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X-Ray Attenuation Coefficients for Pharmaceutical Drugs: A Qualitative Analysis by Non Destructive Technique.

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Research Article

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ABSTRACT

The mass attenuation coefficient of drug was determined at low photon energies ranging from 8 keV to 44 keV using High Purity Germanium (HPGe) detector for the samples of different firms with similar Active Pharma Ingredient (API). Diclofenac sodium tablet is an oral suspension belongs to the NSAIDs group. The qualitative analysis of this opted pharmaceutical drug manufactured by different pharma companies viz., Diclomol, Dynapar, Voveran Plus and Diclogesic, were carried out by use of nondestructive method, through the determination of mass attenuation coefficient (MAC). The obtained results were compared with the theoretical WinXCom values, which gives the light on the quality analysis of the drug. This method confirms that the mass attenuation coefficient can be used as a qualitative analysis of any drug, which is a non-destructive technique compared with other techniques/methods wherein the sample is totally destroyed. Hence evaluation of a quality of the drug of from different companies is discussed in view of the MAC.

INTRODUCTION

Mass attenuation coefficient (MAC), (written symbolically as μ/ρ 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 substance. Hence, the importance of mass attenuation coefficient have been found in different fields viz., radiation shielding, agricultural, medical fields, aeronautical engineering, photon transport, space research, military, security checking purposes (most important now-a-days) and research and development etc,. Hence, in view of the above applications verity of experimental investigations have been performed to determine the mass attenuation coefficient 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] etc. at various photon energies to study the quality of the material under consideration. Hence we are introducing the non-destructive method or a technique to analyze the quality of the drug samples by determining the parameter called Mass Attenuation Coefficient.

A non destructive testing/ technique (NDT) has an important role in the applied physics/medicine/industry. It has multiple applications in the field of qualitative analysis or quality control of industrial products, radioactive materials control, diagnostics of tissue and organs etc. The main task of this method is to determine the technical characteristics and properties of the controlled objects being examined. It is vitally necessary not only to provide enhanced tools for scientific and technological investigation, but to meet current needs for improved protection, safety and health of civil populations. Now a day, a strong interest has been developed to determine the quality control of the products with respect to overall composition without destructing. Single product is manufactured by different firms which may or may not be maintaining the quality and quantity (especially in the drugs). There are different drugs in the market for particular disease with different brand names. In this respect a Non-steroidal Anti-Inflammatory Drugs (NSAIDs) have been selected for the qualitative analysis. NSAIDs are usually prescribed for the treatment of acute or chronic conditions where pain and inflammation are present. These are generally suggested for the symptomatic relief of Rheumatoid arthritis, Osteoarthritis, renal colic, mild-to-moderate pain due to

inflammation tissue injury etc. Diclofenac sodium is one of the NSAIDs pharma drugs which we opted for the present study.

The Diclofenac sodium tablet contains 50 mg Diclofenac sodium ($C_{14}H_{11}Cl_2NO_2$ chemically named as 2-(2-(2, 6-dichlorophenylamino)phenyl)acetic acid) in combination of 500 mg paracetamol ($C_8H_9NO_2$ chemically named as N-acetyl-p-aminophenol). This drug is taken to reduce headache, body pain, and dental pain, sports and accident injuries, rheumatism, arthritis, lumbago, bursitis and sciatica. Four branded drugs of diclofenac sodium manufactured by different laboratories in India have been selected viz., Diclomol and Dynapar from Uttarakhand, Diclogesic and Voveran Plus from Solan (HP) and Karnataka respectively. Once the qualitative and quantitative analyses are carried out by the pharmacists, these drugs are dropped into the markets. But these analyses are very critical and necessary or integral part of the pharma business. Hence, analytical methods as well as the involved analytical tools assume prime importance in the pharma business. Several well known analytical tools viz., HPLC [6,7], GC [8], quantitative thin-layer chromatography (TLC) [9] etc., are available to a pharmaceutical analyst.

The objective of this study is to develop and validate the specific, accurate, precise and reproducible quality control by the non destructive analytical method. And also this article attempts to depict the merits of the mass absorption spectrometer in estimation of quality assurance of the pharmaceutical products. However, in the literature, such reports are not published i.e., on the use of mass attenuation coefficient measurement on pharmaceutical samples in the photon energy 8.036 keV to 44.216 keV through which quality control of the drug can be defined.

MASS ATTENUATION COEFFICIENT (MAC)

Low-Z materials are often used or considered for use as scattering of x-rays. These uses may originate from a desire to reduce the intensity of the x-ray beam, e.g., for diagnostic purposes, or may be required as a result of experimental geometry constraints. When radiations are allowed to pass through any materials its intensity is progressively decreases as a result of interactions between photons and/with matter/atoms in the attenuating media. It is caused by both the absorption and scattering of the 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 an intensity I is given by the exponential law,

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

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 the mass thickness is defined as the mass per unit area and is obtained by multiplying the thickness t by the density ρ i.e., $x = \rho t$ t. Then above equation can be rewritten as,

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

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

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

Where $(\mu/\rho)_i$ is the mass attenuation coefficient for the i^{th} element and ω_i, is its weight fraction of the i^{th} element.

EXPERIMENTAL PROCEDURE

The experimental arrangement is shown in Fig. 1. The experimental consists of a mild steel (MS) stand into which two lead holders can be inserted. The upper holder holds both the source and collimator to collimate the incident beam, while lower one holds both 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. Many investigators have adopted different methods for the measurement of photon intensity for the determination of mass attenuation coefficient. A good geometry setup is adopted for the photon intensity measurement. In good geometry arrangement a rigid stand positioned above the detector holds the source, specimen and collimator in the respective places which ensures vertical alignment. Photons from the radioactive source S were collimated by the lead collimator C1 and were incident on the absorber AB placed normal to beam which is kept midway between the source and detector. The photons transmitted passing through the second lead collimator C2 were detected by the HPGe detector system. A pair of lead collimator each of 3.5 cm thick with 6 mm diameter was used to collimator the photon beam. These two collimators were kept at the middle position of the collimator stand between source and detector of 10 cm distance. The sample/s is kept exactly at the mid position of the two collimators as shown in Fig. 1. No noticeable effects of small and multiple scattered photons by the

absorber and collimators was noticed in the spectra of source spectra observed in a good geometrical arrangement consists of a pair of collimators of size 6 mm diameter. 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, ^{55}Fe and ^{57}Co radioactive isotope 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 370MBq (10 mCi) ^{241}Am is used as the primary source of excitation radiation. The 59.65 keV gamma photons from ^{241}Am were incident on the Copper and Rubidium target to produce fluorescent X-rays with characteristic energies of the target. No noticeable impurities were found in these sources when their photon spectrum was analyzed using an HPGe detector as shown in Fig.2. The inner bremsstrahlung intensity from the sources was found to be negligible compared to the X-ray intensity at the region of interest.

In our experiment, different background levels observed depending on the type of sources used in the experiment. The relative background varies from 10^{-3} to 10^{-1} for sources used in the present investigation; for these the T_{opt}, from the Rose and Shapiro graph, are found to be 0.12 and 0.20, respectively. The statistical error associated with the transmitted intensity is found to be within <1%; the same counting time method adopted for background and incident intensity to obtain good statistical accuracy all data measurements. Obviously this depends on the sources strength.

In the present measurement, Good fellow metal foils in the atomic number range from 12<Z<72 with high purity range from 99.95 to 99.99 were used for the study of X-ray mass attenuation coefficients, but for standardization purposes aluminum/copper foils were used. Three polymers viz., teflon [polytetrafluoroethylene, PTFE-(C2F4)], nylon-6,6 (polyamide 6-6, PA66-C6H11NO) and polyethylene [C2H4] were also studied in addition to some elemental metal foils. All the three polymers with high purity were purchased from Indian Polymer Industries, Mumbai, India. These materials are said to be biological equivalents since these polymers are used for tissue substitutes demanded by medical physicists for materials closely simulating a wide variety of body tissues.

The X-ray spectrometer consists of an n-type X-ray detector of area 500mm2_10mm thick high purity Germanium, connected to DSA-1000 16 k MCA. The spectrometer is operated by Genie 2000 software. The detector is directly coupled to a pre-amplifier through a cool FET device and mounted mechanically over the rigid cryostat with an accompanying 30 lit 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 (22^{0}C) throughout the experimental period. The linearity and stability of electronic equipments is first checked using a precision pulser. Then the HPGe detector spectrometer is calibrated using ^{55}Fe and ^{57}Co, X-rays and γ-rays from ^{241}Am 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. Dead time correction were also made as the count rate show dead time loss of 2–3% in case of ^{241}Am variable energy X-ray source. Photon spectra were recorded 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 thicknesses of a 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 photo 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. Finally the μ_m was obtained from the slope of the straight line fitted by plotting a graph of ln I as a function of thickness; method of least squares.

Creagh and Hubbell suggestions adopted for the measurement of mass attenuation coefficients, but the transmission range adopted here is 0.02<T<0.5. In this transmission range Beer-Lambert's law is rigorously valid which is tested using aluminum absorber for which accurate theoretical and experimental value of μ/ρ are available when HPGe detector is used. Choosing the optimum μ/ρ values determined for aluminum, over different ranges of transmission to establish acceptable range. With these standardized experimental parameters we then determined μ/ρ for remaining materials.

The theoretical values of mass attenuation coefficient have been estimated by using WinXCom programme [10] which is the successor of program XCOM [11]. The relative difference or percentage deviations (PD) between the theoretical and experimental values are presented in the Table 2. They are calculated by using the formula,

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$$PD = \frac{\left(\mu/\rho\right)_{exp} - \left(\mu/\rho\right)_{theory}}{\left(\mu/\rho\right)_{theory}} \times 100$$

RESULT AND DISCUSSION

In order to analyse our experimental data of mass attenuation coefficient values, so obtained by adopting above procedures, for six elements and three biological equivalents are tabulated in the table 1-2. There are two sets of data's in each table. Each set contains the six elements and three compounds, experimental and theoretically estimated WinXCom values and percentage deviation are also shown in the each energy in the tables. The experimental results deviate from theoretically estimated (WinXCom) values by not more than 1% in almost all the cases for all the elements and the compounds for the presented energies. The percentage deviation in all the cases found to be less than 1%, which shows the good agreement between theoretical and experimental results. Hence from the present elemental data concludes that, the accurate measurement of MAC can be obtained with the HPGe detector system by adopting Hubbell and Creagh Criteria long with the transmission range adopted here is 0.02<T<0.5, when using low energy photon detector. The above method concludes that the procedure can be used for the measurement of MAC for any compound or any other material. Hence this method is adopted for the determination of MAC of the pharmaceutical drug and quality analysis is done in following way.

Table 1: The measurement of mass attenuation coefficient for elements and polymers for ^{55}Fe and ^{60}Co k_α X-rays

Element /compound	Mass attenuation coefficient in cm^2/g		PD (%)	Element /compound	Mass attenuation coefficient in cm^2/g		PD (%)
	Experimental Energy 5.895 keV	WinXCom			Experimental Energy 6.404 keV	WinXCom	
Mg	97.87+0.65	98.70	0.8	Mg	78.19+0.43	77.87	0.4
Al	121.1+0.4	121.2	-0.1	Al	96.50+0.26	95.85	0.7
Ni	113.5+0.9	114.3	-0.7	Ni	90.79+0.46	91.25	-0.5
Cu	120.8+0.8	121.3	-0.3	Cu	97.39+0.78	96.81	0.6
Mo	351.9+3.2	353.2	-0.3	Mo	281.7+2.6	283.7	-0.7
Ta	354.5+3.2	353.42	0.3	Ta	288.7+1.5	287.3	0.5
PTFE	32.56+0.3	33.12	-0.8	PTFE	25.69+0.22	25.91	-0.8
Nylon	14.11+0.13	13.888	-0.9	Nylon	10.75+0.09	10.83	0.7
Polyethylene	9.916+0.092	9.951	0.2	Polyethylene	7.769+0.082	7.755	0.2

Table 2: The measurement of mass attenuation coefficient in cm^2/g for elements and polymers for Am-241 source with Cu and Rb target k_α X-rays

Element /compound	Mass attenuation coefficient		PD (%)	Element /compound	Mass attenuation coefficient		PD (%)
	Experimental Energy 8.041 keV	WinXCom			Experimental Energy 13.375 keV	WinXCom	
Mg	39.62+0.33	39.99	-0.9	Mg	8.876+0.061	8.921	-0.5
Al	49.94+0.24	49.58	0.7	Al	11.08+0.13	11.15	-0.6
Ni	48.95+0.38	48.83	0.2	Ni	96.57+0.83	96.86	-0.3
Cu	52.09+0.31	51.82	0.5	Cu	101.8+0.5	101.4	0.4
Mo	156.2+1.3	154.4	-1.1	Mo	38.12+0.39	38.97	-0.8
Ta	162.7+1.1	161.8	0.7	Ta	179.4+1.8	179.1	0.2
PTFE	13.08+0.13	13.06	0.2	PTFE	2.902+0.023	2.897	0.17
Nylon	5.408+0.053	5.449	-0.8	Nylon	1.255+0.013	1.288	-1.1
Polyethylene	3.908+0.035	3.951	-0.1	Polyethylene	0.9701+0.0012	0.9731	-0.3

With the above experimental procedure adopted for the analysis of quality of pharmaceutical drug samples manufactured by different firms through the measurement of MAC. The experimental results of four pharma companies which are manufacturing diclofenac sodium tablets and the theoretically estimated mass attenuation coefficient with their corresponding errors involved are staged/ showcased in the Table 3-5. There are two set of data's are quoted in each table which corresponds to two energies. In each set of data first column gives the manufacturing company/ brand names, second and third column will gives the measured and estimated results of mass attenuation coefficient and in the last column gives the relative deviation or percentage deviation experimental from theoretical values. The WinXCom MAC values correspond to only the active pharmaceutical ingredient only but the outcome of the experimental data MAC values corresponds to the Active and Inactive Pharmaceutical Ingredients present in the compound. The uncertainties involved in the theoretical value are about 1-2%. Since the reproducibility of our experimental value is within 1% and the error contribution from the counting

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statistics, areal density thickness measurement gives about 1%. In the selected sample presented in the Tables 3-5 one can confirm that around 76% attenuation was observed in the low energy region and the probability of attenuation goes on decreases to 40-50% as the energy changes from 32.060 and 44.216 keV attenuation decreased to 23-27 % which is shown in the figure 3. In the low energy region due to the contribution of photoelectric process, which is the predominant process than that of the coherent and incoherent processes in the low energy region, hence MAC value is higher compared to the higher energy region.

Table 3: MAC of the drug samples with WinXCom at 8.041 keV and 13.374 keV.

Compound	Mass attenuation coefficient in cm^2/g Experimental Energy 8.036 keV	WinXCom	PD (%)	Compound	Mass attenuation coefficient in cm^2/g Experimental Energy 13.374 keV	WinXCom	PD (%)
Diclogesic	7.850±0.024	29.695	-73.564	Diclogesic	1.860±0.019	6.932	-73.168
Voveran Plus	8.110 ±0.048		-72.689	Voveran Plus	1.870±0.014		-73.024
Dynapar	8.240±0.020		-72.251	Dynapar	1.940±0.015		-72.014
Diclomol	8.460±0.025		-71.510	Diclomol	2.050±0.015		-70.427

Table 4: MAC of the drug samples with WinXCom at 17.443 keV and 22.103 keV.

Compound	Mass attenuation coefficient in cm^2/g Experimental Energy 17.443 keV	WinXCom	PD (%)	Compound	Mass attenuation coefficient in cm^2/g Experimental Energy 22.103 keV	WinXCom	PD (%)
Diclogesic	0.946±0.014	3.263	-71.008	Diclogesic	0.559±0.008	1.705	-67.214
Voveran Plus	0.948±0.003		-70.947	Voveran Plus	0.559±0.015		-67.214
Dynapar	0.996±0.009		-69.476	Dynapar	0.561±0.003		-67.097
Diclomol	1.030±0.012		-68.434	Diclomol	0.599±0.006		-64.868

Table 5: MAC of the drug samples with WinXCom at 32.06 keV and 44.216 keV.

Compound	Mass attenuation coefficient in cm^2/g Experimental Energy 32.060 keV	WinXCom	PD (%)	Compound	Mass attenuation coefficient in cm^2/g Experimental Energy 44.216 keV	WinXCom	PD (%)
Diclogesic	0.295±0.002	0.680	-56.618	Diclogesic	0.223±0.005	0.366	-39.071
Voveran Plus	0.305±0.006		-55.147	Voveran Plus	0.228±0.007		-37.705
Dynapar	0.299±0.006		-56.029	Dynapar	0.216±0.006		-40.984
Diclomol	0.313±0.005		-53.970	Diclomol	0.241±0.004		-34.153

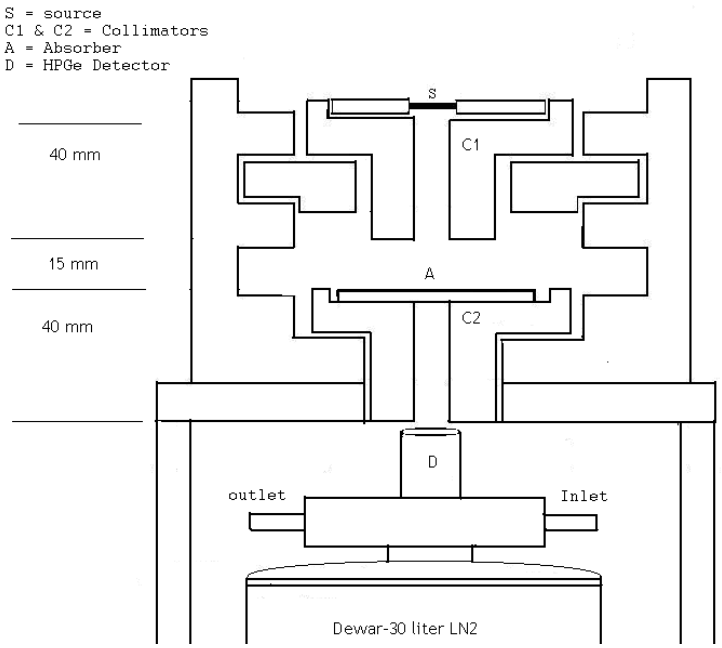

Figure 1: Basic Experimental set for the measurement of Mass attenuation coefficient

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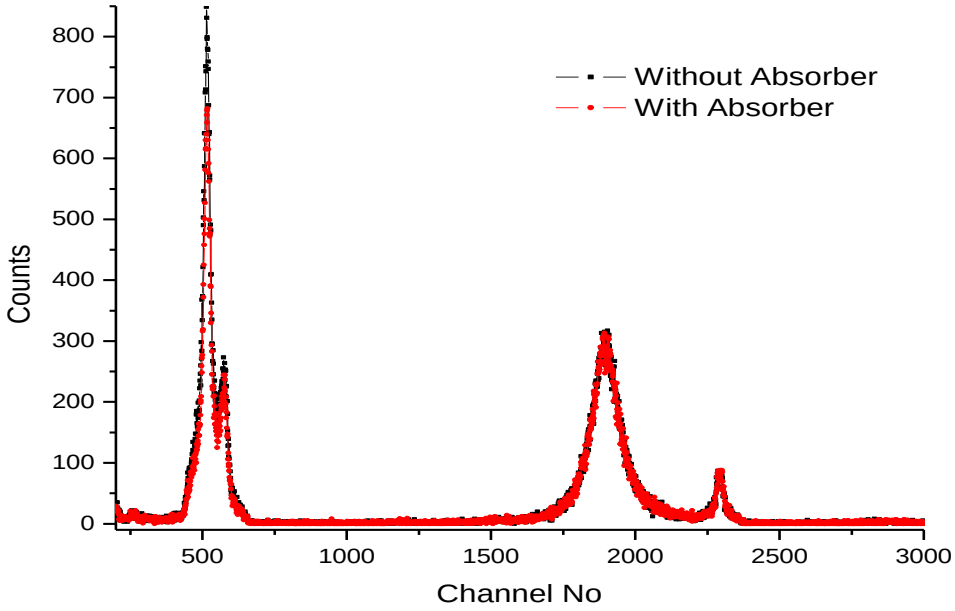

Figure 2: Source Spectrum of Am-241 with Rb target

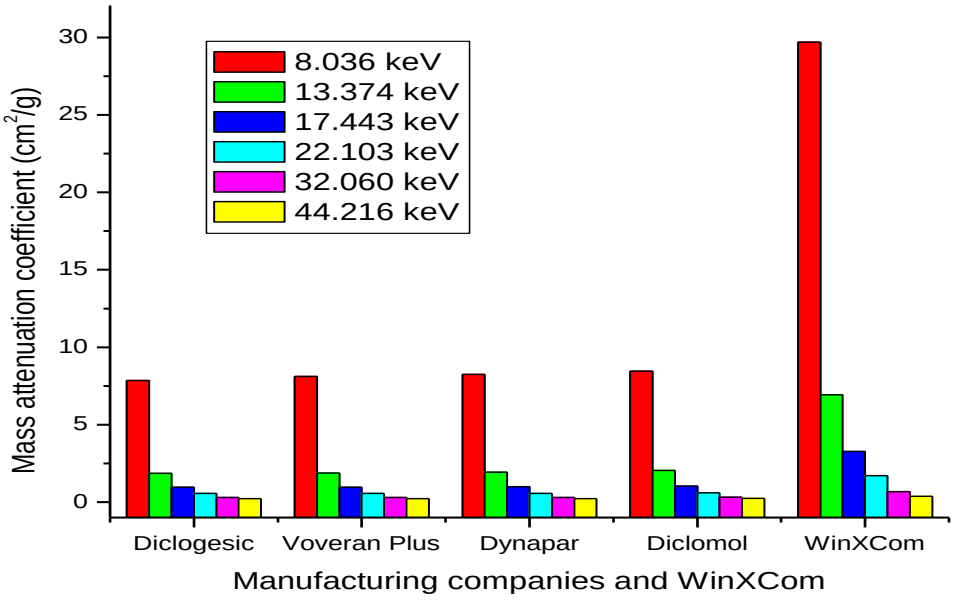

Figure 3: MAC with manufacturing companies at different energies

By the above discussion qualitative analysis of the selected drug and manufacturer were made on the basis of the relative / percentage deviation (PD). PD for all the selected samples is tabulated in the tables 3-5. PD, of about 2%, is treated as good agreement between experimental and theoretical value on the other hand PD greater than 2% should be considered as disagreement between experimental and theoretical value. From the table 1-2 for test data of six elements and three compounds the overall PD is less than 4% and hence is the good agreement. But in the case of pharmaceutical drugs it is varying from 34-40% and 70-73% in higher and low energies respectively. Since the theoretical value corresponds to only the Active Pharmaceutical Ingredient (API) but the experimental results reflects the information about the interaction of photon (X-rays) with inactive pharmaceutical ingredients in addition to API. Hence contribution of inactive pharmaceutical ingredients commonly referred as excipients were more than the API. With reference to fig 4 of the percentage deviation at the entire energy region

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Diclomol has the least exipients than the other. In other words Diclogesic has the highest / more exipients followed by Voveran Plus and Dynapar.

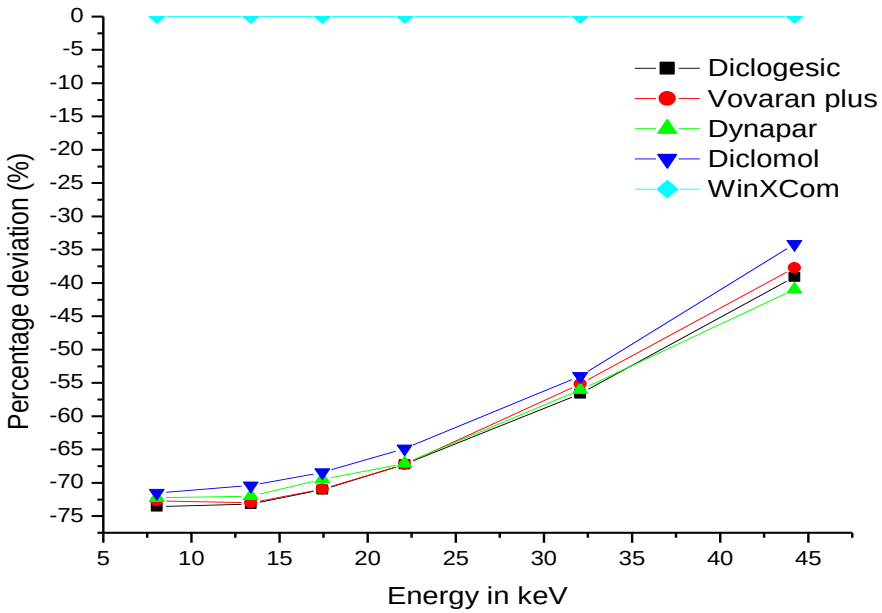

Figure 4: Percentage deviations with Energy

CONCLUSION

An average weight of the each unpacked tablet is 600- 800 mg but the actual active pharma ingredient will be 550 mg (diclofenac sodium 50 mg and Paracetamol 500 mg), remaining up to 30 % contains inactive pharma ingredients called them as excipients viz., coloring agent to pleasant the eye, taste and buffering etc, but this material contribute to MAC values ie., photon interaction with these base materials leads to the large deviation between WinXCom and experimental mass attenuation coefficient values. Therefore, on the basis of experimental results and discussion we can conclude that the technique adopted is the nondestructive, quick to analyze and not much expensive for the pharmaceutical drug testing.

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