was found to be 6.6 nm and within the range of 6-9 nm. The average particle size was also calculated by UV-Vis spectroscopy and found to be 13.60 nm. The energy band-gap was found to be 3.60 eV for Aspirin nano-particles, which was higher than that of the bulk material value of 3.56 eV.

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