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Transforming expired medicines into TiO_2 nanoparticles

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The study aims to synthesize Titanium Dioxide (TiO_2) nanoparticles using expired disprin and paracetamol, exploring an innovative approach to curb the hazards posed by discarded expired medicines thereby reducing drug pollution and improving ecological footprint. The sol-gel method was employed to synthesize TiO_2 nanoparticles using expired disprin and paracetamol. Various characterization techniques, such as X-Ray Diffraction (XRD), Energy Dispersive Spectroscopy (EDS), Field Emission Scanning Electron Microscopy (FESEM), Selected Area Electron Diffraction (SAED), and Vibrating Sample Magnetometer (VSM), were used to analyse the synthesized nanoparticles. The XRD and EDS analyses confirmed the formation of TiO_2 nanoparticles. The nanoparticles synthesized from both paracetamol and disprin showed a dominant anatase phase with stray peaks of rutile and brookite phases. SAED of paracetamol-derived nanoparticles showed a highly crystalline structure. FESEM confirmed the synthesis of uniformly distributed spherical nanoparticles with size range between 5-20 nm. The size of nanoparticles estimated from both XRD and FESEM appear to be in good agreement. VSM confirmed the diamagnetic nature of both paracetamol and disprin-derived nanoparticles. The study demonstrates that synthesizing TiO_2 nanoparticles using expired pharmaceuticals can be a promising approach to mitigate the environmental hazards posed by discarded expired medicines. This novel method has the potential to revolutionize the synthesis of nanoparticles and contribute to a more sustainable future.

Keywords: Characterization, Ecological Footprint, Expired Medicines, Nanoparticles, Sol-gel, Sustainability, Titanium dioxide

Medicines play an important part in our day-to-day life. There are plenty of over-the-counter pills, multivitamins and other prescription drugs which are consumed by the masses on almost regular basis. These medicines come with a date of manufacturing and an expiry date. The date of manufacturing tells the date on which the processing of the medicine was initiated, and the active pharmaceutical ingredient was mixed into the other materials to form the drug. The expiration date of the medicine is that final day up to which the manufacturer guarantees the safety and full potency of the medicine. Food and Drug Administration (FDA), USA is a regulatory body which works for improving the medication safety and to regulate the expiry date of the drugs. Despite knowing the expiration date of the medicine, many people consume the drugs believing that they can still be effective. Even though the medicines might still work after the expiry, but FDA strictly warns the consumers not to use such drugs because of the potential risks that might be involved. The reason being that most of the drugs break down after the expiration thereby losing the effectiveness and, in many cases, they break down into more toxic compounds thereby leading to serious complications. A recent study conducted in a rural village of the state Andhra Pradesh, India found that 78.7% of the surveyed households had unused medications with a mean of 6.3 drugs found per family. The majority of these drugs belonged to the class of antibiotics, antipyretics, antacids, anti-inflammatory drugs and proton pump inhibitors. These drugs were kept for personal use with zero storage safety. The residents were clearly prone to accidental poisoning and various health hazards[1].

FDA strongly urges to properly dispose expired or unused medicines because the data collected from 2015 to 2019 recorded many cases of accidental ingestion and calls made to poison control centres with painkillers being majorly responsible for paediatric fatalities. FDA also recommends flushing the expired medications down the toilet[2]. Another study conducted on the medical personnel revealed that the most common method of drug disposal undertaken by them is disposing the drug with the

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household waste[3]. This practice leads to the menace of drug pollution, which is going to reach an alarming state in coming years. The active molecules in the drugs bioaccumulate in living organisms and result in toxicity across the trophic levels. Recently, European Union has put diclofenac (a non-steroidal anti-inflammatory drug) into the list of drugs "to be watched" as they have come up as a major threat to biodiversity as well as to the environment. Diclofenac is known to cause inflammation, influence the expression of multiple genes, result in malformation of the gills in the fish and is also known to have adversely affected the Asian vulture population. Drugs are known to degrade *via* four possible routes such as volatilization, biotic degradation, abiotic degradation and sorption into the sediments. Diclofenac doesn't volatilize and usually undergoes photo-transformation in water bodies. The photo-transformation products of diclofenac exert six times more toxicity than the diclofenac itself[4]. Most of the pharmaceutical drugs finally end up in drinking water and the food web. Excessive use of antibiotics is the root cause of generation of superbugs. In a nutshell, there is an immense need for public awareness, setting up of a regulatory body and stringent guidelines for proper disposal of the expired drugs[5]. In order to tackle this situation of drug pollution, these expired medicines must be either broken down to non-toxic substances or put to some good use.

The threat posed by these expired drugs can be effectively tackled if these can be utilized in the synthesis of nanoparticles (NPs). Recently, a statistical study conducted among the population of Shri Mata Vaishno Devi University Katra (SMVDU), India revealed significant gap between awareness and understanding of antibiotics and antibiotic resistance, with widespread self-medication practices. Although most participants acknowledge the need to avoid unnecessary antibiotic use, many depend on personal experiences for guidance, especially for conditions like colds and flu, where antibiotics are ineffective. This reliance stems more from a general apprehension towards medication than from informed knowledge[6]. This behaviour often leads to drug abuse and overuse and many times, people do not realize that they are consuming expired drugs. NPs offer a plethora of benefits. Their structural, morphological and other characteristic properties can be optimized to provide applications in the field of medicine, agriculture, electronics, energy and sensing, and many more. NPs can be engineered as nanofibers which offer potential benefits in wound healing[7].Ramakrishnan *et al*. fabricated zinc oxide NPs which exhibit antibacterial and anti-cancerous properties[8]. The manufacturing of the NPs requires a lot of chemicals depending upon the properties required of the resulting NPs. The drugs are also chemical substances made up by mixing a variety of active molecules, linkers and biomolecules and thus possess a specific chemical composition. Thus, the use of expired drug in the synthesis of NPs will cut down the requirement of adding extra chemicals as the need would be fulfilled from the chemical composition of the drug itself. Very limited research has been done in this field and quite a few types of NPs have been synthesized till date using expired medicine. However, the successful synthesis of the NPs depicts that this approach is useful. One such effort was initially made by Jha and team where they used combinations of expired norfloxacin and tinidazole to synthesize Au, ZrO_2 and CdS NPs[9]. The synthesized NPs depicted stability for at least six months. Recently, researchers fabricated silver NPs using expired metrogyl and norflox TZ[10]. The synthesized NPs also possessed significant anti-microbial activity against different stains of gram-positive and gram-negative bacteria. It is merely the beginning of this novel approach of synthesizing NPs.

Nanocrystalline titanium dioxide (TiO_2) has garnered significant attention in the field of material science due to its remarkable versatility and potential applications. Their usage as coatings aims to enhance hot corrosion resistance, addressing a critical concern in the power generation industry[11]. The utilization of TiO_2 thin films for photocatalytic and photovoltaic applications highlights their potential in harnessing solar energy for sustainability and clean energy generation[12]. Nanocrystalline TiO_2 in dye-sensitized solar cells elucidates their potential as a catalyst for efficient solar energy conversion[13]. These applications collectively underscore the versatility of nano-TiO_2, which can be tailored and optimized for specific purposes, making it a promising material for future advancements in various scientific disciplines. By encapsulating drugs within nano-TiO_2 carriers, targeted drug delivery systems can be developed, enabling precise administration and improved efficacy while minimizing side effects[14]. In the agricultural sector, nano-TiO_2 has shown promise in enhancing crop growth and protection[15]. Its photocatalytic properties can be harnessed for the degradation of

pollutants, pesticides, and harmful organic compounds in soil, water, and air. Nano-TiO_2-based sensors offer high sensitivity, selectivity, and stability, making them valuable tools for environmental monitoring, food safety, and medical diagnostics[16]. Furthermore, nano-TiO_2 has potential applications in energy storage and conversion, environmental remediation, water purification, and even cosmetics. Its versatility stems from its tuneable properties, such as particle size, surface area, and surface chemistry, which can be tailored to meet specific requirements in different applications.

In the present paper, two samples of Titanium dioxide NPs (TiO_2 NPs) were synthesized using the aqueous solution of Disprin and Paracetamol, respectively. These two medicines were chosen because these are the most commonly used and easily available over-the-counter pills. TiO_2 NPs are the most versatile NPs with a plethora of applications and their global demand is rising day-by-day. Another reason why TiO_2 NPs can effectively be synthesized from the expired drugs is that bulk TiO_2 has long been playing a very crucial role in the pharmaceutical industry. It goes by the same additive number E171 in both food as well as pharmaceutical industry. TiO_2 acts like a characteristic white pigment which gives white colour to most of the pills. Moreover, it provides protective coating to the medicines in order to protect the quality, potency and efficacy of the active pharmaceutical ingredient present in them. The brilliant ability of TiO_2 to absorb ultraviolet rays make them beneficial for packaging purposes to maintain the drug's shelf life as well as to prevent its premature degradation[17]. Thus, it is anticipated that the content of the bulk TiO_2 present in the medicines might assist in the synthesis of the TiO_2 NPs.

Disprin is a quick water-soluble pain reliever with aspirin as the active ingredient. It is known to have analgesic, antipyretic and anti-inflammatory properties. Paracetamol, also known as acetaminophen a commonly used medicine for reducing fever and relieving mild to moderate pain. It also belongs to the class of analgesics and antipyretics. Disprin (or aspirin) is quite often consumed to prevent the risk of heart problems but taking expired aspirin can maximize the chances of severe heart problems such as stroke[18]. The studies show that about 30% of the paracetamol breaks down between 12 to 24 months once they cross their date of expiration[19].

Various efforts are being made to ensure the reduction in the usage of toxic chemicals in the making of NPs. For the same reason, green synthesis techniques are being adopted where the extracts of different parts of the plants are used in place of acids or bases which regulate the pH conditions of the NPs bearing solution. Like plants extracts, drug solutions can also be expected to bring about the desired pH changes during the synthesis of NPs. The drug systems are designed to respond to the pH changes. Different organs, tissues and cells have different pH levels which work as suitable stimuli for controlled drug release[20]. Since drugs respond to certain specific pH values, these can bring pH-changes in the NPs bearing solution. Thus, instead of using different acids or bases to control the pH levels, these drugs can be used constructively, and the NPs can be synthesized with least number of chemicals.

The novelty of this study lies in the first-time ever synthesis of TiO_2 NPs using disprin and paracetamol medicines and precursor as the only major chemical. These NPs can be used in various environmental remediation and agricultural applications. These NPs have all the characteristics of the otherwise synthesized TiO_2 NPs and thus can treat polluted water. They can also be used in hydroponics or agricultural soil to improve the growth and nutritional content of the crops. This approach offers a solution to address the issue of drug pollution by repurposing drugs to create nanoparticles that can be used in various applications, thus improving the ecological footprint.

Materials and Methods

The materials used for chemical synthesis were Titanium TetraIsopropoxide (TTIP), ethanol and Deionized (DI) water. These were purchased from Sigma Aldrich Pvt. Ltd, Bangalore, India and all the chemicals were used as such without any further purification. TTIP was used as titanium precursor. IKA-RCT basic IKAMAG safety control magnetic stirrer by Merck, India was used for the stirring and heating applications. pH testing kit by INSIF, India was used to correctly detect the pH of the final solution. A muffle furnace by INSIF, India was used for the calcination of the samples. Conical High Alumina Crucibles of volume 30 mL by Thomas Scientific were purchased for calcining the samples at high temperatures in a muffle furnace. Disprin and Paracetamol were purchased from the local chemist in

Chandigarh. The aqueous solution of disprin and paracetamol were prepared using DI water. High Score Plus software was used to analyze the XRD patterns obtained for the two types of NPs.

The synthesis of TiO_2 NPs was performed following the sol-gel route. A stoichiometric amount of TTIP was added to 20 mL ethanol under continuous stirring. The solution turned opaque white and was stirred for an hour. This was followed by the addition of aqueous solution of the tablet (Paracetamol or Disprin) in 40 mL DI water drop wise to regulate the pH of the solution. Addition of the second solution turned the mixture transparent again. Afterwards, the solution was subjected to heat treatment at 60°C (60 degrees Celsius) for 3 h which included opacification of the solution followed by colour change to light earthy green. To bring about the crystallinity, samples prepared from both the medicines were subjected to calcination in a muffle furnace. The samples were poured into the alumina crucibles and then placed into the muffle furnace for calcination at 400°C. After the muffle furnace reached a temperature of 400°C, the samples were calcined at this temperature for 2h. Once the calcination period was complete, the furnace was turned off, and the samples remained inside until the furnace had cooled completely before being removed. They were not taken out immediately after the 2h to avoid temperature shock, which could cause structural and morphological changes. The resulting samples were pristine white in colour, confirming the successful synthesis of TiO_2 NPs. The entire process of the synthesis of the samples is summarized in (Fig. 1).

Results and Discussion

The two samples of the TiO_2 NPs were characterized for X-ray Diffraction (XRD), Selected Area Electron Diffraction (SAED), Field Emission Scanning Electron Microscope (FESEM), Elemental Dispersive Spectroscopy (EDS) and Vibrating Sample Magnetometer (VSM). Figures 2A and 2B depict the XRD plots of the two samples of TiO_2 NPs obtained from the aqueous solution of disprin and paracetamol, respectively. From the two plots, we can easily infer that the NPs synthesized using paracetamol exhibit more crystallinity as the peaks are narrower and sharper, whereas, in case of TiO_2 NPs obtained using disprin, the peaks are wider. However, both the NPs showed dominant anatase phase. Anatase phase is associated with smaller particle size which has been confirmed by many published works[21, 22]. Our previous study has also confirmed that lower calcination temperature ~400°C results in the synthesis of anatase phase titania NPs[21]. In Figure 2A, the anatase peaks were obtained at 25.442°, 38.114°, 48.169°, 54.649°, 62.820°, 70.098° and 75.285°, however, just a single sharp peak of brookite phase was obtained at 57.633°. The pattern of the anatase peaks match with the JCPDS pattern 01-078-2486 and the peak of brookite phase matches with the JCPDS pattern 01-075-1582. The anatase peaks obtained matched with those obtained for green-synthesized CS-TiO_2 NPs[23]. Figure 2B depicts the anatase, rutile and brookite peaks with the dominant anatase phase, one rutile peak and two brookite peaks. The anatase peaks majorly correspond to 25.554°, 37.907°, 48.073°, 54.345° and 62.724° and these match with the JCPDS pattern 01-071-1167. The rutile peak at

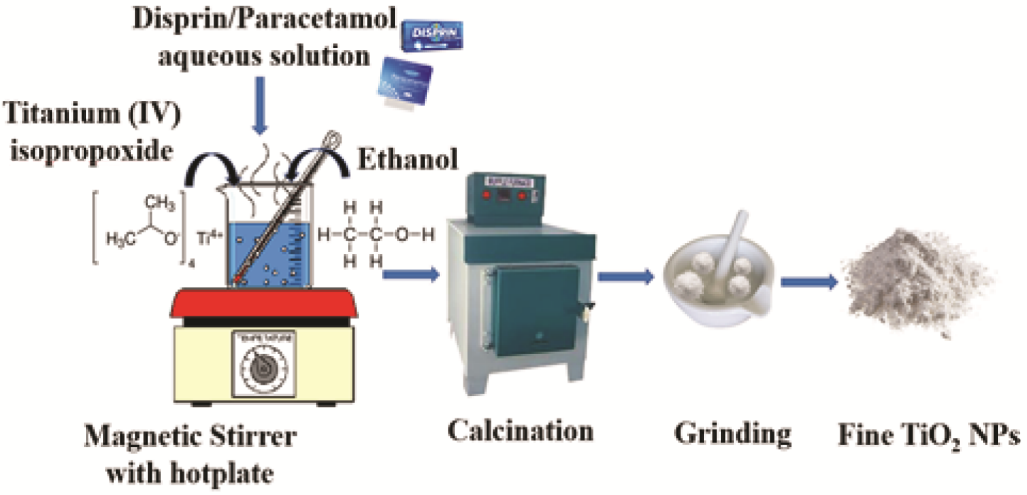

Fig. 1 — The schematic diagram of the synthesis process of the TiO_2 NPs

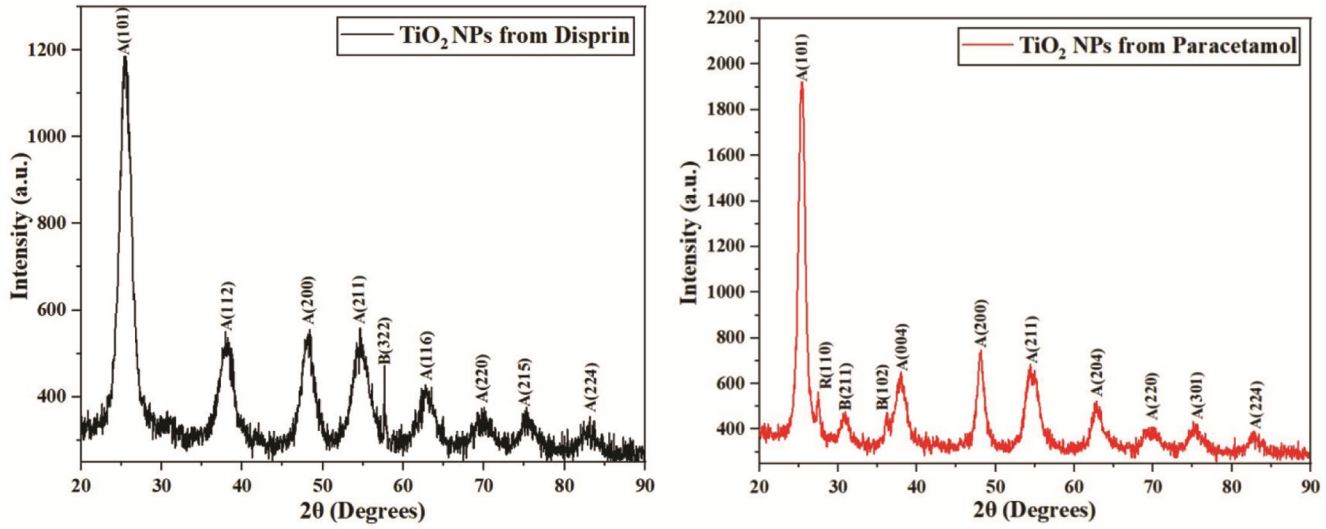

Fig. 2 — (A) XRD of TiO_2 NPs synthesized using aqueous solution of Disprin tablet; and (B) XRD of TiO_2 NPs synthesized using aqueous solution of Paracetamol tablet

27.437° agrees with JCPDS pattern 21-1276. The two brookite peaks at 30.932° and 36.119° agree with JCPDS pattern 72-0100.The alignment of the peak pattern with the established standardized JCPDS patterns confirms that the NPs were successfully synthesized. The Debye-Scherrer equation was used to compute the crystallite size of the two samples which came out to be 4.39 nm and 11.21 nm for the TiO_2 NPs synthesized using disprin and paracetamol, respectively. From the XRD plots, this can be easily confirmed as narrower peaks often lead to bigger crystallite size as compared to broader peaks. Disprin-derived TiO_2 NPs have broader peaks distribution as compared to paracetamol. Furthermore, the less sharpness of the peaks also points towards the presence of amorphous structure as well. One major conclusion drawn from these XRD data is that the samples generated represent TiO_2 and no other chemical compound, which further suggests that the expired medicines were fully utilized in the making of these NPs and no portion of these medicines was left unreacted or converted into any other chemical compound.

The size of the TiO_2 NPs was calculated using Debye-Scherrer formula as given below:

$$D = 0.9\,\lambda/\beta\cos\theta \qquad \ldots (1)$$

where, D is the crystallite size in nm, λ=0.15406 nm (wavelength of the x-ray used), β is full width at half maximum (FWHM) and cosθ is obtained from 2θ values.

Figure 3A depicts the SAED pattern of the disprin-derived TiO_2 NPs whereas, Figure 3B depicts the SAED pattern of the paracetamol-derived TiO_2 NPs. Figure 3A shows diffuse rings which goes well with the broader peaks of the XRD plot in (Fig. 2A). Broader the peaks imply lesser the crystallinity and more diffuse the SAED pattern. Moreover, diffuse patterns also depict the amorphous nature of the sample[24]. On the other hand, Figure 3B shows well-defined ring pattern which clearly accounts for the more crystallinity of the TiO_2 NPs derived from paracetamol. The XRD plot in Figure 2B also confirms the same.

Figures 4A and 4B show the FESEM images of the two samples of TiO_2 NPs derived from disprin and paracetamol, respectively. Both images illustrate uniform distribution of spherically shaped NPs with size ranging between 5-20 nm. Thus, the data received from FESEM agrees with the results obtained from Debye-Scherrer equation. Figure 5A and B denote the histograms plotted based on the FESEM images in (Figs. 4A and 4B), respectively. The histograms also confirm the synthesis of NPs within the range of 5-25 nm. Figures 6A and 6B outline the elemental composition of the two samples and clearly validate the presence of titanium and oxygen in the samples. Figure 7 represents the combined VSM plot of the two samples obtained at room temperature. It is astonishing to find that the hysteresis plot of both the samples simply overlapped to limit their perfect diamagnetic nature. Pure TiO_2 NPs exhibit diamagnetic nature under M-H hysteresis loop obtained at room temperature[25,26].

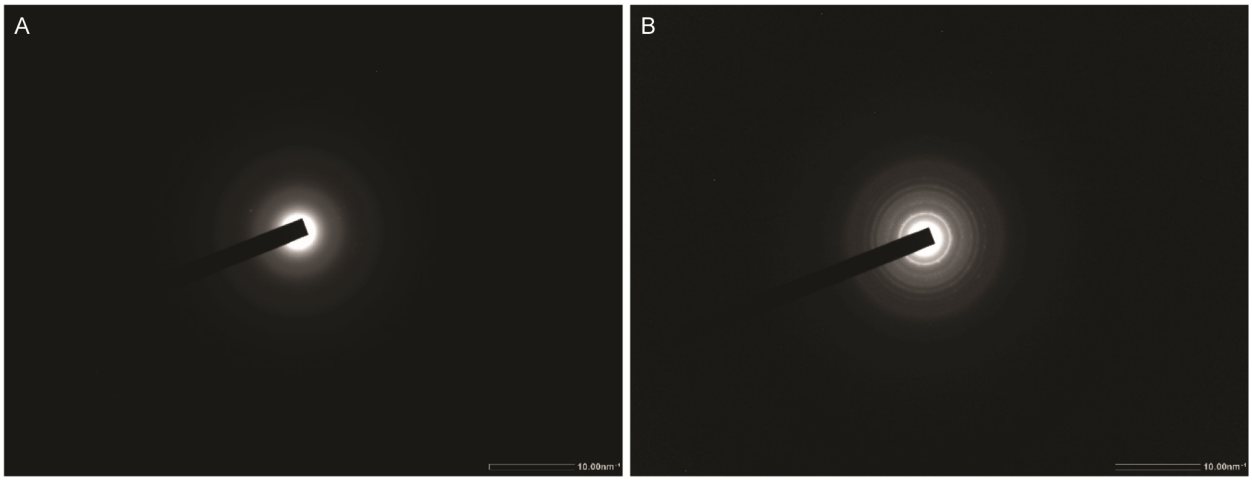

Fig. 3 — (A) SAED of TiO_2 NPs synthesized using aqueous solution of Disprin tablet; and (B) SAED of TiO_2 NPs synthesized using aqueous solution of Paracetamol tablet

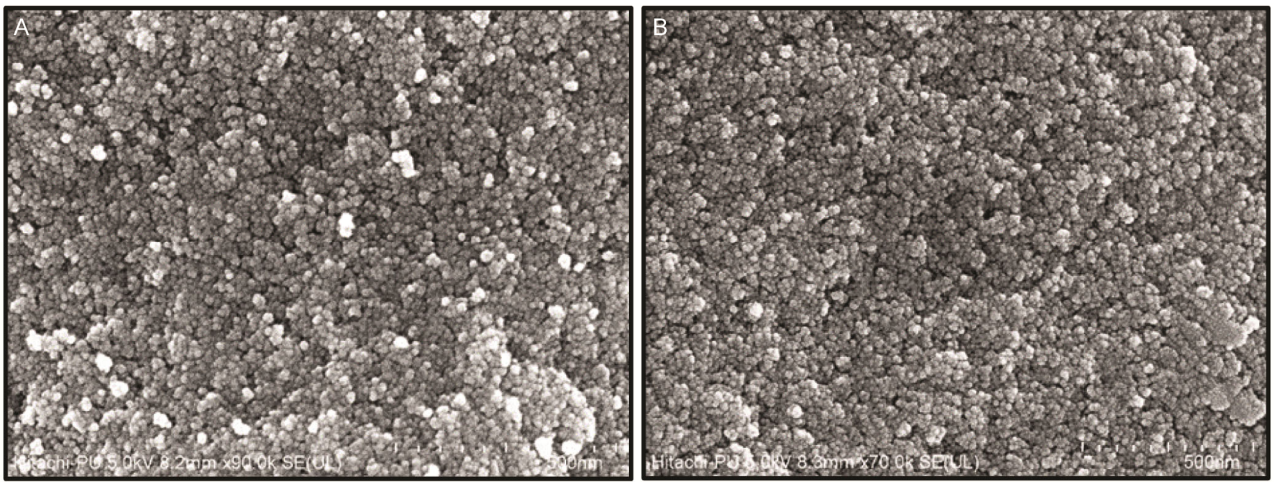

Fig. 4 — (A) FESEM of TiO_2 NPs synthesized using aqueous solution of Disprin tablet; and (B) FESEM of TiO_2 NPs synthesized using aqueous solution of Paracetamol tablet

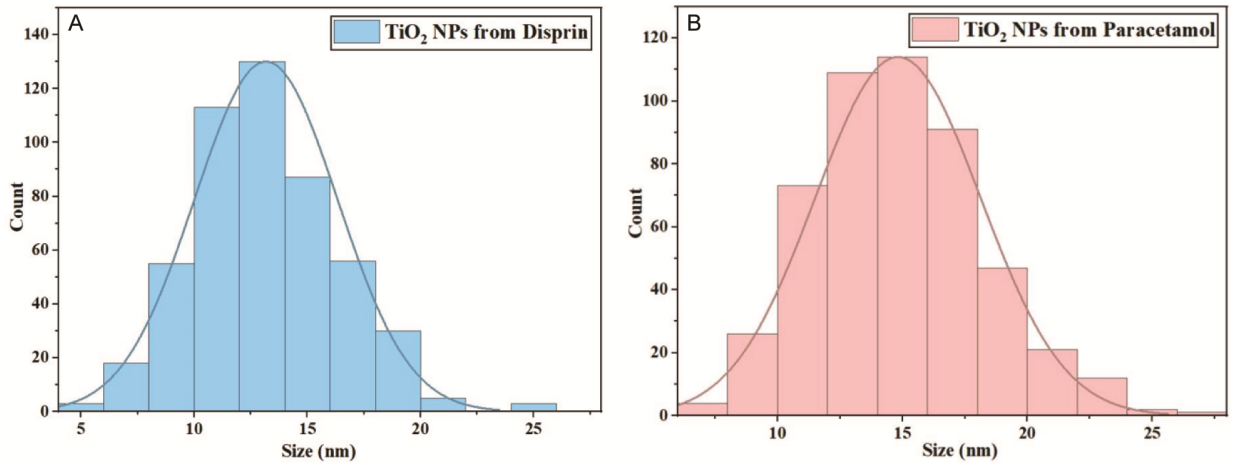

Fig. 5 — (A) Histogram of TiO_2 NPs synthesized using aqueous solution of Disprin tablet; and (B) Histogram of TiO_2 NPs synthesized using aqueous solution of Paracetamol tablet

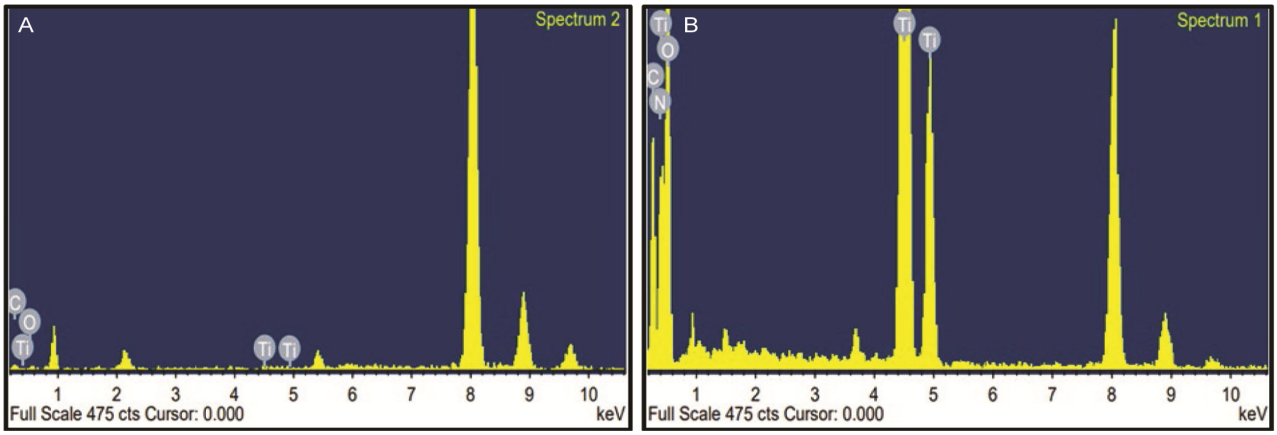

Fig. 6 — (A) EDS of TiO_2 NPs synthesized using aqueous solution of Disprin tablet; and (B) EDS of TiO_2 NPs synthesized using aqueous solution of Paracetamol tablet

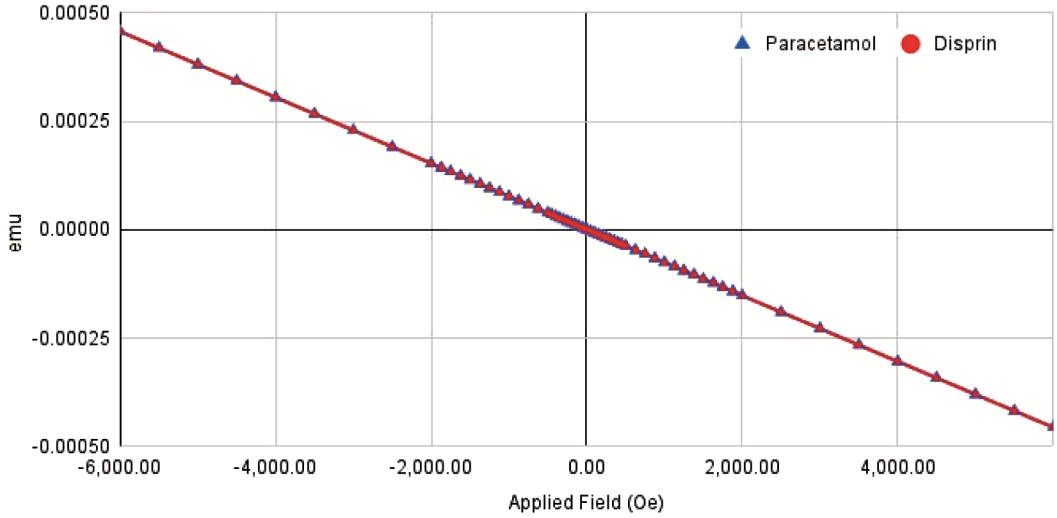

Fig. 7 — VSM plot of TiO_2 NPs synthesized using aqueous solution of Disprin and Paracetamol tablets

Figures 8A and 8B show the chemical structure of disprin and paracetamol, respectively. The chemical formula for disprin is $C_9H_8O_4$ and that for paracetamol is $C_8H_9NO_2$. Thus, disprin does not offer any new element to the solution other than carbon, hydrogen and oxygen. However, paracetamol has an extra element nitrogen to offer, and a little concentration of nitrogen (2.25% by weight) was also detected from the EDS data. Disprin dissolves quickly in water and thus the broth is obtained very quickly. The solubility of paracetamol is quite less in water as compared to other polar solvents, yet its solubility can be maximized with a little heating. Extensive investigation of pharmacokinetic properties and docking fields can help understand the role played by the medicines in the synthesis of NPs[27]. Blind docking helps in the identification of possible target molecules which are key players in the mechanism of any drug's

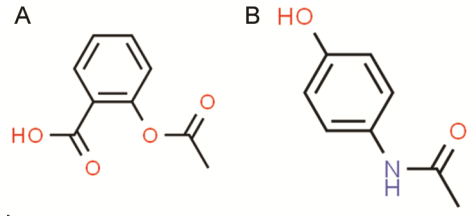

Fig. 8 — (A) Chemical structure of Disprin; and (B) Chemical structure of Paracetamol

action[28]. It is essential to investigate whether certain categories of drugs can be used to synthesize specific nanoparticles. The compatibility of various drugs with the precursor material needs to be meticulously examined. Thoughtful consideration should be given to the selectivity of a particular drug in producing a specific type of nanoparticles. Extending this approach to the production of other types of nanoparticles using different classes of drugs could

represent a significant stride toward ensuring sustainable development.

Conclusion

This paper presents an innovative and environmentally friendly approach to synthesizing TiO_2 nanoparticles (NPs) by utilizing expired drugs. By incorporating drugs, the necessary elemental composition for TiO_2 synthesis can be achieved, reducing the need for additional chemicals. This dual-benefit process not only minimizes the requirement for extra chemicals but also enables effective recycling of expired drugs, thereby addressing the issue of pharmaceutical pollution. The synthesis of TiO_2 NPs with a dominant anatase phase was confirmed through XRD analysis, and FESEM images demonstrated that NPs synthesized using disprin and paracetamol exhibited a uniform spherical size distribution ranging from 5 to 20 nm. Yet another confirmation of their synthesis was provided through VSM study which confirmed the diamagnetic behavior of the resulting nanoparticles. The characterization data provided conclusive evidence for the successful synthesis of TiO_2 NPs from two different drugs, albeit with slight variations in phases, elemental composition, and crystallinity between the two samples. These variations can be attributed to the inherent compositional differences in the drugs used. In summary, the synthesis of NPs using expired medicines represents a distinctive and forward-thinking proposal that contributes to sustainable development. This approach reduces the need for additional chemicals and allows for the effective recycling of expired medications, addressing the issue of pharmaceutical pollution.

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Conflicts of interest

All authors declare no conflicts of interest.

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