Chapter I

Introduction

CHAPTER I

INTRODUCTION*

- *This chapter begins by introducing various categories of metal nanoparticles (NPs), emphasizing their tuneable plasmonic properties and their potential applications as sensors to address the issue of milk adulteration.*
- *A brief overview of milk adulteration is presented, highlighting the limitations of previously reported detection techniques.*
- *The chapter then delves into the properties of plasmonic NPs and various methods employed for their synthesis are also explored, with a specific focus on their application in sensing.*
- *Finally, the chapter concludes by outlining the objectives and structure of the thesis.*

1.1 Overview

In the nano-regime, matter significantly alters the nature of light-matter interactions. There arise deviations from the behaviour as observed in bulk matter, which is predominantly governed by classical principles. The quantum world predominates the properties of particles in the nano-domain, as their dimensions are in range with the wavelength of incident light [1-3]. Meanwhile, metallic nanostructures (NSs) contain free electrons in the conduction band. When irradiated with a suitable electromagnetic field, these free electrons start oscillating, maintaining a constant phase. When the frequency of oscillation of the external field matches that of the free electrons, resonance occurs [4]. This resonance is responsible for significant enhancement of the absorbance of the incoming light that falls on the NSs. This phenomenon is referred to as localized surface plasmon resonance (LSPR) [5], and the free electrons on the metal surface are termed plasmons [6-9] (**Fig. 1.1**).

These NPs have garnered significant attention from researchers for a long time, as they display high absorbance and scattering (**Fig 1.2**), which can be tuned by altering their shape, size, material composition, and the external medium (**Fig 1.3a** & **Fig 1.3b**) [10].

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Particles which are relatively smaller in size absorb light more efficiently as compared to larger particles [11]. NPs could be used in a wide range of applications [12] e.g., sensing [13], photothermal conversion [14], drug delivery [15], cancer therapy [16], catalysis [17], and nonlinear optical devices [18]. The optical traits of these NPs can be finely adjusted through unique functionalization methods [19]. Due to their pronounced absorbance at resonance, they serve as effective colorimetric and plasmonic sensors, especially facilitating the detection of harmful adulterants in milk. This is due to the inherent plasmonic behaviour of metal NPs, which results in visible alteration of their colour due to changes in their interparticle distance upon exposure to specific analytes or the conversion of metallic ions from NPs when interacting with analytes possessing strong oxidizing properties [20,21]. Additionally, these nanomaterials (NMs) function as plasmonic sensors, detecting variations in the surrounding medium induced by binding of analyte on the surface of functionalized NPs, which triggers a shift in position of the absorbance peak [22]. Moreover, plasmonic NPs are also employed as electrochemical sensors due to enhanced surface area-to-volume ratio in NPs, which enables significant analyte adsorption on the NP surface. They also offer easy selectivity through functionalization, rapid response times, reusability as they remain intact even after multiple cycles, with high stability [23].

Using the exquisite properties of plasmonic NSs, one can target solving a pervasive problem that has plagued society for centuries, i.e., the detection of milk adulterants. This refers to the addition of undesirable foreign substances to milk, thereby degrading its' quality and rendering it unfit for consumption [24,25]. Various categories of chemicals such as melamine [26] and urea [27], are intentionally incorporated in milk as adulterants to falsify its net protein content, while other commonly used adulterants, such as hydrogen peroxide [28], formalin, and salicylic acid [29,30], are added in milk as preservatives to increase the shelf life. The use of all these chemicals in food can have adverse health effects. To decrease instances of food adulteration, governmental regulatory bodies across the globe such as the Food and Drug Administration (FDA), Food Safety and Standard Authority of India (FSSAI), etc., have set permissible limits on the presence of these adulterants [31,32]. Further, milk contamination by heavy metal (HM) residues is another significant issue of late. Various types of HM ions, primarily mercury, arsenic, cadmium, and lead, are found to be present in milk. They are often introduced during the

pasteurization process [33]. To prevent the consumption food elements containing HM, the World Health Organization (WHO) has implemented certain maximum permissible limits for the presence of these HM [34]. **Table 1.1** lists various kinds of adulterants being added in various food products and heavy metals present, along with their permissible limits, sources, and corresponding health hazards.

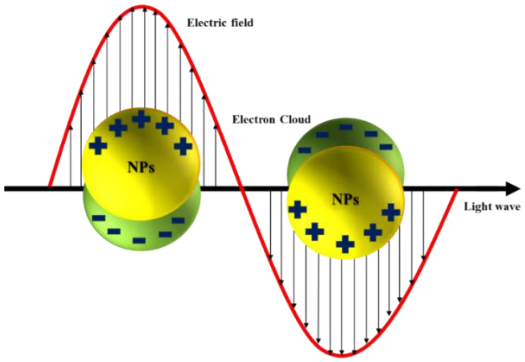

Figure 1.1: *Schematic illustration representing surface plasmon resonance in NPs.*

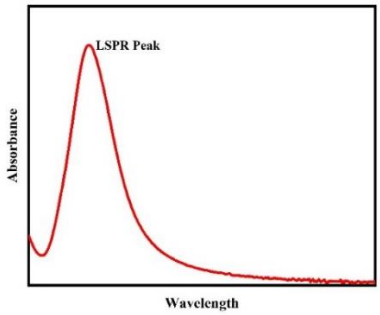

Figure 1.2: *Graphical illustration representing distinct absorbance spectrum in plasmonic NPs at resonance.*

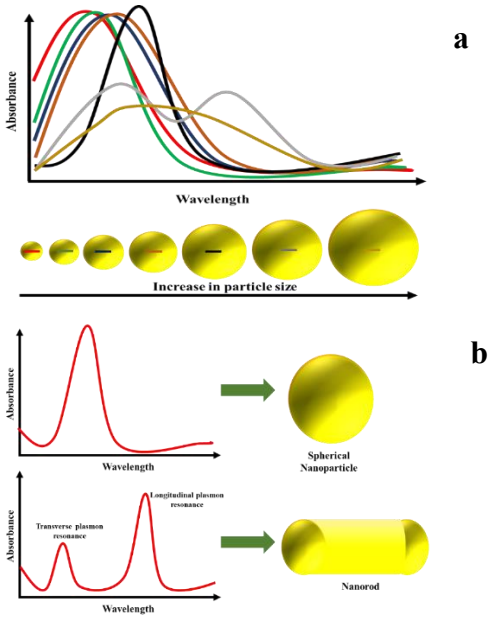

Figure 1.3: *Schematic representation displaying* ***(a)*** *shift in absorbance peak position with increase in NPs size and* ***(b)*** *dependence of absorbance with the shape of NPs.*

Table 1.1: *Prominent adulterants and contaminants, along with their sources, health effects, and permissible limits in food products, as assigned by FSSAI, FDA, and WHO.*

Adulterants/ Contaminants	Reason why added/ Source	Health Effects	Permissible Limit	References
Melamine	Falsify net protein content	Heart, liver, and kidney damage	2.5 ppm	[35]
Urea	Falsify net protein content	Gastrointestinal damage, and kidney failure	700 ppm	[36]
Formalin	Preservative	Cancer, and stomach ulcer	4 ppm	[37]
Hydrogen Peroxide	Preservative	Gastrointestinal problems, and skin problems	5 ppm	[38]
Salicylic acid	Preservative	Breathing problem, and fatigue	-	[39]
Mercury	Contaminated livestock feed, and pasteurisation process	Damages the central nervous system	2 ppb	[40]
Arsenic	Contaminated air, soil, and water can introduce it to the food chain	Cancer	10 ppb	[41]
Cadmium	Feeding of livestock in industrial areas, and through pasteurisation process	Kidney, bone and lung problem	5 ppb	[42]
Lead	Feeding of livestock near industrial areas	Damages brain functioning	10 ppb	[43]

As evident in Table 1.1., it is crucial to properly diagnose and quantify these hazardous adulterants and contaminants as all of them have serious health effects. Currently, the sensing procedures for detecting these substances are highly sophisticated and require trained personnel, which hinders regular monitoring of milk quality. Therefore, the situation demands for an urgent development of user-friendly detection techniques capable of identifying harmful adulterants just above permissible limits.

In response to these concerns, this research reported in the study focuses on the streamlined one-pot synthesis of plasmonic NPs using environmentally friendly or

chemical pathways, coupled with appropriate surface functionalization. The detection of various adulterants through various schemes has been presented in the thesis.

1.2 General introduction to milk adulteration and contamination

Milk is a fundamental dietary component consumed by millions of people worldwide, valued for its rich nutritional profile that includes proteins, vitamins, and minerals essential for human health [44]. However, the integrity and safety of milk are frequently compromised due to adulteration and contamination. These practices not only degrade milk quality but also incur serious health risks to consumers across all age groups, especially infants, children, and the elderly. It is a significant global issue that has persisted for centuries. Adulteration involves the addition of undesirable foreign substances to milk, which degrades its quality and makes it unsafe for consumption [32]. Common adulterants such as water, starch, detergents, and some synthetic chemicals such as melamine, urea, formalin, hydrogen peroxide, and salicylic acid are added [45,46]. Among these, adulterants having utmost concern are toxic substances such as melamine, urea, formalin, salicylic acid and hydrogen peroxide, where some of these substances are added to falsify the protein content. Meanwhile, others are used to preserve milk, but their presence can lead to severe health issues [32].

Melamine: It is organic compound which is highly rich in nitrogen with the chemical formula $C_3H_6N_6$. It is a white crystalline substance containing 66% nitrogen by mass. Primarily, it is utilized in laminates, production of melamine resins, adhesives, countertops, kitchenware, moulded products, coatings, and flame retardants. Melamine has a triazine ring structure with three amine groups (NH_2) attached to a central carbon and nitrogen framework. Due to its extremely hazardous nature, its use in food applications has been completely banned by governmental food regulatory bodies. Despite this, it is still added in milk so as to increase its non-protein nitrogen content. Tests such as the Kjeldahl and Dumas tests assess the net protein amount in milk by estimating its total nitrogen content [47]. Consequently, dealers intentionally introduce it into milk to augment its nitrogen levels, displaying a false increase in net protein content even after dilution of milk. The artificial elevation of nitrogen content falsely suggests a higher protein content in the milk. In 2008, a major food safety scandal emerged in China when it was discovered that melamine had been intentionally added to infant formula and milk

to falsely inflate the apparent protein content. As melamine is not meant for human consumption, its ingestion can result in kidney stones due to formation of melamine-cyanurate crystals in the kidneys which are highly insoluble, further their consumption can also cause renal failure, multi-organ damage and even death if consumed in larger amount. Infants and young children were particularly vulnerable to these adverse effects. The 2008 scandal affected thousands of children, leading to several deaths and widespread health problems. It also resulted in a massive recall of milk products and a significant loss of consumer confidence in dairy products [48].

Urea: It is a nitrogen-rich organic compound where a carbonyl group (C=O) is attached to two amine groups. It is commonly used in fertilizers to enhance soil fertility and promote plant growth. It is also found naturally in urine and is a key product of the nitrogen metabolism in humans and animals. It is illegitimately used as an adulterant to falsify net protein levels in milk. This form of adulteration poses health risks, as excessive urea intake can lead to kidney problems and other metabolic disorders [49].

Hydrogen Peroxide: It is generally a colourless liquid when diluted but appears to be a pale blue in its purest form. It is an inorganic compound where two hydroxy groups (OH) are attached via a covalent oxygen-oxygen single bond. It is utilised in diverse array of applications such as disinfectants, antiseptics, and treatment of waste water owing to its strong oxidizing properties. Due to which hydrogen peroxide can inhibit the growth of microorganisms, thereby increasing the shelf life of food items. However, due to its carcinogenic, toxic, and hazardous nature, all food regulatory bodies have imposed strict restrictions on its use in food products. Its consumption can cause serious health problems such as gastrointestinal damage, oxygen embolism, respiratory distress, and cellular damage [50].

Formalin: It is an aqueous solution of formaldehyde (CH_2O) in water, typically containing 37% formaldehyde by weight, along with a small amount of methanol to prevent polymerization. It is a simple aldehyde with one hydrogen atom bonded to a carbonyl (C=O) group, making it highly reactive. Formalin is used as a preservative for biological specimens and in the production of resins, plastics, and other chemicals. It is a highly toxic

carcinogen, and its consumption may lead to respiratory diseases, skin cancer, and eye irritation [32].

Salicylic acid: It is a beta hydroxy acid (BHA) commonly used in the treatment of skin conditions. It has a white crystalline texture and consists of a benzene ring with a carboxyl group (COOH) and a hydroxyl group (OH) attached, making it both a phenolic and carboxylic acid [51]. It is also used as a food preservative, lowering the pH of milk making less likely for microbial growth. It aids in locking the freshness of milk without the need for refrigeration. However, its addition in food items has been banned due to the ill effects associated with prolonged consumption, such as gastrointestinal issues, salicylate poisoning, and allergic reactions [52].

Meanwhile, milk contamination occurs when milk is exposed to harmful substances during production, processing, pasteurisation, or storage. Contaminants can be biological, chemical, or physical in nature [53]. In general, milk gets contaminated with HM residues which makes it unfit for consumption. HM ions such as lead, arsenic, cadmium, and mercury enter the milk supply through contaminated feed, water, or environmental exposure [33]. These contaminants can have chronic health impacts, including neurological damage and even cancer [54].

It is apparent that detecting adulteration and contamination in milk is critical for ensuring public health and safety. Traditional methods for sensing, e.g., gas chromatography (GC) [55], mass spectrometry (MS) [56], and high-performance liquid chromatography (HPLC) [57], are highly used for milk adulterant sensing. However, they are time-consuming and are highly expensive as they require trained personnel and specialized sophisticated equipment. Recent advancements in nanotechnology offer promising alternatives for milk quality monitoring. Plasmonic NPs, for instance, provide sensitive, rapid, and cost-effective detection methods for various milk adulterants and contaminants [58]. These sensors can be designed to alter their colour in response to the presence of certain specific analytes, allowing easy visual detection. Continuous monitoring and strict enforcement of these regulations are essential to protect consumers. Efforts are also being made to develop portable, user-friendly detection kits that can be used by non-specialists to ensure milk safety at various points in the supply chain. As such

plasmonic NPs has been proven as a promising sensing aid for various applications. In this doctoral thesis, the emphasis has been laid on sensing application of plasmonic NPs towards detection of milk adulterants and contaminants.

1.3 Metal NPs as plasmonic NMs

Depending on the number of dimensions in the nano-regimes the NSs are classified into varied categories, where NPs are referred to zero-dimensional (0D) structure where the motion of electron is confined along all the directions [59]. NPs which are composed of noble metals such as silver (Ag) and gold (Au), are used in varied application owing to their exceptional optical properties [60,61], which depends on their shape and structure. Metal NPs contain abundant free conduction band electrons that oscillate collectively when exposed to light of a specific frequency. This oscillation exhibits resonance, when the wavelength of the electromagnetic field and the physical properties of the NPs, such as size, shape, and surrounding environment, align optimally [4]. At resonance, the absorbance of the NPs increases significantly, the wavelength at which this resonance occurs is known as surface plasmon resonance (SPR) [5] and as the motion of electrons are confined, this kind of resonance is known as LSPR [5,6]. Due to this feature noble metal NPs are often termed as plasmonic NPs. The oscillation of the plasmons occurs due to opposite pull of the restoring force of the nuclei and the electric force of the electromagnetic wave [7].

1.3.1 Properties

Properties of these plasmonic entities can be tuned by altering their shape, size and morphological composition. It also depends on the external surroundings. Salient properties of these plasmonic NPs are appended below.

1.3.1.1 Optical properties

Plasmonic NPs display extraordinary optical properties primarily due to LSPR phenomenon. The LSPR frequency relies on the shape, size, dielectric environment and composition of the NPs. For example, gold nanoparticles (AuNPs) and silver nanoparticles

(AgNPs) typically exhibit LSPR in the visible range [62]. AgNPs are generally yellow in colour and they display a strong surface plasmon resonance between 390-440 nm [63]. As the particle size increases, the position of maximum absorbance shifts towards higher side of the wavelength [64]. Similarly, AuNPs show a strong surface plasmon resonance between 510–530 nm [65]. For instance, these noble metals can almost display any colour and possess diverse absorption bands in any part of the visible spectrum owing to different shape and size of the NSs [66]. Literature reports NMs of varied shapes such as nanorods (NRs), nanowires (NWs), nanocages (NCs), nanospheres (NSPs), nano prisms (NPRs), and nanoplates (NPLs) or nanosheets (NSHs), where all these NSs show absorbance at various wavelengths and display different colours depending on their shape and size [67]. The colour displayed by the NPs is the colour reflected by the NPs due to interaction between the incident light with the NPs [68].

Complex anisotropic NSs exhibit additional plasmonic modes due to their geometry, resulting in a greater number of degrees of freedom in their optical properties. While Mie theory provides an accurate estimation of the absorbance and scattering wavelengths for spherical NPs smaller than the wavelength of incident light, it is less accurate for anisotropic structures. For such NPs, extended theoretical models are required to account for shape-dependent optical effects [69]. Compared to spherical NSs, anisotropic entities provide a larger tuneable LSPR maxima. As for instance, NRs display strong absorbance in the near infrared region [70].

The position of LSPR band is also highly sensitive and can be altered by changing the local refractive index of the surrounding media [71]. This sensitivity is exploited in LSPR-based sensors, where binding of the NPs to the surface resulting in significant shifts in the LSPR peak, allowing detection of various analytes [72]. The plasmonic NPs are also highly stable even under intense light irradiation, and are capable of maintaining their optical properties for long-term applications [73].

1.3.1.2 Morphological properties

Likewise, the morphological characteristics of plasmonic NPs strictly depend on the shape, size, surface structure, and distribution of the NPs. This plays a pivotal role in determining their optical properties. The diameter of NPs directly influences the LSPR peak position

[10]. Smaller NPs tend to have LSPR peaks at lower value of wavelength, while larger NPs shift the LSPR peak towards higher side of wavelength [74]. Dispersity of particles is also crucial in determining the broadness of LSPR peak [75]. While colloidal NPs solution containing particles of uniform size possess narrow LSPR band, broad size distribution results in broadened peaks. This consequently can affect the sensitivity and specificity in applications like sensing [76]. The number of LSPR peak also depends on the shape of NPs, NSPs exhibit a single LSPR peak, whereas, NRs have two distinct LSPR peaks one corresponds to the longitudinal and another corresponds to the transverse oscillations of electrons [77]. Cubic NSs exhibit sharp corners and edges, leading to enhanced electromagnetic fields at these locations. This makes them highly effective for surface-enhanced Raman scattering (SERS) sensing applications [78].

A smoother surface of NPs results in more stable plasmonic properties compared to rough surfaces [79]. Functionalizing the surface with specific molecules can enhance the selectivity and sensitivity of the NPs for particular analytes. This modification can also prevent aggregation and improve biocompatibility [80].

1.3.1.3 Structural properties

Meanwhile, the structural properties of plasmonic NPs can be extensively studied utilising X-ray diffraction (XRD) techniques [81]. Plasmonic NPs such as AgNPs and AuNPs are generally crystalline in nature and thus, they display distinct peaks corresponding to the crystallographic planes of the NPs at specific 2θ values. Peaks such as (111), (200), (220), and (311) are commonly observed for these metals, which suggests that these metal NPs are generally face centred cubic (FCC) in nature [82-84]. Narrow diffraction peaks indicate larger crystallite sizes, whereas broad diffraction peaks suggest smaller crystallites [85]. A significant amount of shift in the position or any kind of asymmetry indicates presence of defects, which influence the plasmonic properties of the NPs [86].

1.3.2 Synthesis of plasmonic NMs

NPs are, in general, synthesised by adopting two routes—one of which is Top-down approach and another is bottom-up approach [87]. Generally, for synthesis of plasmonic NPs, the latter one is more often used as compared to the former one. Further, various

ways for synthesizing metal NSs can be classified into chemical route, physical route and biological or greener methods (**Fig. 1.4**). By using these methods, NSs of different shapes and sizes can be synthesized [88-90].

Chemical synthesis: Chemical reduction mode is one of the most preferred methods for synthesis of NSs due to its cost effectiveness and simplicity [88]. It involves the use of metallic salt, reducing and a stabilizing agent. Here, reducing agent reduces the metallic ions present in the solution of metallic salt into metal NPs and the stabilizing agent stabilizes the NPs which prevents it from further aggregating [91]. Generally, for chemical synthesis of AgNPs, sodium borohydride ($NaBH_4$) and trisodium citrate (TSC) are used as both reducing and stabilizing agent and silver nitrate ($AgNO_3$) is used as silver precursor as the source of silver ion (Ag^+) in the solution [92,93]. Whereas, for synthesis of AuNPs, generally TSC is used as both reducing and stabilizing agent and chloroauric acids ($HAuCl_4$) as the metallic salt precursor. Synthesis of NPs occurs by constant stirring of the solution in a magnetic stirrer at a specific temperature and pH [94].

Hossain *et al.,* synthesized spherical shaped AgNPs of size 5.7 nm, where they used hydrazine as reducing agent [95]. Hussain *et al.,* synthesized AuNPs using ascorbic acid (AA) as reducing and polyvinyl pyrrolidine (PVP) as the stabilizing agent at a pH of 10.5 [96]. Moukarzel *et al.,* synthesized Au nanostars by adding glucosamine to $HAuCl_4$ and further adding mercaptoacetic acid to it to quench the growth of nano stars [97].

***Physical Synthesis*:** Physical mode for synthesis of NSs is one of the most difficult modes as it requires use of highly sophisticated instruments. Despite the varying range of difficulties, this mode becomes one of the top most used modes for synthesis of NSs as this offers complete control on the structure and morphology of the NSs synthesized [98]. This mode is based on transfer of energy occurring in a material when illuminated under any kind of ionizing or non-ionizing radiation—thereby resulting in nucleation in metallic particles [99]. Some of the most used for physical modes for synthesis of NPs are sputtering [100], condensation via inert gas [101], laser ablation [102], sonochemical reactions [103], ionizing radiation [104], gamma irradiation [105], microwave radiation [106], galvanic replacement method [107] etc. Some of the advantages associated with the

use of this method are that in this method no solvent is required. Thus, the NSs are free from solvent contamination and are of uniform size and distribution [108].

Jung *et al.,* synthesized AgNPs of size 6.2-21.5 nm by using a ceramic heater to evaporate metal, when the metal vapor cools down, it facilitates the formation smaller sized, and stable NPs [109]. Mafune *et al.,* used laser ablation mode for synthesis of AgNPs which facilitated formation of uncontaminated metal NSs [110,111]. Tien *et al.,* used the arc discharge method for synthesizing AgNPs where Ag wires were used as electrodes, along with a Ag rod which resulted in the formation of AgNPs of size 10 nm [112]. Siegel *et al.,* synthesized AgNPs sized 3.5 nm by sputtering process [113].

Green synthesis: Biological mode for synthesis of NSs is one of the most favourable modes of synthesis as it is an eco-friendly, cost effective, and biocompatible mode, which reduces the cytotoxicity of end product. In this route, instead of using chemical reducing or stabilizing agent, fruit, plant and many more biological extracts are used to naturally prepare NPs of various shapes and sizes. In case of green extracts, sometimes the reducing agent also helps in stabilizing the NPs [114].

Asnag *et al.* used *Solanum nirgrum*, *Ricinus communis* and *Morus nigra* extracts for synthesis of AuNPs [115]. Lee *et al.,* synthesized AuNPs using *Camellia sinensis* extract. For synthesis of spherical AuNPs, at first, they prepared the extract solution, then it was added to $HAuCl_4.3H_2O$. Finally, sodium hydroxide (NaOH) was added to it which was then incubated at 80 °C for a period of 2 h [116]. Mohapatra *et al.,* prepared AgNPs by using *Piper nigrum* seeds extract as the reducing agent, with the extract solution being prepared first. After which $AgNO_3$ was added to a small amount of the extract and the resulting solution was stirred for 2 h [117]. Varshney *et al.,* also used the similar method to synthesize AgNRs and AgNCs by using *Stevia rebaudiana* leaves extract. The NRs were of diameter ranging between 80-200 nm and of height 400-800 nm and the NCs were of size range between 55-80 nm [118].

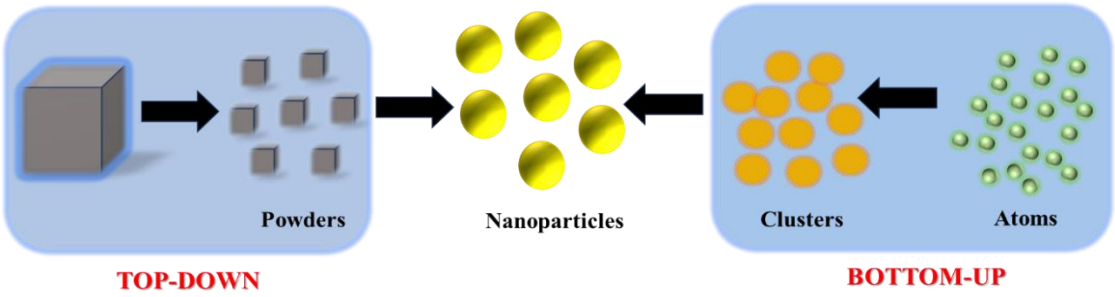

Figure 1.4: *Schematic representation depicting synthesis of NPs.*

1.4 Literature review

As described in the previous section, it is evident that plasmonic NPs show enhanced absorbance at plasmonic wavelength which can be tuned by altering their size, shape, surface functionalisation, composition, and external media. This property of plasmonic materials can be used in various sensing applications, especially targeting the problem of detection of milk adulteration and contamination.

Plasmonic NSs, used as colorimetric sensors, have gathered heightened attention in recent research due to their cost effectiveness, simplicity, and high specificity. These sensors allow qualitative analysis of the presence of any analyte by observing the change in colour of the NP solution with naked eye, eliminating the need for any sophisticated or expensive devices. This technique enables point-of-care analysis of analytes, providing a practical solution for detecting milk adulteration. This mode of sensing is based on three schemes: rapid aggregation-based, interference-based interaction, and non-aggregation oxidation-based sensing [119-121]. The first one relies on the immediate decrease in interparticle distance. Whereas, in the later one the analyte inhibits the growth of metal NPs and third one based on oxidation of NPs by an analyte which needs to be a strong oxidising agent. All of them result in spectral shifts, causing colour change [121].

Ma *et al.* developed dopamine-functionalized AgNPs for colorimetric detection of melamine in raw milk, achieving high selectivity and dynamic sensing range between 10 ppb-1.26 ppm [122]. Similarly, Kumar *et al.* also fabricated another colorimetric detector for sensing melamine in milk, with a limit of detection (LOD) of 0.05 mg L^{-1} [123]. Dutta *et al.* created a colorimetric probe for sensing urea in milk using green tea-synthesized AgNPs, with a LOD value of 1 mM [124]. Aquino *et al.* synthesized

resorcinol-functionalized AuNPs for formaldehyde detection in an aqueous medium; the NPs' colour changed to blue from red in the presence of formaldehyde [125]. Teodoro *et al.* fabricated cellulose nano whisker-functionalized AgNPs for hydrogen peroxide detection, achieving a LOD of 0.014 μM [121]. Aftab *et al.* synthesized selenium NPs (SeNPs) for colorimetric sensing of salicylic acid in milk, using garlic as both a stabilizing and reducing agent. This method achieved a detection limit of 10^{-3} M [126].

Gao *et al.* developed Triton X-100 modified AuNPs for melamine sensing using a smartphone-based colorimetric system. The presence of melamine resulted in a colorimetric change of NPs to blue from wine red, with a LOD of 5.1 nM [127]. Mirzae *et al.* created sericin-capped AgNPs for detecting hydrogen peroxide in milk using an origami paper substrate, achieving a LOD of 0.15 mg/dL [128]. Seebunrueng *et al.* designed a paper-based vapor-test kit coated with Nash's reagent for formalin detection with a LOD of 0.11 mg L^{-1} [129]. Shrivas *et al.* reported a paper-based colorimetric sensor using AgNPs for detecting mercuric ions (Hg^{2+}), achieving a LOD of 10 μg L^{-1} [130]. Similarly, Wi *et al.* fabricated a colorimetric sensor on a paper substrate for detecting arsenic (V) (As^{5+}) using methylene blue-functionalized AuNPs [131]. Wang *et al.* developed a colorimetric fluorescent sensor for detecting cadmium ions (Cd^{2+}) by using glutathione-stabilized Au nanoclusters with ethylenediamine functionalized graphene oxide (GO) along with copper ions (Cu^{2+}). The LOD of the fabricated device was 0.1 μM [132]. Sahu *et al.* developed a paper-based dual colorimetric sensor for simultaneous detection of As (III) (As^{3+}) and Pb (II) (Pb^{2+}) using glucose-functionalized AuNPs, achieving LOD of 5.6 μg L^{-1} for As (III) and 7.7 μg L^{-1} for Pb (II), respectively [133].

Additionally, some studies have reported simultaneous detection of multiple adulterants. Guinati *et al.* fabricated a paper-based sensing scheme for simultaneous colorimetric sensing of hydrogen peroxide, urea, and pH in milk samples using microfluidic based paper pads. The LOD for hydrogen peroxide and urea were 0.1 mM, and 2.4 mM, respectively [134]. Patari *et al.* developed another paper-based microfluidic sensor for detecting seven adulterants: urea, soap, detergents, hydrogen peroxide, starch, salt, and sodium hydrogen carbonate, achieving LOD ranging between 0.05% (vol./vol.)-0.2% (vol./vol.) [135].

LSPR-based sensing using metal NPs enables the detection of target analytes with high selectivity and sensitivity, and low detection limits with high cost-effectiveness. This method can be used to detect food adulterants and contaminants, in medical diagnosis, and for detecting environmental pollutants, etc [136]. For LSPR sensing, optical fibres and glass slides can serve as substrates where NSs of various shapes are immobilized and selectively functionalized to bind with target analytes. The binding of NPs with an analyte changes the local refractive index of the surrounding media resulting in a shift of the LSPR absorbance peak. The amount of peak shift helps to determine the amount of the target analyte.

Oh *et al.* developed a cuvette-based LSPR sensor for detecting melamine in milk using a glass chip immobilized with p-nitroaniline (p-NA) functionalized AuNPs, achieving a LOD of 0.5 ppm [137]. Hedge *et al.* fabricated a glass chip-based amino thiophenol functionalized AgNCs LSPR sensor that could detect formaldehyde with a sensitivity of 161 nm per refractive index unit (RIU) [138].

Plasmonic NPs are also utilized as electrochemical sensors due to their high surface area-to-volume ratio, which facilitates significant analyte adsorption on the NP surface. These sensors offer easy selectivity through functionalization, rapid response times, reusability (as they remain intact after multiple cycles), and high stability [139]. Daizy *et al.* conducted electrochemical sensing of melamine using a reduced Graphene Oxide (rGO)–Copper Nanoflowers Modified Glassy Carbon Electrode (GCE). Cyclic voltammetry (CV) measurements showed that the dynamic range of sensing of the sensor is between 10×10^{-9} to 9.0×10^{-8} M, with a LOD of 5.0×10^{-9} M [140]. An *et al.* developed a screen-printed carbon electrode (SPCE) modified with ferrocenylglutathione and melamine. This modified electrode exhibited an enhanced signal in the presence of melamine, with linear results obtained between 0.20-2.00 μM and 8.00-800 μM, along with a sensitivity of 15.03 $\mu A \cdot \mu M^{-1} \cdot cm^{-2}$ [141]. Magar *et al.* fabricated a non-enzymatic electrochemical impedimetric sensor for urea determination using modified screen-printed electrodes (SPEs), achieving a LOD of 0.223 pM [142]. Sangkaew *et al.* developed bimetallic Au-platinum NPs (AuPt NPs) for detecting hydrogen peroxide in milk by enhancing the electrochemical signal of H_2O_2, obtaining a LOD of 4.8 μM [143].

Despite the significant advancements in plasmonic NSs for sensing applications, several challenges and limitations persist, which served as the motivation for this thesis. Many existing methods suffer from limited sensitivity, failing to detect adulterants or contaminants at trace levels in complex matrices like milk, leading to false negatives or inaccurate results. Additionally, some sensors have a narrow detection range, making them unsuitable for detecting varying levels of adulterants. The interference from milk's complex composition, including proteins, fats, and other natural components, further reduces the accuracy and specificity of detection. Furthermore, several techniques are hindered by high costs, complex synthesis processes, or the need for expensive functionalizing agents, which limit their scalability and practicality. Many methods are also designed for single-adulterant detection, lacking the capability for simultaneous detection of multiple adulterants, which is crucial in real-world applications. Reproducibility issues due to variability in NP synthesis and functionalization also affect the consistency and reliability of sensor performance. While some sensors enable point-of-care analysis, many still rely on laboratory-based setups, limiting their field applicability. Moreover, environmental concerns associated with the synthesis of NPs using hazardous chemicals or generating waste highlight the need for more sustainable approaches. These limitations underscore the necessity for innovative, sensitive, cost-effective, and sustainable sensing platforms, which this thesis aims to address by developing a more efficient approach for detecting milk adulterants using plasmonic NSs.

1.5 Objectives of the present study

The objectives of the thesis are framed as follows:

1. ***Facile Synthesis of Plasmonic NSs via Green and Chemical Routes***: To synthesize plasmonic NSs using eco-friendly materials like plant extracts (green synthesis) and chemical reagents to control NP size, shape, and dispersion (chemical route).
2. ***Characterization and Optimization of these NSs:*** To characterize the synthesized NCs and optimize their properties for enhanced performance in sensing applications.
3. **Detection of Adulterants Using Different Sensing Schemes as per following:**
   a) Colorimetric Sensor (both with and without substrate): To develop and

evaluate a colorimetric sensor utilising plasmonic NSs, where the presence of adulterants induces a colorimetric change. This sensor will be tested both with and without the use of a substrate.

b) Localized Surface Plasmon Resonance (LSPR)-based Sensor: To fabricate and optimize an LSPR-based sensor using plasmonic NSs, where the interaction of adulterants with the NPs leads to a shift in the resonance wavelength, enabling highly sensitive detection.

c) Electrochemical Sensor: To develop and optimize an electrochemical sensor using plasmonic NSs, where the presence of adulterants causes measurable changes in the electrochemical response.

4. ***Comparative Analysis of Sensing Platforms:*** To perform a comparative evaluation of the different sensing platforms to assess their sensitivity, specificity, and practicality for detecting milk adulterants.

1.6 Outline of the thesis

Keeping the objectives in mind, the detection of various adulterants in milk through various schemes has been presented in the thesis in the form of various chapters. The outcomes of the entire study are organized into several parts in the form of chapters. The thesis has been designed as follows.

Chapter I begins by discussing the problem of milk adulteration and contamination, introducing various categories of metal NPs and highlighting their tuneable plasmonic properties. It explores the key characteristics of these NPs, including their optical, morphological, and structural properties, and examines their potential applications as sensors to detect milk adulterants. It further discusses the synthesis methods for plasmonic NSs, focusing on their role in sensing applications. The chapter also provides an overview of the limitations of previously reported detection methods for milk adulteration. The chapter concludes by outlining the objectives and structure of the thesis.

Chapter II is subdivided into two parts.

The **part A** of ***Chapter II*** explores various synthesis and selective functionalization routes for AgNPs fabrication. It highlights *Camellia sinensis*-functionalized AgNPs for

melamine sensing, *Bombax ceiba*-functionalized AgNPs for hydrogen peroxide detection, L-cysteine-functionalized AgNPs for formalin sensing, and *Citrullus lanatus* rind extract-functionalized AgNPs for salicylic acid detection in milk. UV-Vis responses were used to determine selectivity, sensitivity, recovery, and detection limits.

The **part B** of ***Chapter II*** discuses a paper-based sensing method using functionalized AgNPs to simultaneously detect multiple adulterants and contaminants. The paper features seven conduits with selectively impregnated ends, changing colour upon exposure to adulterated milk. Red, green, & blue (RGB) and hue, saturation & value (HSV) data were used for obtaining calibration plot, demonstrating high sensitivity for detecting melamine, formalin, hydrogen peroxide, mercury, arsenic, cadmium, and lead ions in milk.

Chapter III focuses on localized surface plasmon-based sensing for various milk adulterants, highlighting the importance of NP immobilization. Selectively functionalized NPs, such as maleic acid-functionalized AgNPs for melamine, were immobilized on glass substrates and further functionalized. These glass chips, containing immobilized AgNPs, were used in cuvette cells with standard UV-Vis spectrophotometry to detect interactions with analytes, resulting in significant peak shifts. These shifts were used to create calibration plots to estimate detection limits. Similarly, polyvinyl alcohol (PVA)-functionalized AgNPs were used for hydrogen peroxide detection, with peak shifts calibrating detection limits for each adulterant.

Chapter IV discusses the electrochemical schemes for detecting milk adulterants. Functionalised NPs such as (3-Aminopropyl)triethoxysilane (APTES)-coated, green tea-reduced AuNPs were deposited onto an indium tin oxide (ITO) electrode were used for urea detection, with cyclic voltammetry showing increased oxidation peaks with rising urea concentration. Similarly, melamine was detected using poly-ethylene glycol (PEG)-coated, maleic acid-functionalized AgNPs on an ITO electrode, and hydrogen peroxide was sensed using polyvinyl pyrrolidone (PVP)-functionalized AgNPs. Calibration plots determined detection limits and sensitivity.

Chapter V presents a comprehensive comparative study, where the current work is meticulously compared with previously reported studies in the literature. This analysis

highlights the innovative aspects and novelty of the present research. Additionally, a comparative evaluation of all sensing architectures introduced in this work is provided, emphasizing the advancements and contributions made by the current study.

Chapter VI summarizes all the key findings of the thesis and discusses all reported works. It also outlines prospects for future investigations based on the presented work.

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