Mass Attenuation Coefficient for Alprazolam Drug: A Non-destructive Quantitative Analysis

Manjunath. A., B. R. Kerur, S. B. Kaginelli

Abstract— Analysis of the pharmaceutical drug quality and quantity were done by determining the mass attenuation coefficient. by adopting a non-destructive spectrometric analysis technique. Alprazolam is a psychoactive drug manufactured by different laboratories and also marketed by different brand names viz., Trika Restyl and Alprax. Mass attenuation coefficient for these drug samples were determined at different X-Ray energy range from 8.04 keV to 44.48 keV obtained from the Am-241 radioactive variable energy X-ray (VEX) source. Intensities were measured with and without the attenuator of the each sample with the help of HPGe detector system coupled to multichannel analyser (MAC) through transmission beam geometry. Experimentally determined mass attenuation coefficient values are compared with the therotically estimated values (WinXCom). Quantities of inactive gradients added by the manufacturer were also discussed in this paper.

Index Terms— Alprazolam, Active Pharma Ingradient, HPGe, MAC, Pharmaceutical, WinXCom,

1 INTRODUCTION

Medical Physics is contributing, maintiaing and improving the quality, safety and cost-effectiveness of healthcare service through patient-oriented activities. Further, it also requires expert action, involvement or advice regarding the specification, selection, acceptance testing, quality assurance including quality control and optimized clinical use of medical devices and regarding risks from associated physical agents: all activites is based on current best evidence or own scientific research when the available evidence is not sufficient. The scope includes risks to volunteers in biomedical research, careers and comforters; it also includes risk to workers and the public when these have an impact on patient doses.

In this respect we framed our objectives to develop and validate the specific, accurate, precise and a reproduce the quality control test by the nondestrucitve analytical method. Hence the X-ray spectrometric technique ie., mass attenuation coefficients were determined for the pharmaceutical drug samples which are similar chemical composition which were purchased/available in the market of different manufacturers.

Mass attenuation coefficient is a measure of the average number of interactions between incident photons and the matter that occur in a given mass per unit area thickness of the substance. Hence, the application of mass attenuation coefficient have been found in different fields viz., radiation shielding, agricultural, medical fields, aeronotical engineering, photon transport, space research, military, security checking purposes (most impotant now-a-days) and research and development etc,. Hence, in view of the above applications veriety of experimental investigations have been performed to determine the mass attenuation values on the various types of materials such as elements [1], compounds [2], tissue equivalent compounds [3], mixtures (different percentage of elements) [4], alloys [5-6], building materials [7] etc., at different photon energies to study the quality of the material under consideration. Another important parameter through mass attenution coefficient is determined is the effective atomic number and electron density. Effective atomic number may be determined experimentally for particular energies and also generated using the XCOM programme over the energy region from 1 keV to 20 MeV [8-10]. Nowadays there are more number of articles publishing on the effective atomic numbers of biological interesting materials, alloys, etc. But in this work the mass attenuation coefcieint were determined experimentally and then these results are utilized to study drug compositions. Our laboratory seems to be first to present this kind of analysis of durg/s thrugh the mass attenuation coefficients by nondestructive method over certain energy region.

- *Manjunath A, Department of Physics, Gulbarga University, Gulbarga - 585106 (Karnataka) India. E-mail: manjusaw@gmail.com*
- *B R Kerur, Professor of Physics, Gulbarga University, Gulbarga-585106 (Karnataka), India, PH-08472263298. E-mail: kerurbrk@yahoo.com*
- *S B Kaginelli,Asst. Prof. Dept of Radiology M R Medical College, Gulbarga - 585105 (Karnataka), Email: kaginellisbk@rediffmail.com*

2 METHODS AND METERIALS

2.1 Material Desciption

Drug comes in a variety of forms (tablets, pills, capsules, aerosol and sprays) and with a variety of formulations. A single drug may be formualated in dozens of ways to enhance the ability of the drug to enter patient's body. Alprazolam is the one of such drug selected for qualitative analysis by a non-destructive method. Alprazolam ($C_{17}H_{13}ClN_4$) belongs to a group of drugs called benzodiazepines. It works by slowing down the movement of chemicals in the brain that may become unbalanced. This results in a reduction of nervous tension (anxiety). It is used to treat anxiety disorders, panic disorders and anxiety caused by depression.

There are numeraous methods have been reported for the analysis of alprazolam and its combinations/effects in pharmaceuticals or in biological fluids. It has been determined in combination with other drug using, UV-Specrtometry, quantitative thin-layer chromatography (TLC), high performance liquid chromatography (HPLC) and gas chromatography (GC) in pharmaceutical preparations of Alprazolam in the dosage form. But all the above said analytical methods are destructive one ie., which destruct or damage the specimen permanently

being inspected.

The alprazolam drug sample from different manufacturer or brand names were selected for quantitative analysis to study the active and inactive gradients present in tablets. Three manufacturing companies selected in the present work viz., Trika, Restyl and Alprax, the API contant in the drugs were 0.5mg Alprazolam as the prescription mentioned in the manufacturer's on the packet.

2.2 Method Adopted: Mass attenuation Coefficient (MAC)

Low-Z materials are often used or considered for use as scattering of X-ray beams. There uses may originate from a desire to reduce the intensity of X-ray beam, e.g., for diagnostic purpose, or may be required as a result of experimental geometry constraints. When radiations are allowed to pass through any materials its intensity progressively decreases as a result of interactions between radiation and the atoms in the attenuating media. It is causes absorption and scattering of primary photons. A narrow beam of mono-energetic photons with incident intensity I_0, penetrating an absorbing material with mass thickness x and density ρ, emerges with intensity I is given by the exponential law:

$$I/I_0 = exp\left[-\left(\mu/\rho\right)x\right] \quad (1)$$

where I/I_0 is the transmission fraction. From this μ/ρ can be obtained from measured values of I, I_0 and x. note that mass thickness is defined as the mass per unit area and obtained by multiplying the thickness by the density r i.e., x=tρ. This equation can be rewritten as,

$$\mu/\rho = x^{-1} ln\left(I/I_0\right) \quad (2)$$

If the absorber consists of a chemical compound or a homogenous mixture, the mass attenuation coefficient can be calculated approximately form the weighted average (by mass) of the individual mass attenuation coefficients of the constituent elements in the compounds are usually estimated by using Bragg's additivity law, commonly called as mixture rule is given as:

$$\frac{\mu}{\rho} = \sum_i \omega_i \left(\frac{\mu}{\rho}\right)_i \quad (3)$$

where $(\mu/\rho)_i$ is the mass attenuation coefficient for the ith element and w_i is its weight fraction of the ith elelment. The percentage deviation of the experimental results with theoretical values (WinXCom) can be calculated.

3 Experimental Procedure

The experimental arrangement is shown in Fig 1. The experimental set up consists of a mild steel (MS) stand into which two lead holders can be inserted. The upper holeder holds both the source and collimator to collimate the incident beam, while lower one holds the absorber and a collimator to collimate the transmitted beam. Their positions are so fixed that the absorber is at half way between the source and the detector and is placed normal to the beam. A broad beam geometry as well good geometry setup is adopted for the photon intensity measurement. In case of good geometry arrangement a rigid stand positioned above the detector holds the source, specimen and collimator in place and ensures vertical alignment. And for the broad beam, the source is kept at the same distance as expect the collimators. Photons from the radioactive source S were collimated by the lead collimator C1 and were incident on the absorber AB placed normal to beam and midway between the source and detector. The photons transmitted passing through the second lead collimator C2 were detected by HPGe detector. A pair of lead collimator each of 3.2cm thick with 6 mm diameter was used to collimate the photon beam. These two collimator inserted at the middle positions of the collimation stand between source and detector of 10 cm distance. The samples are kept exactly at the mid position of the two collimators as shown in the Fig 1. To study the seffects of small angle and multiple scattered photons by the absorber and collimators in good geometrical arrangement, a pair of collimators of size 6 mm and 9 mm and broad beam geometry were successively used which found to be about the angle acceptance at the detector from the source is around 31 and 71 for 6 mm and 9 mm collimators respectively. The fluorescence intensity due to collimator, stand and other components was found to be either far from the region of interest or negligible found from the observed spectra. In present work, Fe-55 and Co-57 radioactive isotopes each of about 740 kBq (20 mCi) strength were used. Both radioactive isotopes were procured from BRIT, Mumbai, India, in the form of standard X-ray source used in this experiment. The variable energy X-ray (VEX) source of 370 MBq (10 mCi) Am-241 is used as the primary source of excitation radiation. The 59.65 keV gamma photons from Am-241 incident on the Cu, Rb, Mo, Ag, Ba and Tb targets to produce fluorescence X-rays with characteristic energies of the target. No noticeable impurities were found in these source when their photon spectrum was analyzed using an HPGe detector. Inner bremsstrahlung intensity from the source was found to be negligible compared to the X-ray intensity at the region of interest.

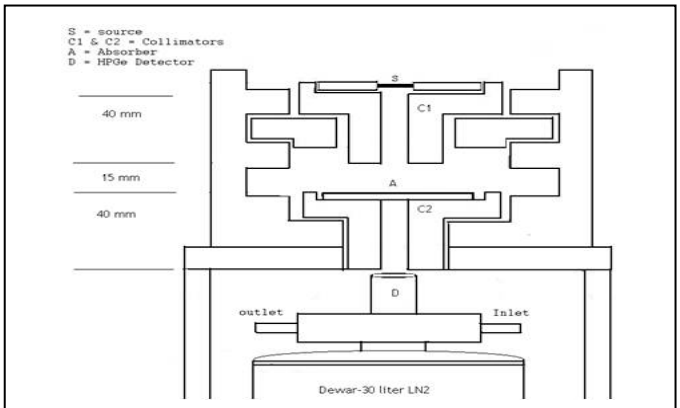

Fig. 1. Experimental set up for the measurement of the mass attenuation coefficient for the Alprazolam drug samples (Trika, Restyl and Alprax).

In our experiment, different background levels observed depending on the type of source used in the experiment. The

relative background varies from 10^{-3} to 10^{-1} for sources used in the present investigation; for these T_{opt}, from the Rose and Shapiro (1948) grph, are found to be 0.12 and 0.20, respectively. Rose and Shepiro also plotted the optimum apportionment of counting times as a function of optimum transmission. From this graph we see that T_{opt}= 0.12 the fraction of counting times for incident, transmission and background intensity α0, α1 and α2 respectivly are 0.2, 0.62 and 0.18 approximately for T_{opt}= 0.25, α_0~0.2, α_1~0.4 and α_3~0.4. This show that in both the cases if we adjust time for transmitted intensity such that the statistical error associated with it is < 1%; tha same counting time method adopted for background and incident intensity to obtain good statistical accuracy for all data measurements. Obvisouly this depends on the source strength.

The X-ray spectrometer consists of an n-type x-ray detector of area 500 mm² and 10 mm thick high purity Germenium connected to DSA-1000, 16 k MCA. The spectrometer operated by a Genie 2000 software. The detector is directly coupled to a pre-amplifier through a cool FEET device and is mounted over rigid cryostat with an accompanying 30 liter Dewar for liquid nitrogen. DSA-1000 allows independent selection of rise time and flat top. The Gaussian shaping (processing time) is set by rise time and flat top selection, which optimizes the performance of the detector, spectral energy, count rate and resolution. HPGe detector along with DSA-1000 has resulted with a resolution of 191 eV at 5.895 keV as against 200 eV by the manufacturers.The ambient temperature of the room was maintained constant throughout the experimental period. The linearity and stability of electronic equipments is first checked using a presision pulser. Then the HPGe detector spectrometer is calibrated using Fe-55 and Co-57, X-rays and γ -rays from Am-241 variable energy X-ray source. The spectrometer was tested for its stability by recording the spectrum at various time intervals on different days. The duration of the intensity measurement at various thicknesses of specimen was fixed by following Rose and Shapiro (1948) conditions.

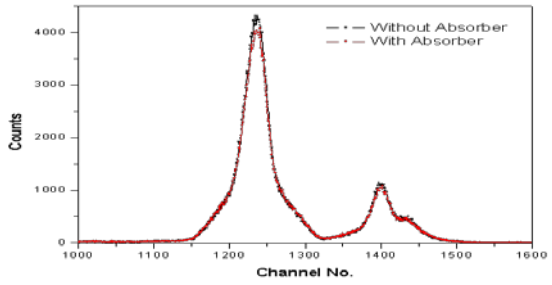

Fig. 2. X-Ray Spectrum of the Ba target with absorber and without absorber.

Dead time corrections were also made as the count rate show dead time loss of 2-3% in case of Am-241 variable X-ray source. Photon spectra were record in the following order: spectrum B-background spectrum recorded without source and sample. Spectrum BS- background plus source spectrum recorded with source but without sample. Spectrum BT-background plus transmitted spectrum recorded with source and sample. Spectrum BT was recorded for each member of set of samples having different thickness of material. Spectrum B and spectrum BS were recorded again.

The incident spectrum was obtained by subtracting Spectrum B from spectrum BS and the transmitted spectrum was obtained by subtracting Spectrum B from Spectrum BT. In both the spectra the photon peak had Gaussian distribution. By integrating the incident spectrum and the transmitted spectrum over selected width of the photo peak, incident intensity I_0 and transmitted intensity I were obtained Fig 2. Finaaly the μ_m was obtained from the slope of the straight line fitted by plotting a logarithmic graph of intensity as the function of thickness; method of least squares.

The theoretical values of attenuation coefficient have been estimated by WinXCom programme [11]. The relative percentage deviations (PD) between the theoretical and experimental values are presented in the Table 2.

4 Result and Disussion

The accurate measurement of MAC were obtained with the HPGe detector system by adopting Hubbell and Creagh criterian along with the transmission range adopted here is 0.02<T<0.5, especially for low energy photon detector. The experimental MAC values along with their associated errors, calculated by least-squares fit are given in the Table 1. First

TABLE 1
EXPERIMENTALLY DETERMINED MASS ATTENUATION COEFFICIENT FOR ALPRAZOLAM DRUG SAMPLES USING HPGE DETECTOR SYSTEM

Sample name	Mass attenuation coefficient in cm²/g at different energies		PD (%)
	Experiment	WinXCom	
Energy = 8.041 keV			
Restyl	7.33 ± 0.053		55.6
Alprax	7.41 ± 0.033	16.515	55.13
Trika	7.81 ± 0.072		52.7
Energy = 13.396 keV			
Restyl	1.77 ± 0.009		48.6
Alprax	1.78 ± 0.011	3.446	48.3
Trika	1.88 ± 0.006		45.4
Energy = 17.479 keV			
Restyl	0.902 ± 0.007		49.3
Alprax	0.911 ± 0.006	1.779	48.8
Trika	0.933 ± 0.007		47.5
Energy = 22.163 keV			
Restyl	0.538 ± 0.002		46.9
Alprax	0.535 ± 0.003	1.013	47.2
Trika	0.551 ± 0.004		45.6
Energy = 32.193 keV			
Restyl	0.290 ± 0.003		36.1
Alprax	0.296 ± 0.004	0.454	34.8
Trika	0.306 ± 0.004		32.6
Energy = 44.481 keV			
Restyl	0.227 ± 0.006		19.2
Alprax	0.212 ± 0.007	0.281	24.5
Trika	0.236 ± 0.002		16.0

column gives the sample or brand name of the Alprazolam drug, second and third column gives the experimentally determined and theoretically estimated mass attenuation coefficient values from 8.041 keV to 44.481 keV and in the last column gives the percentage deviation of experimental and WinXCom values with corresponding energies. The therortical values are estimated by the programme WinXCom [9] which is the successor of XCOM. The WinXCom values so obtained as the information contains on the packet of the drug of selected manufacturer about the presence of API in each tablet, but the outcome of the experimental results reflects the contribution of the inactive pharmaceutical ingradient present in each drug. This can be observed in the last column of Table 1, by the percentage deviation, calculated by using equation 4. Since opted drug sample is a low Z compound (Z<17) and hence, the binding energy of API were far away from the incident characteristic X-ray energy. But the photoelectric process is the predominant in the low energy region; hence the MAC values shows maximum at 8.041 keV in all the cases and hence shows PD value is more than 50% from WinXCom values. Therefore as the X-ray energy increases the percentage contirubtion of coherent and incoherent processes will be added in the MAC values. In the Table 1, at 8.041 keV the MAC values are well resolved, which shows that quatativative and qualtitaive analysis of the drugs can be carried out in the low enrgy region by using the HPGe detector.At low energy region photoelelctroic cross section is larger compared to higher energy region of the studied energy and hence relative biological effectiveness (RBE) of x-ray increases with decreasing x-ray energy, since as the x-ray energy of the photon decreases, the energy of secondary electron emitted in the photon interaction decreases. The studied energy region is considerd as diagnostic energy range hence this range is preffered for the analysis of drug samples. As the X-ray energy is increased from 8.041 keV to 44.481 keV, the difference among determined mass attenuation coefficient and estimated values decrease and all values will mearge at 32.06 keV X-rays, because of the increase in the contribution coming from

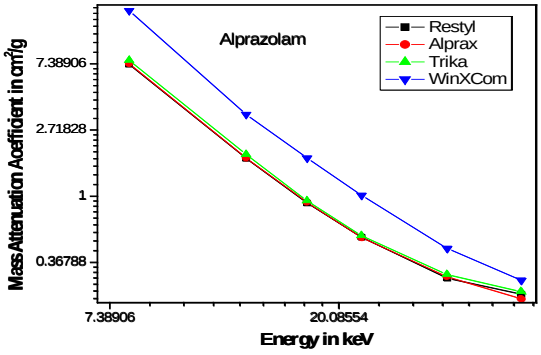

Fig. 3. Logarithmic graph of experimentally determined mass attenuation coefficient for the Alprazolam drug samples (Trika, Restyl and Alprax) and theoretically estimated values (WinXCom)

Compton process to the total mass attenuation coefficient compared with the photoelectric cross section becomes more or less equal to Compton cross section; hence it is very difficult to identifly or detect the quality and quantity of excipients added in formulation process of drugs by the different manufacturers at the higher energy region. The variation of mass attenuation coefficient among the different manufacturers and as well as increase in x-ray energy shown graphically in the Fig 3, which is the logarithmic graph of mass attenuation coefficient vs Energy. The deviation of restyl and Alprax are less than 2% (R= - 0.98), similarly restyl and Trika were 2-6% (R= - 0.98), where R is the regression coefficient. From this graph one can confirm that MAC depends strongly on the incident X-ray energy as well as chemical composition of the material.

5 Conclusions

By above experimental findings and also from the fig. 3 that, the following conclusion may be drawn. The actual average weight of the drugs lies between 96-113 mg, and the concentatrion of actual active pharmaceutical ingradient (API) ie., Alprazolam concentration in each tablet is only 0.5 mg as the manufacturer given an information on the each tablet packet. Though, API percentage content in each tablet is very small quantity because of its chemical nature (Psychoactive). Hence around 99 % contains the multiple excipients i.e., coloring agents to pleasant the eye, taste and buffers etc. Thus, the contribution of these excipients used in the each samples by the respective manufacturer is detectable in this non-destructive analytical method: through X-ray interactions i.e., the variation of mass attenuation coefficients with energy. Therefore the method outlined here in this paper is simple, quick to analyse the quality control of the pharma compound through the relative intensity measurements.

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