

Effects of X-Ray Inspection on Pharmaceutical Products



Contents

-
- 1 Introduction
 - 2 The Nature of X-rays
 - 3 How X-ray Systems Inspect Products
 - 4 Research and the Effects of X-rays on Pharmaceutical Products
 - 5 Conclusions
 - 6 References
 - 7 Recommended Reading
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1. Introduction

X-ray inspection of pharmaceutical products and over-the-counter (OTC) medications are steadily increasing in use as pharmaceutical manufacturers worldwide strive to safeguard their brand reputations, protect consumers' welfare and comply with national and international regulations and legislation.

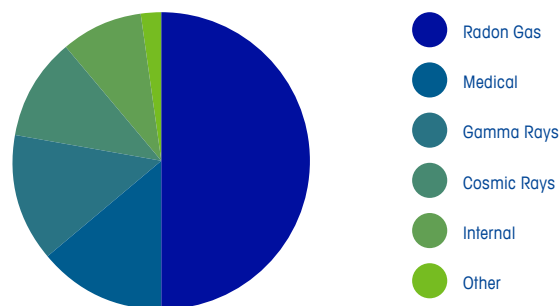
Some manufacturers, however, still have reservations about adopting x-ray inspection as a safe method of product inspection. Their primary concern is that products being inspected could be affected by radiation during the inspection process, and that their therapeutic effectiveness might be compromised.

This white paper examines the potential effects of x-ray inspection on pharmaceutical products. The paper begins by exploring the nature of radiation, outlining the difference between man-made x-rays and naturally occurring radiation ('background radiation'). The document then discusses why and how manufacturers use x-rays to inspect a wide variety of products to detect potentially harmful contaminants and defects that can damage brand reputation, potentially leading to costly recalls and lawsuits. There then follows a summary of the published research conducted on the effects of x-ray inspection on the efficacy and other physical properties of pharmaceuticals. The available research shows that the pharmaceutical and OTC products tested are not affected in terms of their chemical makeup and efficacy following exposure to x-ray in inspection systems.

2. The Nature of X-rays

X-rays are a form of radiation. Two main sources of radiation exist: natural and man-made.

The main sources of natural radiation are cosmic rays and naturally occurring radioactive materials on Earth. Cosmic rays come from space and can be x-rays, gamma rays and other forms of high energy radiation. Naturally occurring radioactive materials on the Earth's surface and atmosphere, such as uranium or radon gas, also emit radiation in the form of alpha particles, beta particles, and gamma rays. Natural or 'background radiation' is always present, although the levels vary from place to place, and are particularly high in the upper atmosphere due to the high level of cosmic rays, as an example activities such as air travel exposes passengers to relatively high levels of background radiation.



Background Radiation

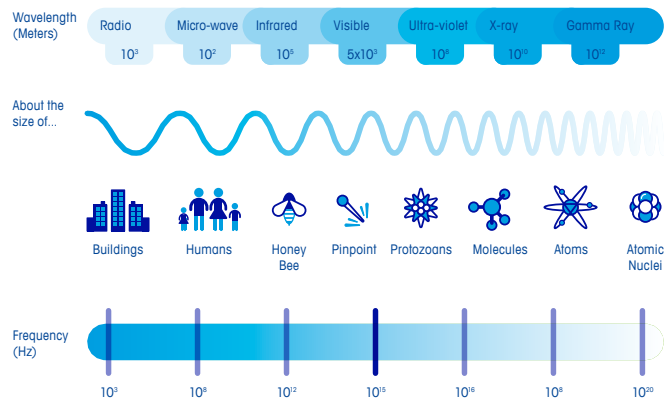


X-rays used in the inspection of pharmaceutical (and food) products are not generated from naturally occurring radioactive materials. The x-rays are man-made, generated within the inspection equipment itself, and like an electric light bulb, they can be turned on and off at will. When electricity supply to the system's x-ray generator is switched off, the flow of x-rays instantly ceases. Provided safety guidelines are followed, these x-rays are safe for those operating the equipment and at normal operating levels they are not expected to have negative effect on the products they inspect.

Man-made x-rays are used for many purposes, from medical examinations to the identification of contaminants in materials of all kinds, including pharmaceutical medications and OTC products.

The wavelength of x-rays enables them to pass through materials that block out visible light to a greater or lesser degree. The transparency of a material to x-rays is broadly related to its density, which is why x-ray inspection is so useful in the industry: the denser a material, the fewer x-rays can pass through. Hidden contaminants in pharmaceutical products, such as glass and metal, show up under x-ray inspection because they reflect more x-rays than the surrounding product or material.

It is worth noting that the level of exposure to x-rays, or 'dose', is generally much lower in pharmaceutical inspection when compared to other sources of radiation, such as medical x-rays, security scanning, food irradiation or naturally occurring background radiation. This is because the energies of the x-rays are low, the quantity of x-rays used (the x-ray 'flux') is minimal and the exposure time is very short.



3. How Companies Use X-rays to Inspect Products

X-rays are used in a wide variety of industries to inspect products and packaging, with the primary objective of an x-ray inspection system being to provide brand protection. A poor quality pharmaceutical or OTC product can damage—even ruin—a company's reputation and expose it to recalls and to liability lawsuits. A damaged product or a missing product from a multiple-product package (e.g., a packet of tablets) can seriously undermine a company's brand image with consumers. An x-ray system that is properly selected to specifically meet the individual manufacturer's requirements can reduce the risk of contaminated and defective products reaching consumers.

X-ray inspection systems provide exceptional detection of dense foreign bodies that are contaminating products, including metal, glass, calcified bone, mineral stone and high-density plastic and rubber within a product. In addition, x-ray systems can simultaneously perform a wide range of in-line quality checks such as identifying missing and damaged products within packaging.

Manufacturers of pharmaceutical products or OTC medications and supplements are among the companies that use x-rays to inspect individual and packaged products. It is particularly useful to them that x-rays can successfully inspect products contained in metalized film or aluminum-backed blisters, since those are among the most common packaging methods they use.



4. Research into X-ray Inspection Effects on Pharmaceutical Products

During inspection of pharmaceutical products, the quantity of x-rays is low, the energies of the individual x-rays are relatively low and the inspection period is very brief. Tablets under x-ray inspection are typically exposed to low energy x-rays for less than 0.2 seconds. The dose levels of background radiation received by pharmaceutical products while on the shelf, in transit, or during the time they are owned by the consumer are much higher than the levels delivered by an end of production line x-ray inspection system. The US Food and Drugs Administration (FDA) estimates the dose level received by an object going through an x-ray inspection system is lower than the background radiation dose level for one day. Moreover, the FDA asserts that there is no known danger to consuming medicines that have been inspected by x-ray¹.

Scientific studies have been also conducted on the effects of x-ray inspection on pharmaceutical products.

Scientists at the Department of Drug Delivery and Nano Pharmaceutics, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan conducted a study to investigate the effect of x-rays on the pharmaceutical quality of drug tablets. Acetaminophen, loxoprofen and mefenamic acid tablets were exposed to x-ray doses of 0.34 mGy (three times the typical dose delivered by x-ray inspection) to 300 Gy (approx. 1 million times the typical dose delivered by x-ray inspection). Following exposure, samples were evaluated by formulation tests; these tests revealed that exposure to x-rays did not affect the pharmaceutical quality of the drug content.

The exposed samples exhibited almost the same profile in formulation tests (dissolution, disintegrating and hardness tests) as control samples exposed to 0Gy. In addition, x-ray exposure combined with accelerated temperature and humidity tests (equivalent to six months of exposure) also did not affect the pharmaceutical quality of the samples. The study concluded that x-ray exposure at levels much higher than product inspection systems had no significant effect on the efficacy or other properties of the drug tablets².

In another study conducted by Robert Bosch Packaging Technology and the PHAST Society for Pharmaceutical Quality Standards, model pharmaceutical substances tramadol HCl and nifedipine were exposed to x-ray radiation for a period of 2 hours. This was a much higher period than the fraction of a second that pharmaceutical products are exposed to during industrial x-ray inspection. No degradation was observed in either substance after the 2 hours of exposure³.

5. Conclusions

X-ray inspection has an established record of bringing great value to manufacturers of pharmaceutical and OTC products by detecting contamination and damaged or missing products within packages. These are defects that can result in costly recalls, lawsuits and loss to brand image if not detected and prevented from reaching the marketplace.

Some manufacturers may have concerns that the x-ray exposure during inspection can affect the quality of their products. This possibility has been tested in published studies using a range of different pharmaceuticals with no significant degradation in drug efficacy or other physical properties. These results are unsurprising, given the very low doses of x-ray radiation needed to inspect pharmaceutical products. Doses are less than a single day's exposure to the average naturally occurring background radiation.

However not all formulations have been studied, and METTLER TOLEDO Safeline's x-ray inspection capability, combined with the laboratory capabilities of the manufacturers developing the medication, can address any particular concerns quickly and thoroughly.



6. References

1. Based on an airport security X-ray system, typically of higher dose than an inspection system for pharmaceutical products. From the FDA website: "There are no known adverse effects from eating food, drinking beverages, using medicine, or applying cosmetics that have been irradiated by a cabinet x ray system used for security screening. The radiation dose typically received by objects scanned by a cabinet x-ray system is 1 millirad or less. The average dose rate from background radiation is 360 millirad per year." <https://www.fda.gov/radiation-emittingproducts/radiationemittingproductsandprocedures/securitysystems/ucm116421.htm>
2. Kazuaki Uehara, Tatsuaki Tagami, Itaru Miyazaki, Norikazu Murata, Yoshifumi Takahashi, Hiroshi Ohkubo & Tetsuya Ozeki (2015) Effect of X-ray exposure on the pharmaceutical quality of drug tablets using X-ray inspection equipment, *Drug Development and Industrial Pharmacy*, 41:6, 953-958, DOI: 10.3109/03639045.2014.917093
3. Martin Vogt, Elke Sternberger-Rutzel, Manuel Birke & Christoph Jacobs (2012) Influence of X-ray radiation as PAT method on the model substances tramadol HCl and nifedipine compared to the influence of UV-Vis radiation, *TechnoPharm* 2, Nr. 3, 1–12





7. Recommended Reading

Further information can be found at:

- Guide to Building an Effective X-ray Program
mt.com/xray-guide
- How Do X-ray Systems Find Contaminants
mt.com/PIUS_XR-Contaminants
- Metal Detection, X-ray Inspection or Both?
mt.com/md-xr
- Solutions to Industry Challenges for Pharmaceutical Manufacturers
mt.com/pi-pharma-solutions
- OEE and Product Inspection Efficiency in the Pharmaceutical Industry
mt.com/pi-pharma172
- Security of Pharmaceuticals Comparing US and EU Standards
mt.com/pce-security-pharmaceuticals
- Serialization of Pharmaceuticals
mt.com/pce-key

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The Product Inspection Division of METTLER TOLEDO is a leader in the field of automated inspection technology. Our solutions increase process efficiency for manufacturers while supporting compliance with industry standards and regulations. Our systems also deliver improved product quality which helps to protect the welfare of consumers and reputation of manufacturers.



Checkweighing



Metal Detection



Track & Trace



Vision Inspection



X-ray Inspection

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