Original article

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EFFECTS OF GAMMA RAYS ON THE PHYSICAL STABILITY OF CARBOMERS AND CELLULOSE DERIVATIVES GEL BASES

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ABSTRACT

This study was designed to investigate the effects of gamma rays on the physical stability of gel bases. The influences of amounts of gamma rays (0, 16.5 and 25 kGrays), gelling agents and gel concentrations were assessed. Five gelling agents (Carbomer 934, Carbomer 940, methylcellulose (MC), hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC)) were employed in this study. The physical stability of the gel bases, before and after freeze-thaw cycle, was evaluated from the physical appearance, viscosity and pH of the gel bases. The results revealed that the studied parameters of all gel bases changed after being exposed to the grammar ray. The higher the gamma rays used resulted in the lower viscosity of the gel bases. Gamma rays also had an effect on the viscosity of the gel bases after freeze-thaw cycle. Thus, the stability of the gel bases needs to be taken into account when using gamma rays as an alternative to sterilize or inhibit the microbial growth in gel bases.

Keywords: gamma ray, gels, carbomer, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose

Introduction

The drug delivery via a topical route is a fascinating mean for local and systemic treatments. Topical drug delivery is widely used in the treatment of skin disorder and inflammatory conditions e.g. acne, musculoskeletal injuries[1–3]. The treatment via a topical route offers many more advantages than the conventional oral medication, especially to avoid some systemic adverse effects[4]. Moreover, a number of pharmaceutical dosage forms can be exploited for a topical drug delivery system. The common dosage forms are gels, creams, ointments, liniments, solutions and sprays[5,6]. Gels are semisolid formulation comprising large amounts of water[7]. They can enhance the resident time of the drug on the skin leading to the improvement in delivery efficiency and release of the drug at the site of application[8]. Moreover, their local effects and percutaneous absorption make them appropriate to be used as carriers for various drugs[9]. In addition, the evaporation of the water in the formulation provides a delightful sensation. The remaining film generally stays on the skin and provides protection; however, it is simply taken away by washing as needed[10].

However, gel preparations usually contain high water content in the formulation. This could be a problem concerning the formulation stability and the overgrowth of microbes in the formulation. In addition, the contamination from the raw materials especially herbal products and the product handling may heighten the microbial burden[11]. These could lead to instability and degradation of the drug formulation. These issues can be diminished by adding appropriate preservative chemicals into the formulation or using sterilization techniques[12]. Preservative is a substance added to pharmaceutical products, cosmetics or foods to prevent the growth of microbes and protect the product from being spoiled. The established preservative groups consist of alcohols, amides and amines, carbanilides, formaldehyde donors, inorganic, metal and organic compounds, paraben esters, phenol derivatives, pyridine, and quaternary compounds[13]. However, certain chemical groups which are usually harmful to living cells might cause certain risks when used in human[14,15]. Thus, the use of other sterilization techniques such as radiation may be an alternative.

However, the use of radiation may also have an effect on both chemical and physical stabilities of the pharmaceutical formulation. Therefore, this study aimed to investigate the effect of gamma-rays on the physical stability of gel bases. Various gel formulations had been prepared, and the gels were exposed to gamma rays at different radiation intensities. The physical properties of the gels were assessed after the irradiation.

Materials and Methods

Materials

Carbomer 934, Carbomer 940, methyl-cellulose (MC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC) and triethanolamine (TEA) were purchased from Sigma-Chemical Co. (St. Louis, MO, USA). All other reagents and solvents were of analytical grade and were used without further purification.

Types and concentrations of gel bases

Five gelling agents commonly used in gel formulations were used at different concentrations as follows: Carbomer 934 (0.5%, 0.75% and 1%), Carbomer 940 (0.5%, 0.75% and 1%), MC (2%, 3% and 4%), HEC (1%, 2% and 3%) and HPC (1%, 2% and 3%). The concentrations used were based on those commonly used in the topical gel formulations.

Preparation of Gel bases

Carbomer 934 and Carbomer 940

The Carbomer gel bases were prepared at room temperature by an indirect dispersion method. Briefly, accurately weighed quantity of Carbomer was dispersed in deionized water under stirring. Afterwards, triethanolamine was added to the mixture to adjust the pH to pH 6.5 before the smooth gel base was obtained.

Methylcellulose

The methylcellulose gel base was prepared by adding methylcellulose powder to the one-third amount of hot water with being stirring until the particles were thoroughly dispersed. The remainder of the water was then added as cold water to the mixture, and the mixture was stirred until the homogeneous gel was obtained.

Hydroxyethylcellulose and hydroxypropylcellulose

The hydroxyethylcellulose and hydroxypropylcellulose gel bases were prepared at room temperature by dispersing hydroxyethylcellulose or hydroxypropylcellulose in deionized water under being stirred until the homogeneous gel was obtained.

Doses of gamma radiation used

The gamma radiation used as a sterilization dose should be the minimum permissible and necessary to provide the required or desired sterility assurance level (SAL). This requirement is dependent upon the intended use of the product[16]. As the matter of fact, American National Standards Institute and Association for the Advancement of Medical Instrumentation substantiate 25 kGy as the sterilization dose for medical products. The radiation doses available in Co-60 gamma source (Kendall-Gammatron Co. Ltd., Thailand) were only at 16.5 kGrays and 25 kGrays. Therefore, these doses were selected to be used in the study.

Stability of the gel bases after being exposed to gamma rays

The irradiation was performed using Co-60 gamma source at ambient temperature. The gel bases were irradiated with 16.5 and 25 kGrays of gamma radiation. The physical stability including physical appearance as well as the properties of the gel bases after freeze-thaw cycle were determined after the irradiation. The pH and viscosity of the gel bases were measured at ambient temperature using a pH meter (Schott instrument slab 850 pH-meter, Germany) and a Brookfield viscometer (DV-III ultra, Brookfield Engineering Laboratories, USA), respectively.

Freeze-thaw cycle

The freeze-thaw experiment was performed by exposing the product to freezing temperatures (approximately -20 ± 2°C) for 24 hours. The sample was then placed in a higher temperature (approximately 25°C ± 2°C) for 24 hours. The freeze-thaw experiment was carried out for 3 cycles.

Results

Effects of gamma radiation on the color of the gel bases

After being exposed to the gamma radiation at the doses of 16.5 and 25 kGrays, the gel bases made of MC, HEC or HPC did not display any significant change in color at all gel concentrations. However, the precipitation of the gel bases was observed as presented in Figure 1, Figure 2 and Figure 3, respectively.

On the other hand, the gel bases made of carbomer 934 and Carbomer 940 exhibited the significant change in color from clear gel to yellow as displayed in Figure 4 and Figure 5, respectively. Increasing the dose of gamma ray resulted in more change in color.

The color of the radiated gel bases after freeze-thaw cycle

After being exposed to the gamma radiation, the gels were subjected to the freeze-thaw cycle to determine the gel stability under accelerated condition. The results showed that the gel bases did not show good stability. The color of MC, HEC and HPC gel bases changed from clear to pale yellow. Moreover, the Carbomer 934 and Carbomer 940

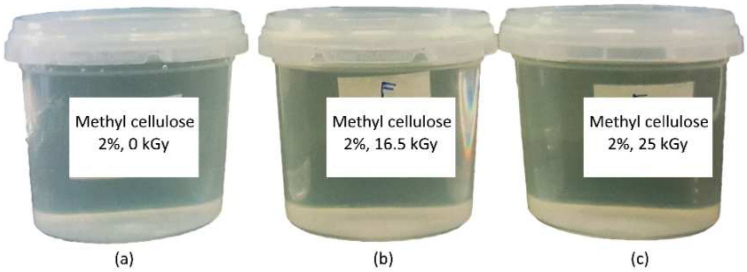

Figure 1 Physical appearance of the 2% MC gel bases after being subjected to gamma radiation at the dose rate of (a) 0 kGy (b) 16.5 kGy and (c) 25 kGy. (For color figure, please refer to the web version of this article)

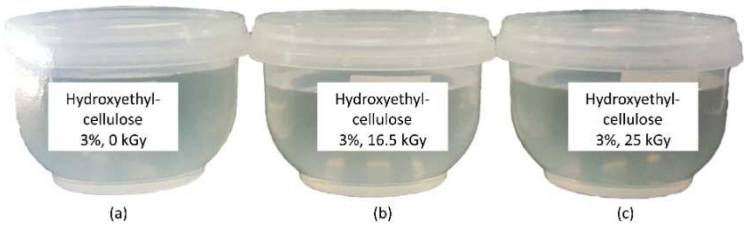

Figure 2 Physical appearance of the 1% HEC gel bases after being subjected to gamma radiation at the dose rate of (a) 0 kGy (b) 16.5 kGy and (c) 25 kGy. (For color figure, please refer to the web version of this article)

Figure 3 Physical appearance of the 1% HPC gel bases after being subjected to gamma radiation at the dose rate of (a) 0 kGy (b) 16.5 kGy and (c) 25 kGy. (For color figure, please refer to the web version of this article)

Figure 4 Physical appearance of the 0.5% Carbomer 934 gel bases after being subjected to gamma radiation at the dose rate of (a) 0 kGy (b) 16.5 kGy and (c) 25 kGy. (For color figure, please refer to the web version of this article)

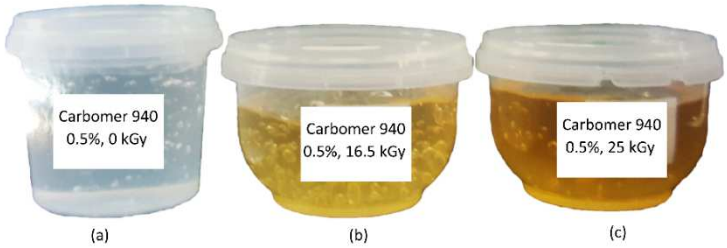

Figure 5 Physical appearance of the 0.5% Carbomer 940 gel bases after being subjected to gamma radiation at the dose rate of (a) 0 kGy (b) 16.5 kGy and (c) 25 kGy. (For color figure, please refer to the web version of this article)

displayed strong vivid yellow color. The precipitation of the gel bases could be observed in the gel bases of MC, HEC and HPC. The physical appearance of the 2% MC and 0.5% Carbomer 934 gel bases after being exposed to different dose rates of gamma radiation is shown in Figure 6 and Figure 7, respectively.

Effect of gamma radiation on the pH of the gel bases

The pHs of the gel bases being exposed to 0, 16.5 and 25 kGrays of gamma radiation before and after freeze-thaw cycle are displayed in Table 1. The gamma ray had an effect on the pH of MC, HEC and HPC gel bases but had no effect on Carbomer 934

Figure 6 Physical appearance after freeze-thaw cycle of the 2% MC gel bases after being subjected to gamma radiation at the dose rate of (a) 0 kGy (b) 16.5 kGy and (c) 25 kGy. (For color figure, please refer to the web version of this article)

Figure 7 Physical appearance after freeze-thaw cycle of the 0.5% Carbomer 934 gel bases after being subjected to gamma radiation at the dose rate of (a) 0 kGy (b) 16.5 kGy and (c) 25 kGy. (For color figure, please refer to the web version of this article)

and Carbomer 940. The pH of all gel bases decreased after being exposed to the gamma ray, especially at high intensity (25 kGrays). The further pH change was observed after the freeze-thaw cycle.

Effects of gamma radiation on the viscosity of the gel bases

The exposure of the gel bases to the gamma radiation resulted in the reduction in viscosity of the gel bases at all concentrations. Increasing the dose of gamma ray used led to the further reduction in the viscosity of the gel bases. After the freeze-thaw cycle, the additional decrease in the viscosity of the gel bases was observed. The viscosity of the gel bases being exposed to 0, 16.5 and 25 kGrays of gamma radiation before and after freeze-thaw cycle is shown in Table 2. There are some differences in the percentage reduction of the viscosity of the gel bases prepared from different polymers. The reasons of these differences may be due to the differences in the properties of the polymer used and the gel bases such as molecular weight, polymer concentration, initial viscosity, etc.

Table 1 pH of the gel bases being exposed to 0, 16.5 and 25 kGrays of gamma radiation before and after freeze-thaw cycle. The data are expressed as mean ± standard deviation from three independent experiments.

Polymer	Conc. (%)	pH of the gel bases					
		Before freeze-thaw cycle			After freeze-thaw cycle		
		0 kGy	16.5 kGy	25 kGy	0 kGy	16.5 kGy	25 kGy
Methylcellulose	2	5.5±0.1	3.3±0.2	3.2±0.3	6.5±1.7	3.2±0.3	3.2±0.3
	3	6.5±0.1	3.4±0.2	3.2±0.3	6.5±0.1	3.3±0.2	3.2±0.3
	4	6.5±0.1	3.5±0.1	3.3±0.3	6.5±0.1	3.5±0.1	3.3±0.3
Carbomer 934	0.5	6.5±0.2	6.5±0.2	6.5±0.2	6.5±0.1	6.5±0.2	7.0±1.0
	0.75	6.5±0.1	6.5±0.2	6.5±0.2	7.0±0.5	6.5±0.2	6.5±0.2
	1	6.5±0.1	6.5±0.1	6.5±0.1	7.0±0.5	7.0±1.0	6.5±0.1
Carbomer 940	0.5	6.5±0.1	6.5±0.2	7.0±1.0	6.5±0.3	7.0±1.0	6.5±0.2
	0.75	6.5±0.1	6.5±0.2	6.5±0.2	6.5±0.5	7.0±0.7	7.0±0.7
	1	6.5±0.2	6.5±0.2	6.5±0.2	7.0±0.5	6.5±0.2	6.5±0.2
Hydroxyethyl cellulose	1	6.5±0.1	5.5±0.1	5.1±0.8	6.5±0.1	5.3±0.4	5.1±0.8
	2	5.5±0.2	5.8±0.2	5.3±1.0	6.5±1.8	5.5±0.7	5.4±0.9
	3	6.0±0.2	5.7±0.1	5.5±0.4	6.0±0.2	5.6±0.3	5.4±0.6
Hydroxypropyl cellulose	1	6.0±0.2	3.3±0.2	3.2±0.1	6.0±0.2	3.3±0.2	3.1±0.2
	2	6.0±0.1	3.5±0.1	3.2±0.4	6.0±0.1	3.3±0.3	3.1±0.6
	3	6.0±0.2	3.4±0.2	3.2±0.5	6.0±0.2	3.3±0.4	3.1±0.7

Table 2 Viscosity of the gel bases being exposed to 0, 16.5 and 25 kGrays of gamma radiation before and after freeze-thaw cycle. The data are expressed as mean ± standard deviation from three independent experiments.

Polymer	Conc. (%)	Viscosity of the gel bases (cPs)					
		Before freeze-thaw cycle			After freeze-thaw cycle		
		0 kGy	16.5 kGy	25 kGy	0 kGy	16.5 kGy	25 kGy
Methyl cellulose	2	1840±53	16±3	13±1	1760±53	15±1	11.6±1
	3	4600±173	29±2	20±2	4320±159	25±1	17.2±1
	4	15040±197	96±5	50±3	11640±314	70±1	40±5
Carbomer 934	0.5	27200±200	13760±701	8880±72	19840±295	10160±1268	6720±72
	0.75	39600±400	25200±529	14800±173	31360±151	17840±144	11040±941
	1	50800±529	34000±346	24560±318	37360±314	22400±361	16640±556
Carbomer 940	0.5	28160±160	7040±122	3840±53	13920±72	4320±106	2400±100
	0.75	36880±337	13680±589	9760±66	16480±288	8240±212	5840±53
	1	40160±125	20400±346	17600±361	18000±200	12960±197	10640±164
Hydroxyethyl cellulose	1	2080±180	10±1	10±2	1000±50	9±1	4±1
	2	15680±278	15±1	14±2	7040±144	13±1	11±1
	3	46800±265	4520±106	98±3	19600±529	1880±106	38±2
Hydroxypropyl cellulose	1	80±10	10±2	8 ±1	80±10	10±1	8±1
	2	1360±197	13±1	10±1	1200±100	11±2	10±2
	3	4440±53	21±3	13±2	4160±53	18±1	12±3

Discussion

The use of radiation for the sterilization of medical and pharmaceutical materials as well as pharmaceutical products has increased due to the concern about the toxicity of chemical preservatives. However, the effect of radiation on the stability of the pharmaceutical products should also be concerned. In this study, various gel bases including Carbomer 934, Carbomer 940, MC, HEC and HPC had been investigated for radiation stability after being exposed to gamma radiation at different dose rates. The results revealed that the physicochemical properties such as color, pH and viscosity of the gel bases were altered after being exposed to the gamma radiation. These changes indicated the degradation or instability of the gel bases. These may be because the polymers undergo radiation-induced degradation leading to discoloration and worsening in the properties. In the literatures, some reports state that when polymers are subjected to irradiation of ionizing radiation such as γ-rays, numerous consequences can be expected. The radiation could lead to crosslinking or degradation of the polymers depending on their structure and irradiation condition[17]. Crosslinking or chain scission can occur simultaneously when the polymer is subjected to the radiation of ionizing radiation[18]. In addition, radiation also has some other effects on the polymers; for example, generation of radicals and hydrogen, increase unsaturation, coloration and oxidation[19]. As observed from the viscosity of the gel bases after being exposed to gamma radiation, the viscosity of all gel bases (especially cellulose derivatives) decreased dramatically especially at high dose rate and after freeze-thaw cycle. This may be explained by the chain scission mechanism and water radiolysis resulting from the γ-radiation. Lower polymer concentration seemed to have more effect. These results correspond with previous studies which reported that cellulose had a relatively low resistance to radiation and the degradation increases with decreasing of the polymer concentration due to the enhanced OH radical mobility[20,21]. The degradation of the gel bases depended on the polymer concentration and the radiation intensity. The change in pH of the gel bases especially the cellulose derivatives may be due to the generation of by products (small chain molecules) resulting from the polymer chain scission.

Conclusions

The present study investigated the effect of gamma radiation (0–25 kGy) on the stability of the gel bases prepared from Carbomer 934, Carbomer 940, MC, HEC and HPC. The physicochemical properties including color, pH and viscosity of the gel bases were altered after being exposed to gamma radiation. All the gel bases demonstrated the reduction in pH and viscosity which may be resulted from the polymer chain scission mechanism after being exposed to the gamma ray. Higher dose rate of the gamma ray had more effects on the gel stability. The changes in the physicochemical properties of the gel bases were witnessed after the freeze thaw cycle. Therefore, the physical stability of the gels should be concerned when using gamma ray in the sterilization process.

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