Colloidal gold as innovative raw material in pharmaceutical industry

Keywords: Nano gold, cytotoxic effect, properties of scavengers, immune system, Immunoglobulin E-Reduction, lecithin coating

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1. Properties of colloidal gold

Gold is a natural product and as old as the earth. Colloidal gold is certainly found in the nature, e.g. in marine waters. In marine waters soluble gold salts build colloidal gold reductively together with organic matter.
Colloidal gold has different colors depending on different particle size. Particles of ca. 5 nm appear yellow-orange. Particles from 100 nm on appear violet.

In biomolecules colloidal gold binds particularly on sulfur containing functional groups. Because of the high symmetry of the multi-atomic gold clusters colloidal gold exhibits a high surface potential. Therefore it can be loaded with active ingredients or with DNA-components (see e.g. FAZ from 30.5.06: „Gentaxis aus purem Gold“).

2. State of scientific discussion

Colloidal gold exhibits a broad application spectrum in medical research. E.g.: Cytotoxic active ingredients can, under favorable conditions, directly be implemented at the location of the cancer, without harming the whole organism, as it is the case in chemotherapy. Due to the high surface to volume ratio the small gold nano clusters can also save resources and is the cheaper to handle.

2.1 The application of colloidal gold in cancer therapy

…”Because of their …biocompatibility gold nanoparticles have proven to be powerful tools in various nanomedicinal and nanomedical applications”…
These applications refer amongst others to the use of colloidal gold loaded with active ingredients in cancer therapy, whereas the efficiency increases with decreasing particle size. The efficiency varies as due to different surface stabilization. Another application lies in the colloidal gold itself, that means without loading with active ingredients (e.g. certain proteins and antibodies). In experiments this has shown cytotoxicity for diverse cancer cells.
P. C. Chen et.al. Nanotechnology, Science and Applications 2008, I, p. 45 – 66: “Gold Nanoparticles: From Nano medicine to Nano sensing“ (Institute for Bioengineering and Bioscience, Atlanta, USA).

2.2 The application of colloidal gold as scavenger

The properties of scavengers, opposite to peroxide radicals, that are discharged out of mitochondria and that negatively affect surrounding DNA-components, are impressively approved by the following publication:
……"studies with immune system cells also showed that gold nanoparticles were not cytotoxic and that they reduced the amount of potentially harmful reactive oxygen species in the cells"…
C.J. Murphy et.al. Gold Nanoparticles in Biology: Beyond Toxicity to Cellular Imaging in: Accounts of chemical research, University of Virginia, (2008) http://pubs.acs.org (8.3.2011)

2.3 The effect of colloidal gold on the immune system

…"Both gold nanoparticles and their antigen conjugates stimulated the respiratory activity of the macrophages and the activity of macrophage mitochondrial enzymes… Due to the surface potential of colloidal gold it binds in the organism directly on protein- or DNA-components. Therefore it is phagozyticed by macrophages. Quickly growing cells would accumulate more colloidal gold and therefore provoke an amplified antibody-antigen-reaction:
…our data show that colloidal gold is not toxic to the phagocytic peritoneal cells and that it even alleviates the effect of the toxic antigen conjugated to colloidal gold"…
The positive effect on the immune system corresponds with the application of colloidal gold in cancer therapy. According to modern cancer therapy the phagozyticed B-cells of the immune system display the cellular main defense to cancer cells. Accompanying mechanisms similar to inflammation correspond with the release of certain messengers in the body.
S.A. Staroverov et.al., Gold Bulletin, Vol. 42, No. 2 (2009): "Effect of gold nanoparticles on the respiratory activity of peritoneal macrophages" (Institute of Biochemistry and Physiology of Plants and Microorganisms, Russian Academy of Sciences, Saratov, Russia)

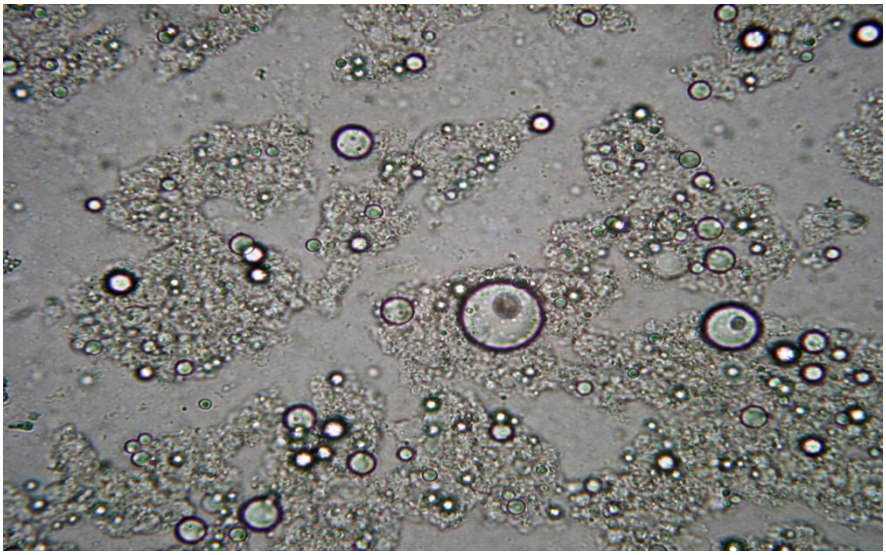
2.4 Effect of colloidal gold on the complex actions of the immune system

…"the analysis of the viability of the cells after their incubation in the presence of gold nanoparticles shows that these nanoparticles are not cytotoxic even at high concentration…Furthermore the secretion of cytokines is significantly modified after such internalization"…(with gold nanoparticles)…
C.L. Villiers et.al. J. Nanopart. Research (2009) (Centre de Recherché Albert Bonniot, Grenoble, France)

3. Study results of colloidal gold

Lecithin coated colloidal gold lead under appropriate process conduct to particles with sizes in µm-area. (See also patent application DE102009042459A1 from 7.4.2011 "Modified colloidal noble metal for therapy and prophylaxis of illnesses")

The following figure 1 shows lecithin coated colloidal gold in µm-size, optical enlargement 1:400



The single spherical particles of violet lecithin coated colloidal gold exhibit an average size of ca. 5 -20 µm.

The degree of lecithin coating is shown in figure 2:

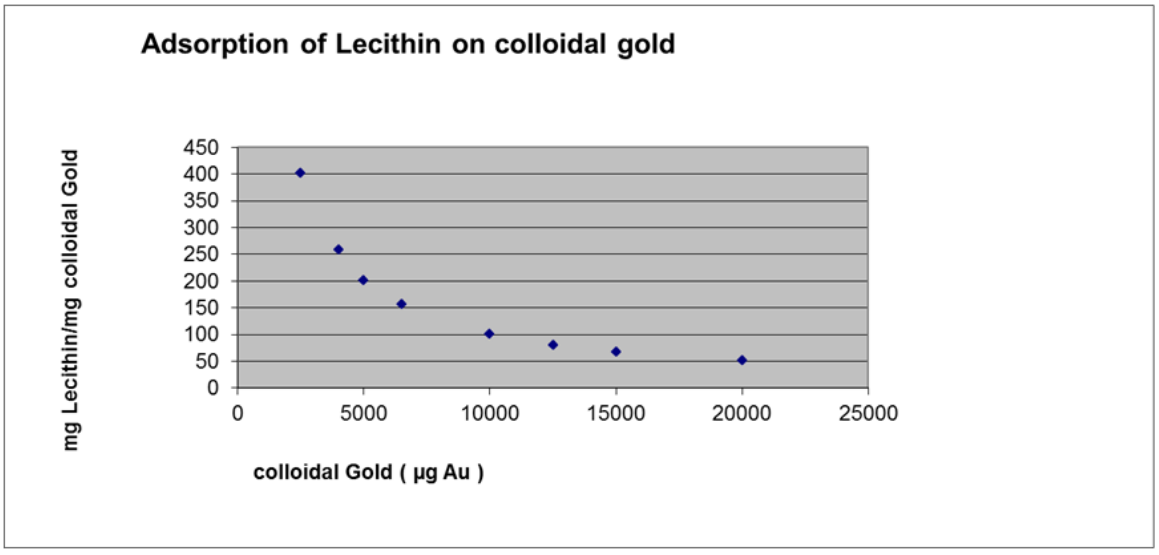


Figure 2: Load of lecithin with colloidal gold

As shown in figure 2 the load lays the load in the area of 44 – 500 mg lecithin per µg colloidal gold. For methodic reason it was not possible to measure higher lecithin loads.

Lecithin coated colloidal gold shows very interesting properties as light stabilizer:
It has the advantage that it is not affected by the Estradiol-discussion of organic light stabilizer. It absorbs UV A-, B- and C-Radiation completely already in the ppm-area (see figure 3).

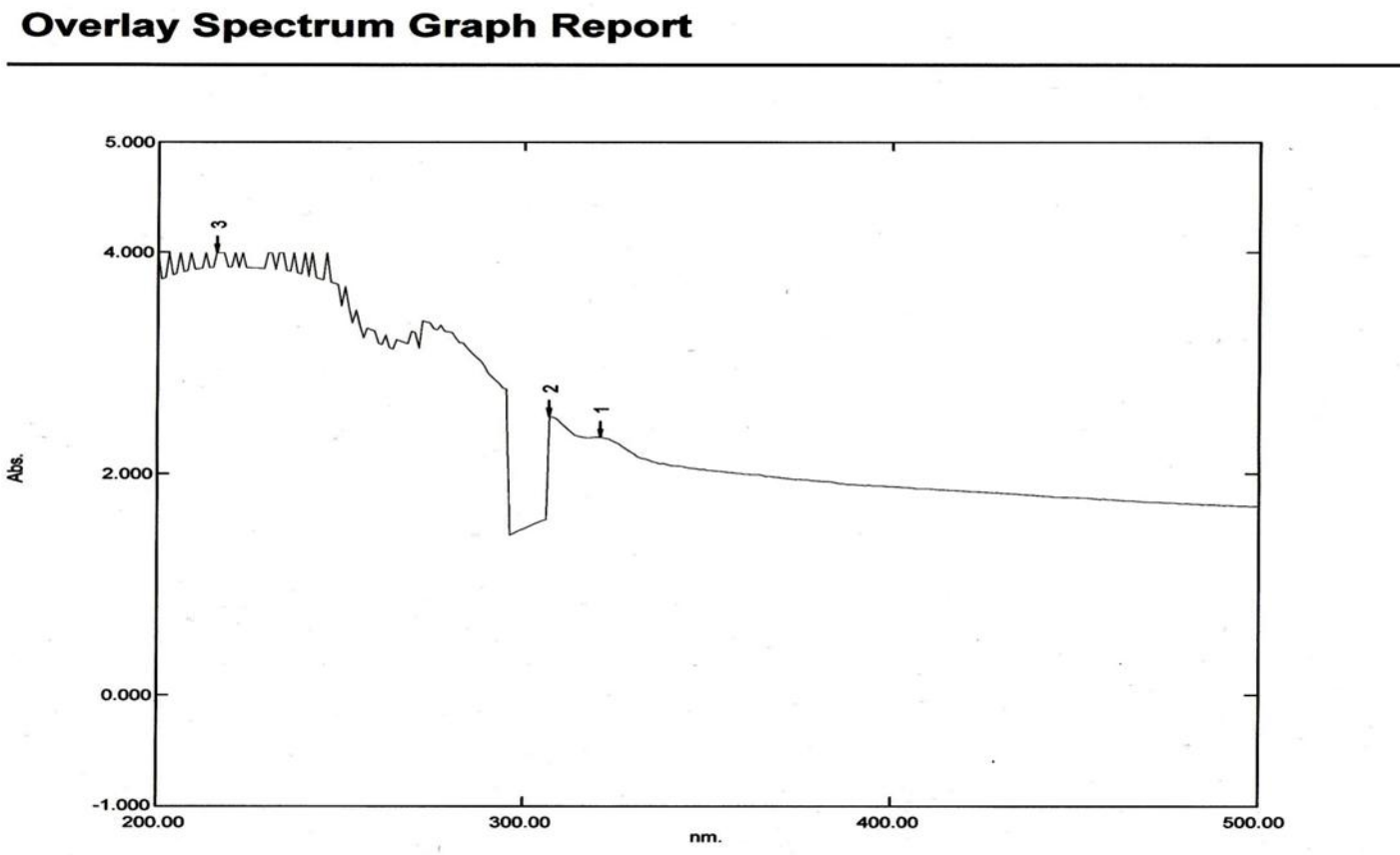


Figure 3: UV-absorption of lecithin coated colloidal gold (at 300 nm the light source is changed, which is included in the figure)

3.1 Drug packaging from polystyrene with UV-protection out of colloidal gold

Drug packaging charged with colloidal gold can have certain advantages:

- UV-protection
- germ reduction

Through the doping of polystyrene with colloidal gold the UV-light-absorption is clearly increased in comparison to pure polystyrene. Therefore, drugs and particularly antibiotics can be stored longer without harming the action of the drug by decomposition of the active ingredients by UV-Radiation. Figure 3a shows the absorption of nano gold doped polystyrene in comparison to pure polystyrene.

Figure 3a “Pure” polystyrene without doping. UV-A-Radiation is absorbed completely only at ca. 350 nm. UV-B and UV-C are absorbed completely by polystyrene.

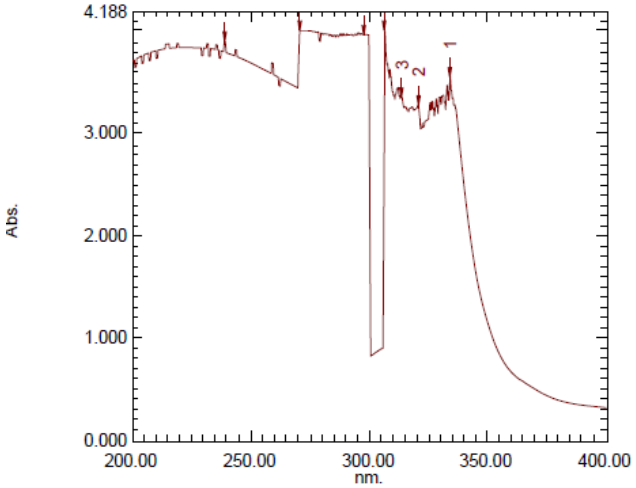
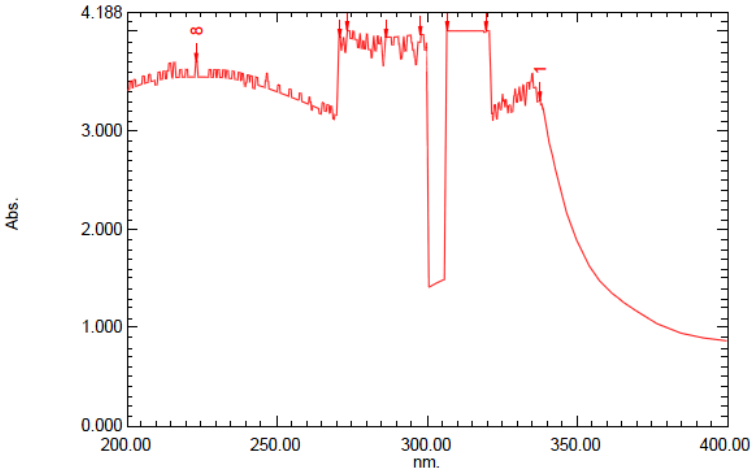


Figure 3b, Polystyrene with 600 ppm Au. UV-A-Radiation is absorbed at ca. 385 nm. UV-B and UV-C are absorbed completely by polystyrene.



3.2 Assessment of germ reduction action of polystyrene doped with colloidal gold

In order to examine the antimicrobial efficiency a microbial test of polystyrene with and without doping is performed. Therefore, polystyrene coated glass plates are suspended in a solution containing E.coli (Escherichia coli, a typical fecal germ, which is to be found in human and animal intestine) and Staphylococcus aureus (a dermal germ). The germ suspension contains ca. 10^5 CFU (colony forming unit) per mL. The glass plates are suspended in the above mentioned germ suspension. After a period of 2 hours and 24 hours the glass plates are removed from the suspension, put in a sterile container and are dried. After drying of the samples the germs are suspended in 100 mL sterile NaCl (Sodium chloride) and the germ number is measured. After this the germ number of a reference sample without doting of noble metal is measured. This germ number counts as baseline. The baseline is at $5 * 10^5$ CFU/mL.

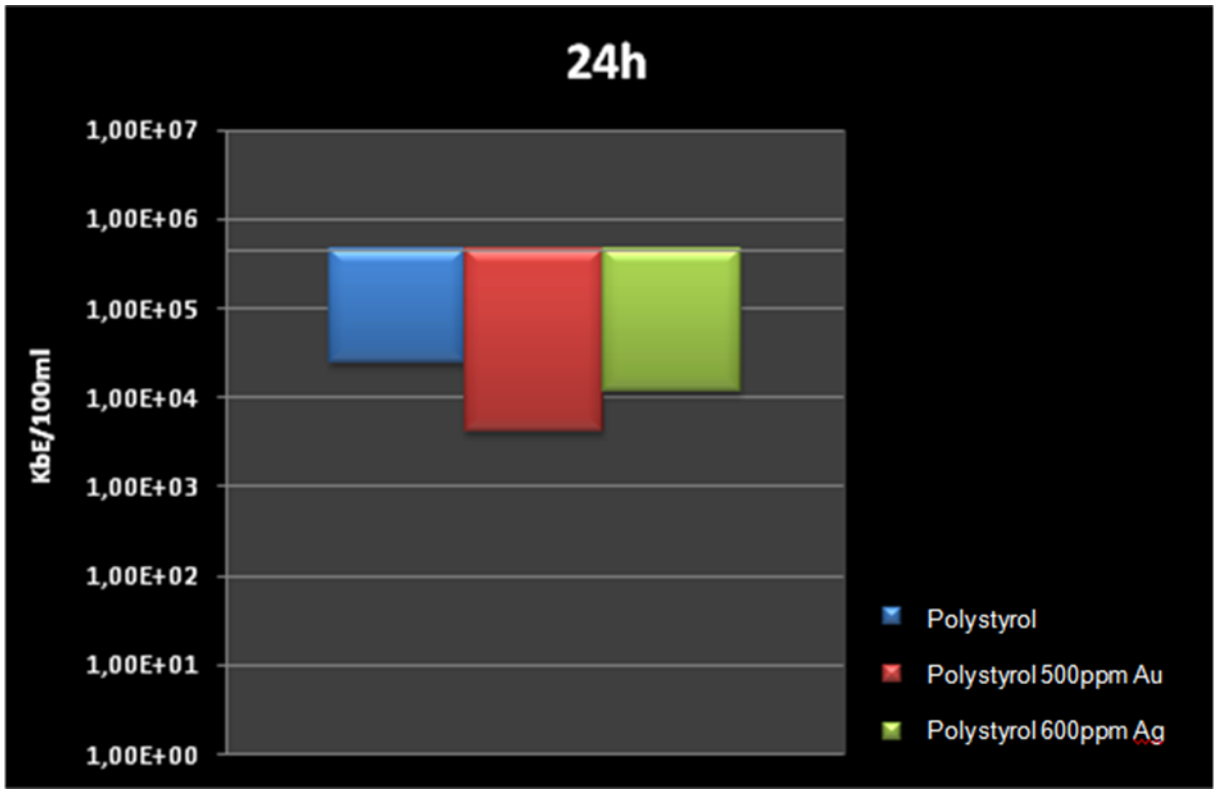


Figure 3c: Germ number after 24 hours of incubation

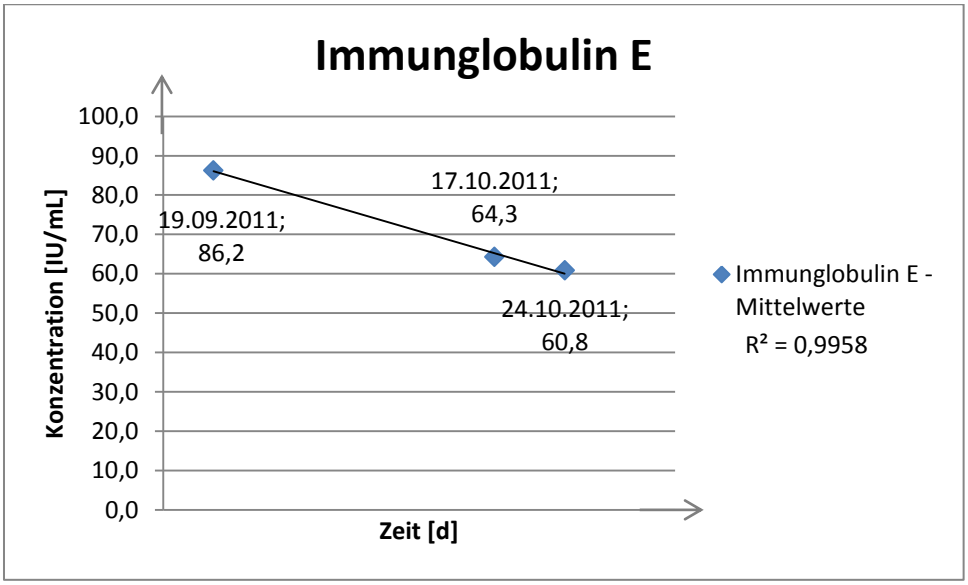
Figure 3c shows the influence of the silver doping (green bar) and gold doping (red bar) on the germ number after 24 hours of incubation in comparison to polystyrene coated glass plates without coating (blue bar). After 24 hours of incubation the germ number of the treated polystyrene was reduced by ca. 1 log-unit more than by the “graphic” reduction of the untreated polystyrene. The “graphic” reduction by untreated polystyrene is equivalent to the failure of the microbial systematic analysis.

3.3 Results of a four week study with three probands taking lecithin coated colloidal gold orally

A four week study was taking out, where three voluntary probands took 100 µg lecithin coated colloidal gold daily. The aim of the study was, to evaluate generally the tolerance of the preparation. The probands underwent regularly laboratory control to assess possible effects on the immune system. The blood picture, the humoral and cellular control and the effect on the metabolism, on liver and on kidney were observed. There was no abnormal blood picture observed at any of the probands. Deviation of the single laboratory parameters was concordant within the normal limits except for one sample. No evidence was found concerning potential harming of the apparatus.

The concordantly and proportionally reduction of immunoglobulin E was eye catching. Considering the immunomodeling properties of gold, there are possible

effects of the used formulation on allergies or allergic reaction to be discussed (see also following figure 6).



Results [IU/mL]	19.09.2011	17.10.2011	24.10.2011 (one week after daily intake)	Reference range per measurement
Proband 1	210,8	151,4	143,1	< 85
Proband 2	27,2	23,5	22,0	< 85
Proband 3	20,7	17,9	17,4	< 85
Mean value	86,2	64,3	60,8	< 85

Figure 4 and related table: linear reduction of the Immunoglobulin E of the realized three proband study

The measurements of the immunoglobulin E are interesting, because they show a concordant negative slope. According to the coefficient of determination R the line is nearly straight. The measurements of the immunoglobulin E decline for all three probands. The proband with the overall higher immunoglobulin E measurements stands out through a notably strong decrease of concentration.
The analysis of other blood parameters shows, that the intake of nanogold does not provoke a considerable change in physiological standard values. The subjective condition of all of the three probands was good. No observable changes were reported.

4. Summary

Nanomaterials made of gold and silver offer interesting pharmacological properties, which is mainly due to the high surface to volume ratio of nanoparticles. The investigations carried out by us to show not only the physiological properties of nano-gold. It is documentated in a 4-week oral study with 3 probands a sustainable reduction of the IgE immune parameter which is essential for allergies of type 1.
In addition, nano-gold and silver-doted polymers show advantageous UV absorption properties and bacteria-reducing properties. This offers distinct advantages in drug packaging and its durability.

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