ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Confirmation Of Quantity Of Inactive Gradients Added In The Pharma Drugs By Determining Mass Attenuation Coefficient

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ABSTRACT

Analysis is a critical and integral part of the pharma business. Its only upon clearance of products on the analysis can the products be even released into the market. Therefore, analytical methods as well as the involved analytical tools assume prime importance for the qualitative and quantitative test. Hence a non-destructive technique has been developed for the rapid quantitative analysis of active and inactive pharmaceutical ingredients present in the Alprazolam, Famotidine and Diclofenac sodium drug samples by determining mass attenuation coefficient in the low energy (X-ray) region. The x-ray mass attenuation coefficients were studied for above said drug samples at different characteristic x-rays obtained in the energy range from 8 keV to 44 keV from targets viz., Cu, Rb, Mo Ag, Ba and Tb using Am-241 as a primary source of radiation. X-ray intensities were analyzed with and without the attenuator of the each sample using HPGe detector system coupled to multichannel analyzer (MCA) by narrow beam transmission geometry. The obtained mass attenuation coefficient values are compared with the WinXcom values (theoretical). Percentage deviation of WinXCom values and experimental results will signify the quantities of inactive pharmaceutical ingredients are added in the drug samples.

Keyword: HPGe detector, MCA, WinXCom, Mass attenuation coefficient

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ISSN: 0975-8585

INTRODUCTION

Analysis of pharmaceutical drugs by their purity is the prime importance in the pharma and medicine field. Now-a-days single drug can be obtained by different branded names; each brand corresponds to different manufacturing company/laboratories. Since analyzing the API (Active Pharmaceutical Ingredient) in every brand is the necessary aspects in the pharmacology by means of biochemical and/or physiological effect on the cells, tissues, organ or organism. 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 [1-2], GC [3], quantitative thin-layer chromatography (TLC) [4] etc., are available to a pharmaceutical analyst. These methods are all destructive in nature or in other words quality and quantity of the drug was analyzed by destructing their original sample/drug which can't be reused. Hence it is better to adopt a non destructive testing/technique (NDT) for the drug analysis. NDT 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 forums which may or may not be maintaining the quality and quantity (especially in the drugs). Objective of this article reflecting an idea about the confirm the amount of active pharmaceutical ingredient and excipients material were added in the selected three drug samples such as Diclofenac sodium, Famotidine and Alprazolam.

Famotidine is a histamine H_2- receptor antagonist that inhabits stomach acid production and is commonly used in the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD/GORD). Famotidine is N'(aminosulfonyl)-3-[[[2-[(diaminomethylene) amino]-4-thiazolyl]methyl]thio]propanimidamide. The empirical formula of Famotidine is $C_8H_{15}N_7O_2S_3$. It is white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Alprazolam is a short-acting anxiolytic of the benzodiazepine class of psychoactive drug. It is commonly used for the treatment of panic disorder and anxiety disorders such as generalized anxiety disorder (GAD) or social anxiety disorder (SAD). The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-α] [1,4] benzodiazepine and the empirical formula is $C_{17}H_{13}ClN_4$. Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Paracetamol (*p*-hydroxy acetanilide) is a compound with analgesic and antipyretic properties. It is much safer than aspirin in terms of gastric irritation, ulceration and bleeding [1, 2]. Diclofenac sodium [2-[(2, 6-dichlorophenyl)] amino] benzene acetic acid monosodium salt]

is a compound with potent anti-inflammatory property. It affords quick relief of pain and wound edema [3, 4]. Diclofenac sodium belongs to a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs). These are commonly used for the reduction of mild to moderate pain, inflammation, fever and stiffness as well as for medical conditions related to pain and inflammation. They work by inhibiting the action of certain hormones that cause inflammation and pain in the body. Diclofenac in combination with Paracetamol helps reduce headaches, body pain, period and dental pain, sports and accident injuries, rheumatism, arthritis, lumbago, bursitis and sciatica. A few common side effects include sickness, an unexplained rash, and stomach pain. Each diclofenac sodium Tablet contains 500mg Paracetamol and 50mg Diclofenac Sodium

The objective of our study will focus on the qualitative and quantitative analysis of above said three drug samples by non-destructive X-ray spectrometric technique; determining the mass attenuation coefficient (MAC). Mass attenuation coefficient is a measure of the average number of interaction between incident photons and the matter that occur in a given mass per unit area thickness of the substance. Hence, the importance of mass attenuation coefficient have been found in different /verities of 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 [5], compounds [6], tissue equivalent compounds [7], mixtures (different percentage of elements) [8], alloys [9] etc. at different photon energies to study the quality of the material under consideration. However, in the literature, almost no were reports published on the study of mass attenuation coefficient measurement on pharmaceutical samples in the photon energy 8 keV to 32 keV through which quality control of the drug can be defined.

MASS ATTENUATION COEFFICIENT

Low-Z materials are often used or considered for use as scattered of x-ray beams. 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 complex series of interaction between photon 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,

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

ISSN: 0975-8585

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., $x = \rho t$. 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 $(\mu/\rho)_t$ 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. A broad beam geometry as well as 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 except 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 the HPGe detector. A pair of lead collimator each of 3.5cm thick with 6mm diameter was used to collimator the photon beam. These two collimators are inserted at the middle positions of the collimation stand between source and detector of 10cm distance. The sample/s is kept exactly at the mid position of the two collimators as shown in Fig. 1. To study the effects of small and multiple scattered photons by the absorber and collimators in a good geometrical arrangement, a pair of collimators of size 6 and 9mm and broad beam were successively used which found to be about the angle of acceptance at the detector from the source is around 31 and 71 for 6 and 9mm 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, ^{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. 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 (1948) graph, are found to be 0.12 and 0.20, respectively. Rose and Shapiro also plotted the optimum apportionment of counting times as a function of optimum transmission. From this graph we see that for T_{opt}= 0.12 the fraction of counting times for incident, transmitted and background intensity, $\alpha 0$, $\alpha 1$ and $\alpha 2$, respectively, are 0.2, 0.62, and 0.18 approximately, and for T_{opt}= 0.25, 0.25, α_0~0.2, a_1~0.4, and a_2~0.4.. This shows that in both the cases if we adjust time for the transmitted intensity such that the statistical error associated with it is <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 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 (2271 1C) 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 □-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

ISSN: 0975-8585

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 Fig 2. 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.

The theoretical values of mass attenuation coefficient have been estimated by 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,

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

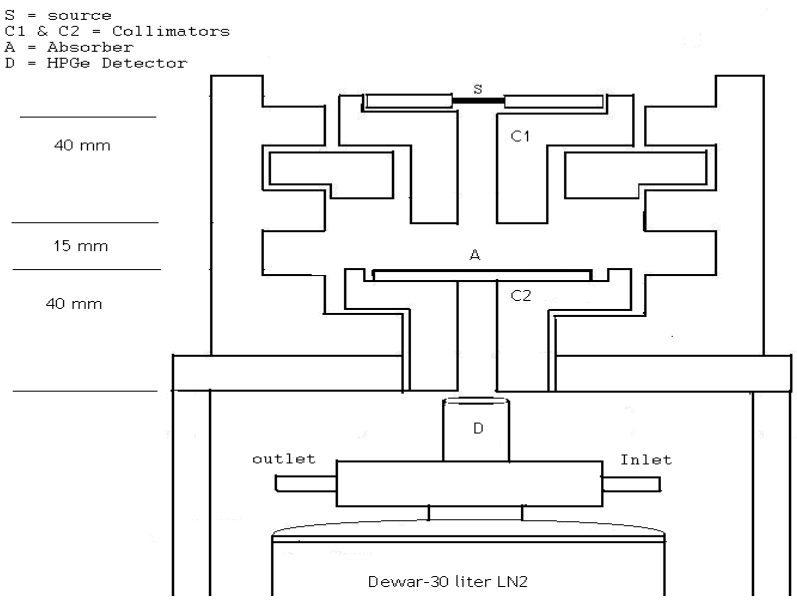

Figure 1 Basic Experimental set for the measurement of Mass attenuation coefficient

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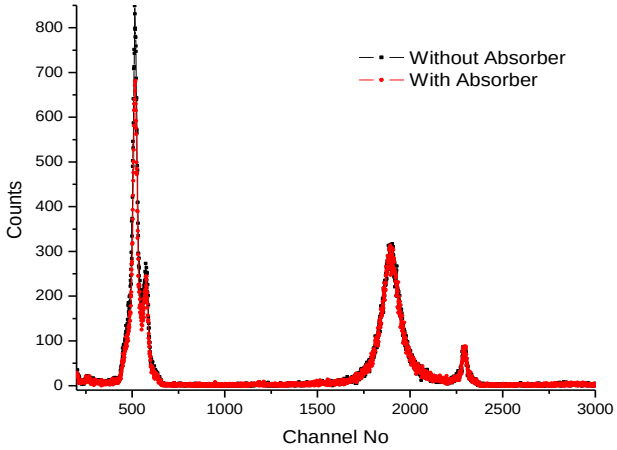

Figure 2 Source Spectrum of Am-241 with Rb target

RESULT AND DISCUSSION

The plots of the logarithm of transmitted intensity versus specimen thickness were linear for all the samples and the μ/ρ was obtained from the plots by linear regression over the 50%-2% transmission range over which the Beer-Lambert's law is rigorously valid under good geometry condition. The obtained results of the mass attenuation coefficient with above condition for six elements and three biological equivalents are tabulated in the Table 1 and 2. In Table 1&2, column 1 & 5 contains name of six elements and three biological equivalent compounds, column 2 & 6 contains experimental results for the elements and compounds, and column 3 &6 contains theoretically estimated WinXCom values for six elements and three compounds at energy 5.895 keV, 6.404 keV, 8.041 keV and 13.375 keV. And column 4&8 gives the percentage deviation between WinXCom and experimental values. A The experimental results deviate from theoretical results as estimated by WinXCom programme by not more than 1% in almost all the cases. Hence from the present elemental and biological equivalent 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, especially using low energy photon detector.

The experiments were further extended to three pharmaceutical drug samples namely Famotidine, Diclofenac sodium & Alprazolam at an energy range from 8.036 keV to 44.216 keV and the obtained results are tabulated in the Table 3. The WinXCom values so obtained as the information contains on the packet of drug about the presence of API in the each drug but the outcome of the experimental results reflects the contribution of inactive pharmaceutical ingredients in respective drugs with API. The uncertainties involved in the theoretical value are about 1-2%. Since the reproducibility of our experimental value is within 2% and the error contribution from the counting statistics, areal density thickness measurement gives about 2%.

ISSN: 0975-8585

All the drug samples are low Z compounds (Z<17) since the binding energy of these drugs samples are far away from the incident characteristic X-ray energy. But the photoelectric process is predominant in the low energy region; hence the mass attenuation coefficient values were maximum at 8.036 keV in all the cases. Therefore as the energy is increased coherent and incoherent processes will contribute in the experimental results.

The weights of each uncoated tablet of Famotidine were 138-152 mg, Diclofenac sodium were 651-677 mg and Alprazolam were 96-113 mg but the API present in all the samples were 40 mg, 550 mg and 0.5 mg respectively. By the simultaneous observation with experimental results and weights will gives an idea regarding the mass attenuation coefficient is the Z dependent parameter. About 99.5 %, 72.41 % and 17.17 % of excipients were added in the alprazolam, Famotidine and diclofenac sodium drugs as on weight method and by experimental mass attenuation coefficient values conforms that the contribution of excipients is more in the alprazolam in comparison with Famotidine and diclofenac sodium drugs. Diclofenac sodium contains least additive (excipients) but the MAC values are less than the Famotidine, this is because of diclofenac sodium contains 2 Chlorine, 2 Nitrogen and 1 Sodium, (hence total of 48 atoms including carbon, hydrogen, oxygen) but Famotidine contains 3 sulfur (dosimetric element) and 7 nitrogen atoms.

Logarithmic graph of mass attenuation coefficient with energy were plotted for the selected drug samples in the Fig. 3, in which first three lines from the top (Red, Blue and Pink) are represents the WinXCom values are always higher than the experimental results (next three lines). Since mass attenuation coefficient is a measure of the average number of interaction between incident x-ray energy and the matter. Therefore by this definition it conforms that the drug samples contains a base or excipients or inactive pharmaceutical ingredients were added by the all the manufacturer depending on their concentration and effect of API on the health. Fig 4, remarked here that the deviation of mass attenuation coefficient with theoretically estimated values by WinXCom programme [10] which is the successor of program XCOM [11].

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	WinXCom			Experimental	WinXCom	
Energy 5.895 keV				Energy 6.404 keV			
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

ISSN: 0975-8585

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_{β} X-rays

Element /compound	Mass attenuation coefficient		PD (%)	Element /compound	Mass attenuation coefficient		PD (%)
	Experimental	WinXCom			Experimental	WinXCom	
Energy 8.041 keV				Energy 13.375 keV			
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

Table 3: Experimental and theoretical results of mass attenuation coefficient in cm^2/g for selected drug samples 8.036 keV and 44.216 keV.

Energy in keV	Famotidine			Diclofenac sodium			Alprazolam		
	Expt	Thr	Pd	Expt	Thr	Pd	Expt	Thr	Pd
8.036	14.900 ± 0.171	31.198	-52.240	8.46 ± 0.062	29.69	-71.510	7.810 ± 0.072	16.515	-52.710
13.374	3.520 ± 0.019	7.228	-51.300	2.05 ± 0.015	6.932	-70.427	1.880 ±0.006	3.446	-45.444
17.443	1.710 ± 0.004	3.391	-49.572	1.03 ± 0.007	3.263	-68.434	0.933 ±0.007	1.779	-47.555
22.103	0.940 ± 0.007	1.766	-46.772	0.60 ± 0.006	1.705	-64.868	0.551 ±0.004	1.013	-45.607
32.06	0.423 ± 0.004	0.701	-39.658	0.31 ± 0.005	0.680	-53.970	0.306 ±0.004	0.454	-32.599
44.216	0.266 ± 0.003	0.376	-29.255	0.24 ± 0.004	0.366	-34.153	0.236 ±0.002	0.281	-16.014

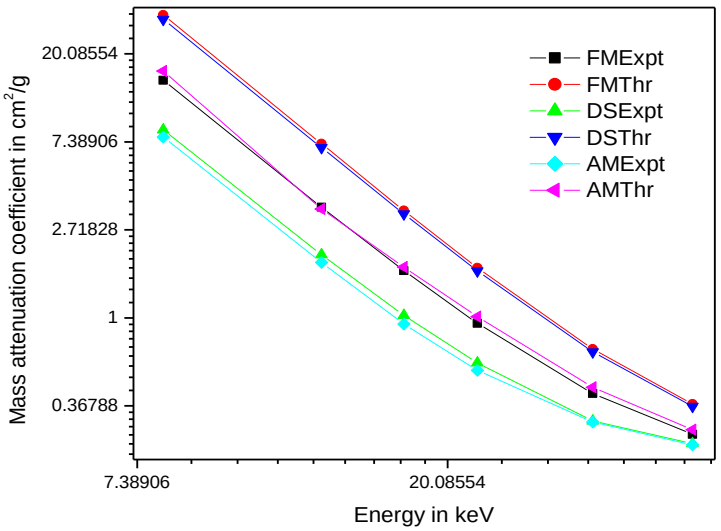

Figure 3 Logarithmic graph of mass attenuation coefficient in cm^2/g with energy in keV

ISSN: 0975-8585

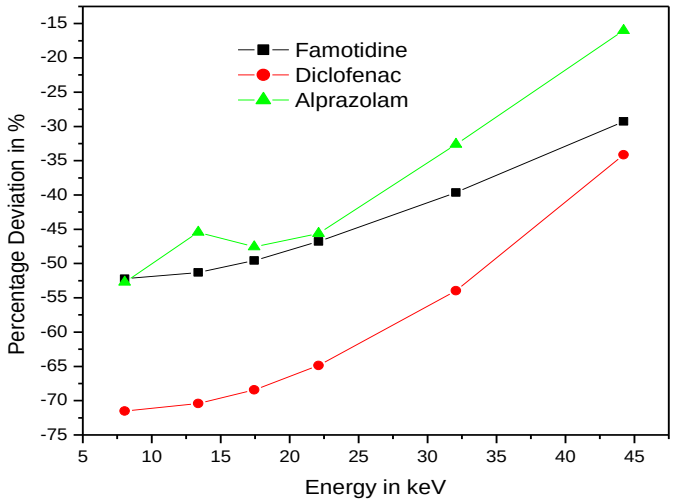

Figure 4 Percentage deviations of Pharmaceutical drug samples with Energy

CONCLUSION

Thus, the contribution of multiple excipients used in the tablets by the manufacturer is detectable in this non-destructive analytical method; x-ray interactions through the determination of mass attenuation coefficient. Therefore the method outlined here in this paper is simple, quick and non-destructive method to analyze the quality control of the pharma compound through the relative intensity measurements.

ACKNOWLEDGEMENT

Authors acknowledge the University Grants Commission, New Delhi for providing the financial support to carry out this work.

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