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Effect of Neutron Irradiation on the Physicochemical Properties of Naproxen Sodium

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Abstract

Pharmaceutical drug delivery systems for non-steroidal anti-inflammatory drugs involve targeted delivery or controlled release of the drug. The most common method to monitor the *in vivo* behavior of pharmaceutical dosage form is neutron activation based gamma scintigraphy. It is necessary to ensure that the process of neutron irradiation does not affect the physicochemical properties of the formulated drug and its dosage form. This study, the effect of neutron irradiation on the physicochemical properties of naproxen sodium is investigated and it is also; selected as the model drug. The process of neutron irradiation was carried out at the Malaysian Nuclear Agency using the TRIGA MK II reactor. After irradiation times of 1, 2, 3, 4, 5 and 30 min, the effect of neutron irradiation on physicochemical properties of naproxen sodium was investigated using scanning electron microscope (SEM), gas chromatograph-mass spectrometer (GCMS), Fourier transform infrared spectrometer (FTIR) and differential scanning calorimeter (DSC). The physicochemical properties of non-irradiated naproxen sodium were compared to the irradiated naproxen sodium samples. Colour changes after irradiation was observed. Results of analysis of SEM and FTIR spectrometer showed changes in the physicochemical properties of naproxen sodium when duration of irradiation was increased. There were no major changes in the result of GC-MS and DSC. Based on the results obtained, it can be concluded that naproxen sodium is a suitable drug that can be used for neutron activation based gamma scintigraphy. The maximum irradiation time that naproxen sodium can withstand without changes in its physicochemical properties is 3 min.

Keywords: ***Neutron irradiation; Naproxen sodium; Anti-inflammatory; Scintigraphy; TRIGA MK II***

Introduction

All matter contains atoms. Atoms consist of the nucleus which contains protons and neutrons, and an outer shell that contains electrons. The electrons are negatively charged and the protons are positively charged. In a stable atom, there is sufficient binding energy to hold the nucleus together. However, in an unstable atom, the binding energy is insufficient to bind the

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nucleus together. The unstable atom emits a quantity of energy in order to reach stability. These emissions are known as radiation. Unstable atoms are radioactive. Radiation can occur as electromagnetic waves or particles. Alpha (α) particles and beta (β) particles are examples of particle radiation. Electromagnetic radiation consists of photons. Examples are gamma-rays and x-rays. Neutrons are particle radiation. They are high-speed nuclear particles with an immense ability to penetrate other materials. This process is known as neutron activation. The neutron activation process is used to produce radioactive sources that are used in research, medical and industrial applications. In this study, we investigated the effect of neutron irradiation on the physicochemical properties of naproxen sodium. The source of neutron radiation for this research is from the nuclear reactor of the Malaysian Nuclear Agency. The Malaysian Nuclear Agency has a which is known as PUSPATI TRIGA Mark II reactor (RTP).

Background information

The PUSPATI TRIGA reactor is the only nuclear research reactor available in Malaysia. It is a pool type reactor. TRIGA stands for training, research, isotope production and general atomic. The core of the reactor sits at the bottom of a 2.5 metre thick and 7-metre high aluminum tank with high density concrete as a biological shield. The solid fuel elements of the reactor consist of zirconium-hydride moderator combined homogenously with enriched uranium sheathed in stainless steel. These fuels are arranged in six circular rings in the core of the reactor. Demineralized light water acts as a coolant whereas the core cooling takes place via natural convection method. Neutrons are produced in the reactor through chain fission reaction of uranium-235 nuclei in the fuel elements. In order to sustain the chain fission reaction of Uranium-235, the fuel rods contain 20% of enriched uranium-235. A neutron is absorbed by the Uranium-235 nucleus in order to fission into two new nuclei with an average of two fast neutrons with energies of 10 MeV. The neutrons will either collide with water molecules and lose their energy or thermalise into energies in the range of 0 eV to 0.025 eV before it is absorbed by another two uranium-235 nuclei to generate the chain reaction.

Safety features of the nuclear reactor

In order to ensure that the reactor functions safely, it is equipped with a control system. There are four boron carbide control rods that are used to control the reactor power. It is of utmost importance to monitor the radiation levels in the reactor hall. Thus, area radiation monitors (ARM) are located strategically around the reactor hall. The ARM system is linked to the reactor control room. It is capable of giving out audible and visual warnings to the reactor operator in the event of any radiation contamination in the reactor hall.

***In vivo* study of pharmaceutical dosage forms**

Once a modified release dosage form is formulated, it is necessary to know about the transit of the dosage form in the human body. *In vitro* testing methods alone is inadequate to show the transit of oral dosage forms in the gastrointestinal tract. For oral dosage forms, factors like altered gastrointestinal (GI) tract transit due to physiological, pharmacological or individual variations can affect drug absorption [1].

Gamma scintigraphy

It is becoming evident that *in vitro* studies alone are insufficient for the development of modified-release drug formulations. It is pertinent to study the *in vivo* behaviour of these formulations at an early stage. The *in vivo* behaviour of pharmaceutical dosage forms can be studied using gamma scintigraphy. It is said that gamma scintigraphy is the best known radionuclide

imaging technique [2]. Gamma scintigraphy is the most prevalent method used for the investigation of GI performance of pharmaceutical dosage forms [3]. It is a technique that allows non-invasive imaging of the transit of a dosage form through its intended site of delivery by using a short-lived gamma-emitting radioisotope. The transit of the dosage form is correlated with the rate and extent of drug absorption by using human subjects or a suitable animal model. The conventional radiolabeling method involves radiolabeling the dosage form by incorporating a short-lived radionuclide into the formulation. However, this method has its disadvantages. The conventional radiolabeling method is limited to simple dosage forms.

Model drug: Naproxen sodium

Naproxen, 4-2-(6′-methoxy-2′-naphthyl)-propionic acid is an analgesic NSAID (Non- steroidal anti-inflammatory drug). It is a compound with anti-inflammatory activity [4]. Both COX isoforms are inhibited by Naproxen. It inhibits functions of leukocytes at the inflammatory site. It is mostly used for enclosing spondylitis, rheumatoid arthritis, and traumatic damage to joints and surrounding tissues. The most common side effects of naproxen are GI irritation, headache, vertigo, and depression [5]. The model drug of this research is naproxen in its sodium salt form, naproxen sodium. The chemical formula of this drug is $C_{14}H_{13}NaO_3$ and its molecular weight is 252.23. Naproxen sodium is a white to creamy crystalline powder which is odorless [6]. Naproxen sodium [(+)-(S)-2-(6-methoxynaphthalen-2-yl) sodium propionate is a well absorbed drug with half-life of 12 to 24 hours. It is very soluble in water and has good ability to permeate through oral mucosal tissue [7].

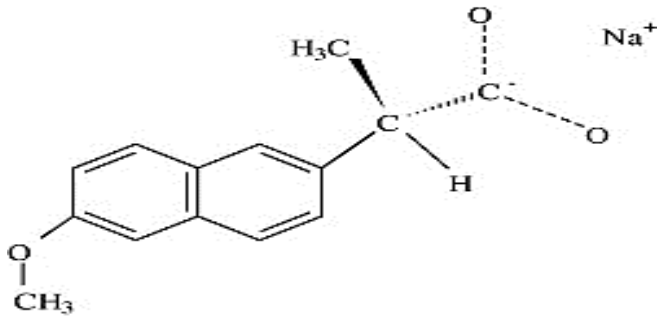

FIG. 1. **Structure of Naproxen sodium source [12].**

Analysis of physicochemical properties of non-irradiated and irradiated Naproxen sodium

In order to determine the effects of neutron irradiation on naproxen sodium, it is fundamental to investigate the physicochemical properties of non-irradiated naproxen sodium and compare it to the physicochemical properties of irradiated naproxen sodium. The method of analysis used should be accurate, sensitive and reliable. It is necessary to observe the crystal morphology of irradiated and non-irradiated naproxen sodium. This is because crystal morphology is important in product development and pharmaceutical processing of modified solid (FIG. 1).

Dosage forms. Any changes in crystal habit will influence the compaction, compressibility, dissolution characteristics and modify the flow ability of the powdered drug [8]. The crystal morphology of non-irradiated and irradiated naproxen sodium is viewed using the Scanning Electron Microscope (SEM). The next preferred method of analysis employs the use of Gas Chromatography-Mass Spectrometry (GC-MS). Mass spectrometry plays an indispensable role in the structural characterization of drugs. This technique has good selectivity and high sensitivity and is known to be one of the most powerful analytical techniques [9]. Fourier Transform Infrared Spectroscopy (FTIR) is an analytical method that is useful for

the identification of drugs. This method of analysis is quantitative and can be used for the simultaneous analysis of different components of the same sample [10]. The result obtained from the FTIR is known as the infrared spectrum, which is the plot of absorption intensity versus wavelength. Thermal analysis is a part of material science that studies the properties of material with change in temperature. DSC is used to characterize chemical and physical events through the changes in either heat capacity or enthalpy of a sample. This technique is a well-established method of thermal analysis [11].

Problem identification

Before progressing to *in vivo* evaluation of a pharmaceutical dosage form of naproxen sodium via gamma scintigraphy, it is necessary to investigate the effect of radiation on the physicochemical properties of the drug itself. The effects of longer duration of radiation can affect the results of *in vivo* study of naproxen sodium tablets. The maximum radiation time required to irradiate naproxen sodium without causing changes in its physicochemical properties can be estimated.

Materials

Naproxen sodium and methanol (analytical grade) were purchased from Sigma Aldrich Merck, Germany.

Preparation of samples for irradiation procedure

The naproxen sodium powder that needs to be irradiated is weighed using a Mettler Toledo weighing balance. Naproxen sodium was weighed and put into six clean polyethylene vials, as shown in FIG. 2a. Each polyethylene vial had 1.35 g of naproxen sodium. Each vial was labelled accordingly using the alphabets A to F. After weighing, the vials were sealed using a soldering iron as shown in FIG. 2a. The sealed vials were then put into a pneumatic cylinder prior to the process of irradiation as shown in FIG. 2b.

FIG. 2. **(a) Polyethylene vials containing naproxen sodium.**

FIG. 2. **(b) Pneumatic cylinders containing polyethylene vials.**

Process of irradiation

The process of irradiation was done in the TRIGA MK II nuclear reactor (Malaysian Nuclear Agency) with a neutron flux of 3.126×10^{12} ncm^{-2} s^{-1}. The pneumatic cylinders were transferred to the nuclear reactor using a pneumatic transfer system. The duration of irradiation of each sample of naproxen sodium is shown in TABLE 1. After irradiation, the samples of naproxen sodium were stored in a lead container for 2 weeks in order to ensure that the level of radiation has reduced to background

radiation level. The changes in colour of the irradiated naproxen sodium at different time intervals were compared to the non-irradiated naproxen sodium.

TABLE 1. **Duration of irradiation of pneumatic cylinders containing naproxen sodium.**

Samples	Duration of irradiation (min)
A	1
B	2
C	3
D	4
E	5
F	30

Scanning electron microscope

The observation, examination and analysis of microstructure morphology and chemical composition characterizations of drugs and other materials can be done using the scanning electron microscope (SEM). The SEM is versatile equipment that is able to provide myriads of imaging techniques with resolutions in the range 1 µm to 1 nm, depending on the type of microscope and the method used to form the image. The formation of image in the SEM is dependent on the interaction between electrons with the samples. The electron gun in the SEM generates a beam of high energy electrons. The beam of electrons is processed by magnetic lenses which then focus at the surface of the sample. The sample is then systematically scanned to produce an image [12]. The non-irradiated sample and the irradiated samples were viewed under a scanning electron microscope. Prior to examination, samples were gold sputter-coated to render them electrically conductive [13].

Gas chromatography-mass spectrometry (Gc-Ms)

Gas chromatography-mass spectrometry (GC-MS) uses a combination of two analytical techniques known as gas chromatography and mass spectroscopy. GC-MS is used to separate volatile compounds. The GC-MS system works by injection of the sample into the system, separation of the samples in the capillary column and detection of the separated compounds. This technique of analysis is a powerful pharmaceutical analytical technique that is highly sensitive [14].

Preparation of samples for GC-Ms

Then on-irradiated naproxen sodium samples and the irradiated samples were accurately weighed to 1.5 mg using an analytical balance. 1 ml of methanol of analytical grade from Merck was used to dilute each sample of naproxen sodium. It is ensured that the naproxen sodium was completely dissolved in methanol before proceeding to GC-MS analysis.

GC-MS analysis

The GC/MS system used is a Shimadzu QP 5050A gas chromatograph equipped with an AOC-20i auto-injector. The samples were injected in split less (or splitless?) mode into a SGE capillary column (30 m × 0.25 mm × 0.25 µm) with helium carrier gas at a constant flow of 1.3 ml/min. The injector was heated to 200°C. Initial oven temperature is 70°C. This temperature is maintained for 5 min. Next, the temperature is increased to 300°C at a rate of 10°C per minute. The mass range was 50 m/z to 250 m/z.

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) is a chemical analytical technique that can be used for the identification of substances. FTIR uses the measurement of the molecular bond vibration of compounds excited by infrared radiation of a suitable frequency [15]. The Fourier Transform Infrared Spectra of non-irradiated and irradiated naproxen sodium samples were recorded on Perkin Elmer Frontier using Spectrum 10 Spectroscopy Software. The sample holder was cleaned using 100% methanol. About 1 mg of sample was placed on the sample holder. The scanning range was from 650 cm^{-1} to 4000 cm^{1}.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) is a thermo-analytical technique that measures the difference in heat flow between a sample and reference as a function of temperature [16]. Thermal analysis was carried out using a Mettler Toledo Differential Scanning Calorimeter. In order to calibrate the temperature and enthalpy scale, indium standards were used. The weights of the non-irradiated naproxen sodium and irradiated samples used were 5 mg to 8 mg. The samples were hermetically sealed in aluminium pans and heated at a constant rate of 10°C per minute over a temperature range of 80°C to 300°C. Nitrogen gas was purged in at a rate of 50 ml/min to maintain an inert temperature [17].

Results and Discussion

Changes in colour of naproxen sodium after neutron irradiation

The non-irradiated sample of naproxen sodium is white in colour. The colour of naproxen sodium samples that were irradiated for 1, 2 and 3 min was the same as the non-irradiated naproxen sodium. Samples that were irradiated for 4 and 5 min were slightly yellow compared to the non-irradiated sample as shown in the FIG. 3 below.

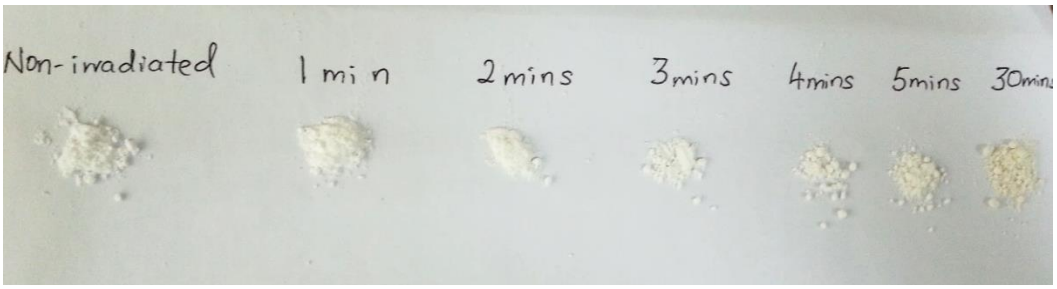

FIG. 3. **Changes in colour of Naproxen sodium after irradiation.**

The sample that was irradiated at 30 min was brown in colour because of prolonged duration of irradiation. Changes in colour of irradiated samples with increase in irradiation duration were also observed in an experiment involving neutron irradiation of suppositories and its excipients [18]. In another research that studied the influence of neutron irradiation on Eudragit® coated tablets found that the colour of the cores of the tablet changed from white to an increasing brown colour with an increase in duration of irradiation [19].

Scanning electron microscope analysis

The crystals of non-irradiated naproxen sodium are rough surfaced with irregularly shaped longitudinal crystals (Bhise et al. 2008). The microphotograph of non-irradiated, irradiate by 2 mins 5 min and 30 min naproxen sodium at 2000x magnification is shown in FIG. 3a-3d below. After the process of irradiation, the surface morphology of the crystals changed.

FIG. 3b-3d shows the scanning electron microphotographs of irradiated naproxen sodium at 2000x magnification. The irradiated naproxen sodium samples had more rougher surface than the non-irradiated samples. There were appearance of smaller needle like crystals in the irradiated samples. This shows that the process of neutron irradiation can change the surface morphology of naproxen sodium. In a study, it can be seen that clear differences can be observed in the structure and surface morphology of Eudragit® tablets that have undergone neutron irradiation using scanning electron microscope [20]. It is important to analyse the effect of neutron irradiation procedures on the surface morphology and structure of naproxen sodium particles. This is because any changes in the crystal habit will cause a change in the dissolution characteristics, flowability of the powdered drug and the compaction of the tablet [21]. The changes in crystal structure will eventually affect the properties of a modifed release dosage form.

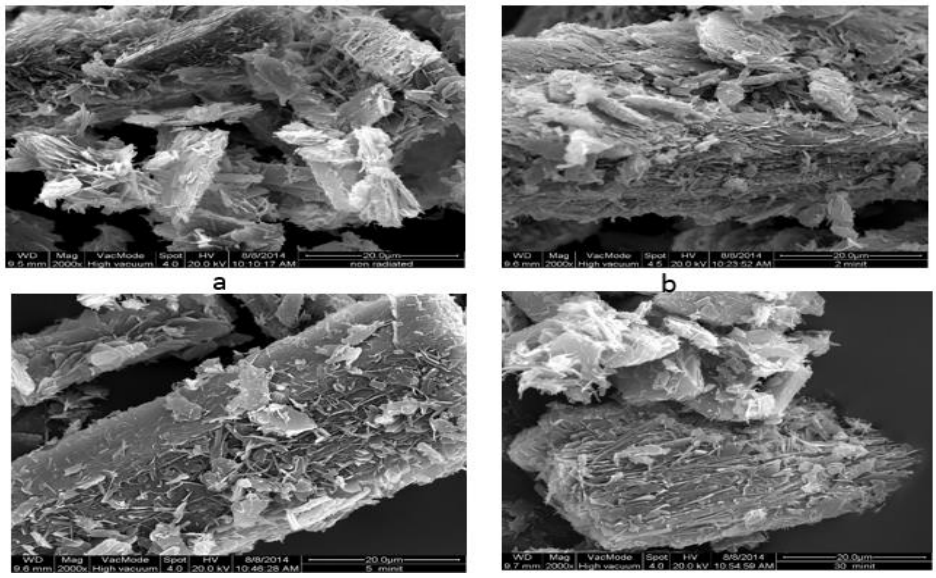

FIG. 3. **(a,b,c, d) SEM microphotograph of (a) non-irradiated, (b) irridiate by 3 mins, (c) irridiate by 5mins and (d) irridiate by 30 mins naproxen sodium at 2000x magnification.**

Analysis of gas chromatography-mass spectrometry (GC-Ms)

Total ion chromatography (TIC) and mass spectrometry of non-irradiated Naproxen sodium

The TIC is a plot along y-axis and x-axis of the abundance of total ion current and retention time in min, respectively, obtained from a chromatography experiment coupled with mass detection. The total ion chromatography of non-irradiated naproxen sodium shows a total retention time of 27 min. The parent peak and base peak is obtained from the mass spectrometry results. The base peak signifies the most intense ion in the sample. The parent peak is 252 and the base peak is 44.00. The GC-MS results are shown in FIG. 4a and 4b.

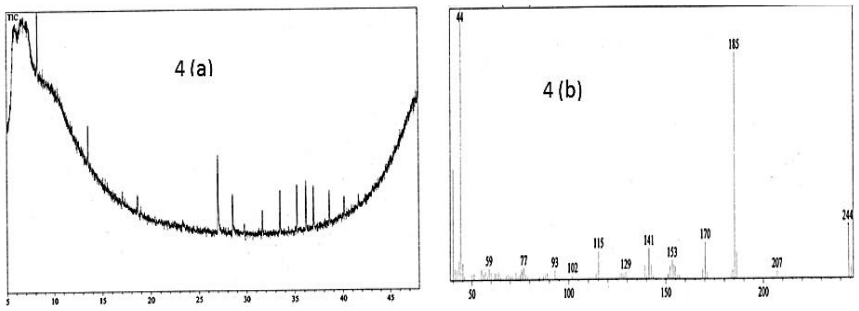

FIG. 4. **(a, b) Total ion chromatography and Mass Spectrum of non-irradiated naproxen sodium.**

Total ion chromatography (TIC) and mass spectrometry of irradiated Naproxen sodium

The TIC of irradiated naproxen sodium at different times show similar retention times, base peak and parent peak.The retention time, parent peak and base peak of irradiated naproxen sodium is shown in the TABLE 2. The results are shown in FIG. 4(c-h)

TABLE 2. **Retention time, parent peak and base peak of irradiated naproxen sodium samples.**

Duration of irradiation of naproxen sodium (min)	Retention time (min)	Parent peak	Base peak
1	27	252	185
2	27	252	185
3	27	252	185
4	27	252	185
5	27	252	185
30	27	252	185

GC-MS Results of Irradiated Naproxen Sodium

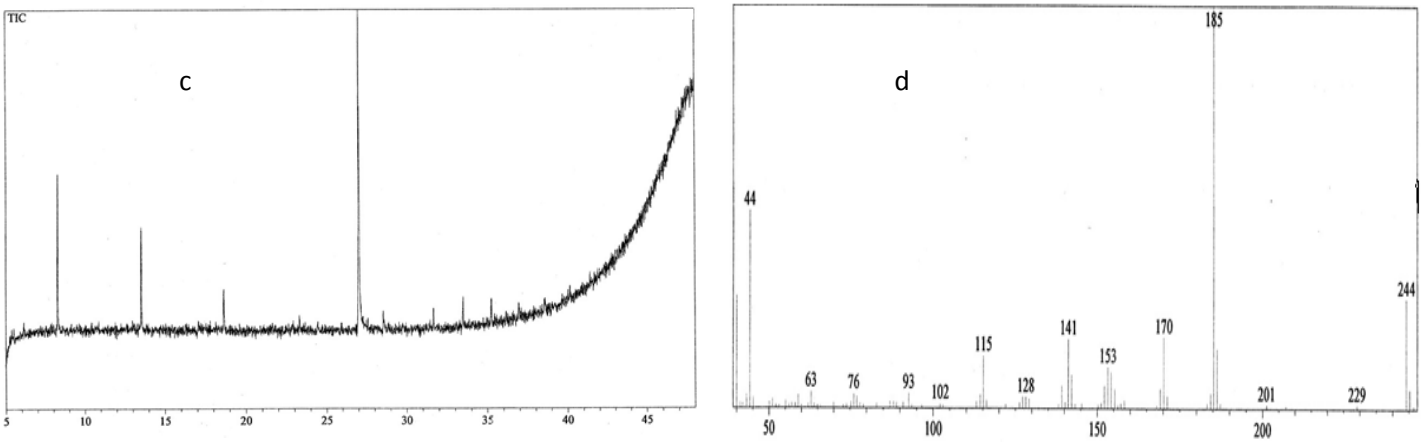

FIG. 4. **(c, d) Total ion chromatography of irradiated naproxen sodium at 2 min and Mass Spectrum of irradiated naproxen sodium at 2 min.**

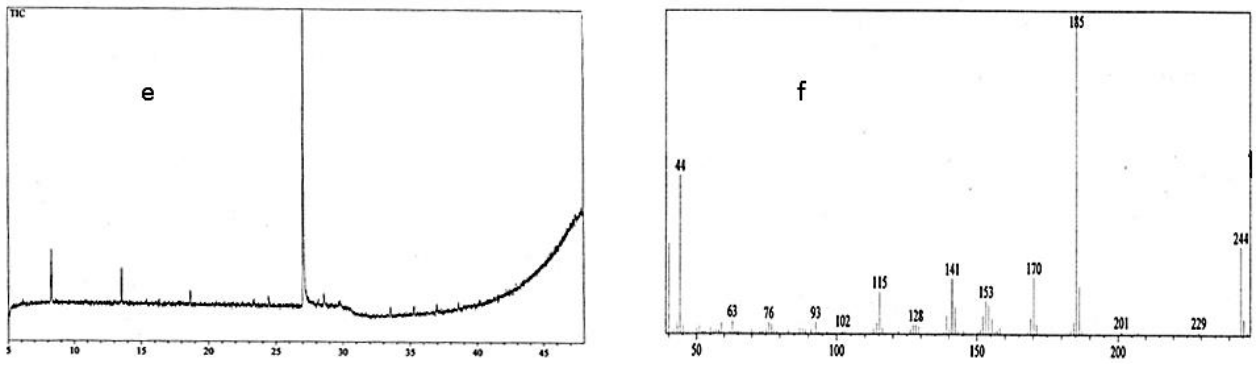

FIG. 4. **(e, f) Total ion chromatography of irradiated naproxen sodium at 5 min and Mass Spectrum of irradiated naproxen sodium at 5 min.**

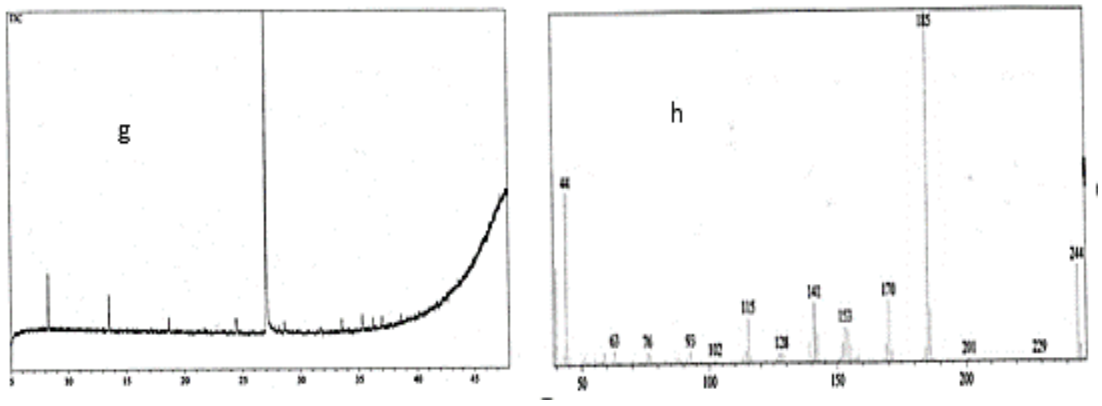

FIG. 4. **(g, h) Total ion chromatography of irradiated naproxen sodium at 30 min and Mass Spectrum of irradiated naproxen sodium at 30 min.**

Discussion on results of GC-MS analysis

Based on the results shown, it can be seen that the retention time of non-irradiated naproxen sodium and irradiated naproxen sodium is 27 min. There are 3 major peaks that can be seen in the TIC of non-irradiated naproxen sodium and irradiated naproxen sodium at retention time of 8 min, 13.5 min and 27 min. The abundance of the total ion current of the peak at 27 min is the same for every irradiated sample. However, the abundance of the total ion current of peak 8 min and 13.5 min reduces with increasing irradiation time. The parent peak from the mass spectrum of non-irradiated naproxen sodium and irradiated samples is 252. This proves that the sample is Naproxen sodium as the molecular weight of naproxen sodium is 252 [22]. The base peak of non-irradiated naproxen sodium is 44 but the base peak of irradiated naproxen sodium is 185. This is the only difference that can be seen when comparing the mass spectrum of non-irradiated and irradiated naproxen sodium. Based on the mass spectrum of irradiated naproxen sodium, the fragment ion at signal m/z =185 represents the most prominent ion $[C_{13}H_{13}O]^{+}$and is mainly due to the rupture of COOH molecule from the main molecular ion [23].

Analysis of Fourier transform infrared spectroscopy (FTIR)

The results of analysis of non-irradiated and irradiated naproxen sodium at intervals of 2 min to 5 min and 30 min are shown in the FIG. 5a and 5d. The FTIR spectrum is a plot of transmittance (%T) against wavelength (cm^{-1}).

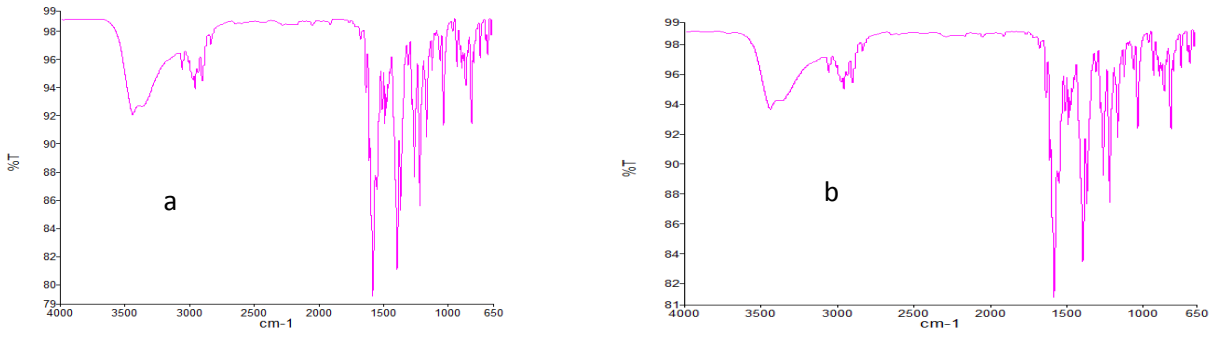

FIG. 5. **(a, b) FTIR spectrum of non-irradiated naproxen sodium and irradiated naproxen sodium at 2 min.**

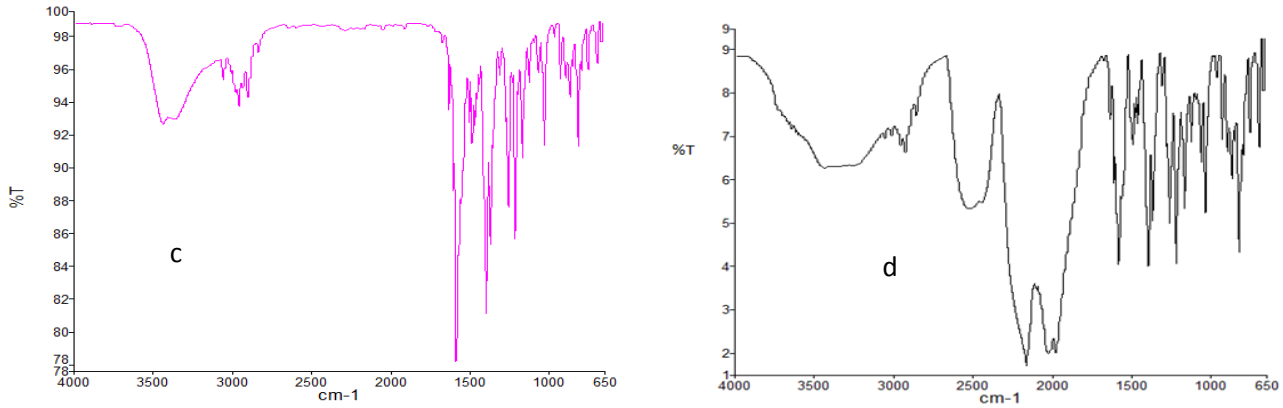

FIG. 5. **(c, d) FTIR spectrum of irradiated naproxen sodium at 5 min and at 30 min.**

Discussion on results of FTIR spectroscopy

The infrared absorption and the related functional groups of non-irradiated and irradiated sample are shown in the Table 3 below.

TABLE 3. **Infrared absorbance for functional groups in non-irradiated and irradiated samples of naproxen sodium.**

Functional Group	**Wavelength (cm^{-1})**						
	Non-irradiated naproxen sodium	**Irradiated naproxen sodium**					
		1 min	**2 min**	**3 min**	**4 min**	**5 min**	**30 min**
O-H	3448	3448	3448	3448	3447	3446	3444
C-H (aromatic)	3000	3000	3000	3000	3000	3000	3017
C=O (acid)	1631	1631	1630	1630	1630	1630	1630

COO^-	1584	1584	1584	1584	1584	1584	1584
C-O- (ether)	1210	1211	1211	1210	1210	1210	1210
CH_3	1364	1364	1364	1364	1364	1364	1364

Based on TABLE 3, the FTIR spectra of non-irradiated and irradiated naproxen sodium had similar wavelengths for the relevant functional groups. The FTIR spectrum of naproxen sodium exhibits sharp bands at 1210 cm^{-1} due to C-O- stretching (ether), 1394 cm^{-1} to 1365 cm^{-1} due to CH_3 bending, 1480 cm^{-1} due to asymmetrical COO^-stretching, 1580 cm^{-1} due to symmetrical COO^- stretching, 1628 cm^{-1} due to C-C aromatic skeletal stretching [24].

The peaks at the wavelength of 1364 cm^{-1} are due to methyl (CH_3) bending as shown in FIG. 5b to 5d. Due to the stretching of the ether(C-O) functional group, there are peaks at the wavelength 1210 cm^{-1} in the non-irradiated and irradiated samples of naproxen sodium. The peaks at 1584 cm^{-1} in the non-irradiated and irradiated FTIR spectrum can be seen due to symmetrical COO^- stretching.

The FTIR spectrum of non-irradiated and irradiated samples from 2 min to 5 min and 30 mins is almost similar in the wavelength region of 650 cm^{-1} to 1500 cm^{-1} as shown in FIG. 5b to 5d. The most changes in the FTIR spectrum can be seen in the 30 min irradiated naproxen sodium as shown in FIG. 5d. The 30 min irradiated sample had significant new peaks in the region of wavelength of 1500 cm^{-1} to 3000 cm^{-1}. The new peak is due to the degradation of naproxen sodium caused by prolonged duration of irradiation. Studies show that ionizing radiation under extreme conditions or prolonged duration can lead to the scission of bonds which results in the appearance of new peaks [25].

Analysis of differential scanning calorimetry (DSC)

DSC analysis of non-irradiated Naproxen sodium: The thermo gram of naproxen sodium shows prominent and sharp endothermic peak at 256.50°C (ΔH=-133.23J/g) represents its melting point [24]. Based on the experiment done, the thermo gram of non-irradiated naproxen sodium showed prominent and sharp endothermic peak at 255.79°C (ΔH=-138.75J/g). The thermo gram of non-irradiated naproxen sodium is shown in FIG. 6a.

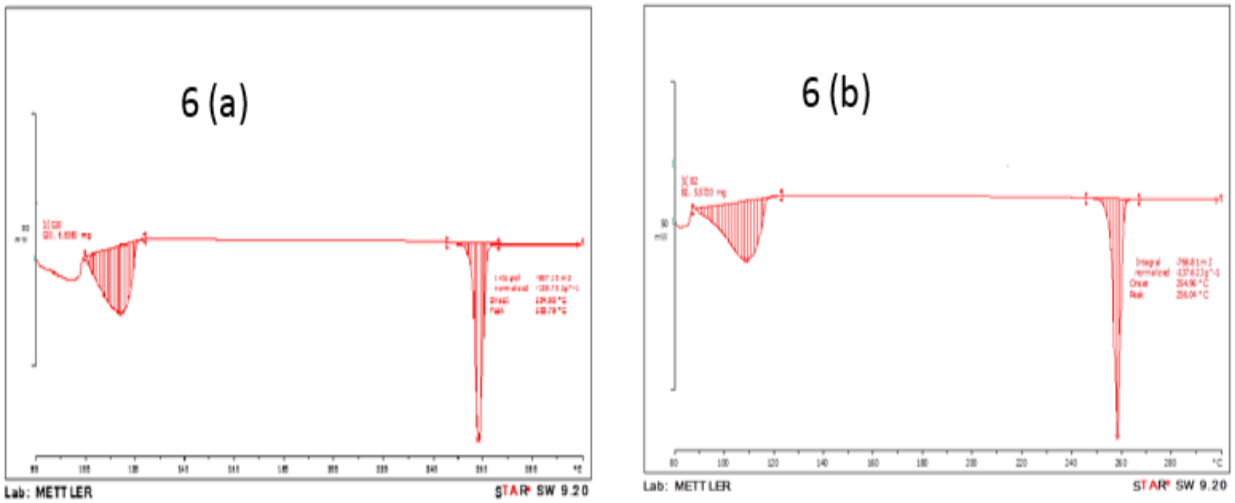

FIG. 6. **(a, b) Thermogram of non-irradiated and 2 min irradiated naproxen sodium.**

DSC analysis of Naproxen sodium irradiated for 2 min

The thermo gram of 2 min irradiated naproxen sodium is shown in FIG. 6b. this sample showed a prominent and sharp endothermic peak at 256.04°C
(ΔH= -137.62J/g).

DSC analysis of Naproxen sodium irradiated for 5 min: The thermo gram of 5 min irradiated naproxen sodium is shown in FIG. 6c. This sample showed a prominent and sharp endothermic peak at 256.13°C (ΔH= -141.60J/g).

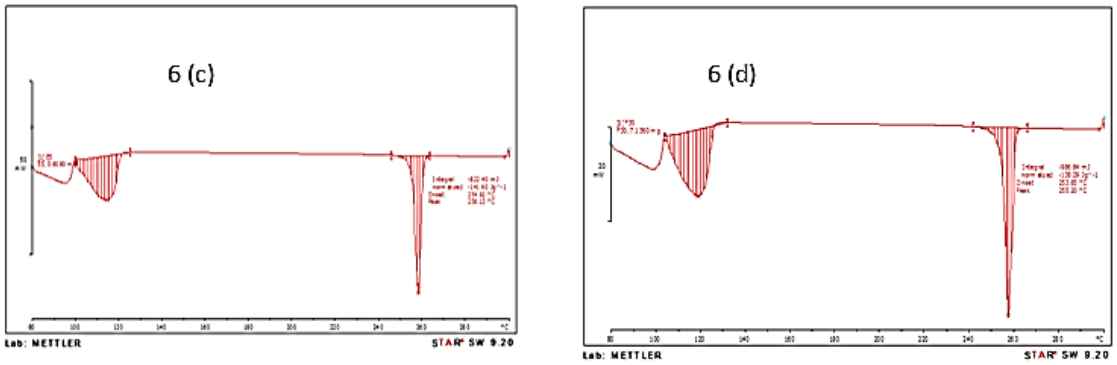

FIG. 6. **(c, d) Thermo gram of 5 min and 30 min irradiated naproxen sodium.**

DSC analysis of Naproxen Sodium irradiated for 30 min: The thermo gram of 30 min irradiated naproxen sodium is shown in FIG. 6d. This sample showed a prominent and sharp endothermic peak at 255.20°C
(ΔH=-138.29J/g).

Discussion on results of DSC analysis: The peak melting point and the enthalpy change of non-irradiated and irradiated naproxen sodium is shown in TABLE 4. below.

TABLE 4. **Melting point and enthalpy of heat of non-irradiated and irradiated naproxen sodium.**

Sample of Naproxen Sodium	**Peak Melting point (°C)**	**Enthalpy Change (ΔH)(J/g)**
Non-Irradiated	255.79	-138.75
1 min irradiation	256.12	-141.08
2 min irradiation	256.04	-137.62
3 min irradiation	256.16	-133.31
4 min irradiation	256.38	-133.95
5 min irradiation	256.13	-141.60
30 min irradiation	255.20	-138.29

In pharmaceutical sciences, differential scanning calorimetry (DSC) is known as a well-established method of thermal analysis. The technique can be used to characterize physical and chemical events via changes in either enthalpy or heat capacity of a sample.

Naproxen sodium that was irradiated for 2 minute up to 5 min and 30 min showed a sharp endothermic peak from 255°C to 256.12°C. When compared to non-irradiated naproxen sodium with an endothermic peak of 255.79°C, the endothermic peak of all the irradiated samples did not differ greatly. The endothermic peak of non-irradiated and irradiated naproxen sodium samples are within the range of 255°C to 257°C, which encloses the value of melting point reported for naproxen sodium [26]. This shows that the endothermic peak of non-irradiated and irradiated naproxen sodium samples is within the melting point reported for naproxen sodium, which is 256.50°C. Even after prolonged duration of irradiation, naproxen sodium is thermodynamically stable [27].

Summary of physicochemical analysis results

The effects of neutron irradiation in the physicochemical properties of naproxen sodium are analyzed using scanning electron microscope analysis (SEM), analysis of gas chromatography mass spectrometry (GC-MS), Fourier transform infrared spectroscopy (FTIR) and analysis of differential scanning calorimetry (DSC). The colour of white powder of non-irradiated naproxen sodium changed to yellow for samples irradiated for 4 min and 5 min. The 30 min irradiated naproxen sodium turned to brown in colour. This shows that the colour of the white powder of naproxen sodium changed to brown in colour as the duration of radiation is increased. Based on the results of scanning electron microscope analysis (SEM), the surface morphology of the crystalline structure of naproxen sodium changed as the duration of irradiation was increased. It can be seen that the rough surfaced irregularly shaped longitudinal crystals of non-irradiated naproxen sodium changed after irradiation [28]. The results of the gas chromatography mass spectrometry (GC-MS) showed that the non-irradiated and irradiated naproxen sodium samples had a retention time of 27 min. There are 3 major peaks that can be seen in the TIC of non-irradiated naproxen sodium and irradiated naproxen sodium at retention time of 8 min, 13.5 min and 27 min. The abundance of the total ion current of the peak at 27 min is the same for every irradiated sample. With an increase in duration of irradiation, the abundance of the total ion current of peak 8 min and 13.5 min decreased. The results from the FTIR analysis showed the most changes in the FTIR spectrum in the 30 min irradiated sample. The 30 mins irradiated sample had significant new peaks in the region of wavelength of 1500 cm^{-1} to 3000 cm^{-1}. The new peak is due to the degradation of naproxen sodium caused by prolonged duration of irradiation. There were no major changes in the results obtained from the DSC when comparing the non-irradiated naproxen sodium with the irradiated naproxen sodium samples [29,30].

Conclusion

By comparing the results obtained from all the physicochemical analysis done, it can be concluded that naproxen sodium is a suitable drug that can be used for experiments involving gamma scintigraphy using the neutron activation method. It is important to ensure that the duration of irradiation through neutron activation of naproxen sodium does not exceed 3 min. This is to ensure that the drug does not undergo degradation that may affect its physicochemical properties and the way it behaves as an active ingredient. It is recommended that further studies should be done to design a site specific drug delivery of naproxen sodium using sodium alginate microspheres coated with the pH- sensitive polymer Eudragit S-100. This dosage form is targeted to the colon to minimize or avoid local side effect by avoiding drug release in the upper gastrointestinal tract.

The colon specific delivery of naproxen sodium is effective and convenient to deliver the drug at a specified time which can be useful to patients with nocturnal rheumatoid arthritis. Before proceeding to *in vivo* studies, it is highly recommended that relevant tests should be done to ensure that the dosage form and the excipients used are stable after neutron irradiation.

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