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"Before anything else, preparation is the key to success."

Alexander Graham Bell

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I want to thank you to the all of my friends who studied for those processes that are mentioned above. By the valuable contribution of our friends in the publishing team, this was a successful start for our journal.

Our main goals are having a strong international editor and referee team, to increase the recognition and index number of the **JPharmTech** and to be one of the most cited journals. That's why, your contribution and support to our journal with your papers and refereeing, are really important and valuable for us.

Thank you in advance & Best regards,

Müzeyyen Demirel

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The publication language of the **JPharmTech** is English. Please perform spell and grammar check of the article. Authors, for whose native language is not English, are strongly encouraged to have their manuscript carefully edited prior to submission. Before submitting, all contributors must agree and sign the Copyright Form. The following three documents must be uploaded for article submission.

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Clearly indicate the given name(s) and family name(s) of each author. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a superscript number.

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The introduction section of the articles (particularly research articles) should include the following topics;

- establish current knowledge of the field,
- summarize previous research, providing the wider context and background and the importance of the current study,
- set the stage for the present research, indicating gaps in knowledge and presenting the research question,
- introduce present research, stating its purpose and outlining its design.

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The Methods should describe clearly how you carried out your study. Provide sufficient details like study design and data collection to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference.

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A combined Results and Discussion section is often appropriate; but optionally can be written separately. Provide a concise and precise description of the all experimental data, their interpretation as well as the experimental conclusions that can be drawn. Discussion should explore the significance of the results of the work, not repeat them. The P values and/or the specific statistical tests performed for each experiment should be included to the results and discussion section in the appropriate figure legend or main text. Results should include the name of the statistical test, followed by a colon, the test statistic and its value, degrees of freedom or sample size (depending on which is most appropriate for that test), and the P value, with indication if it is one-or two-tailed (unless you address this issue in the methods).

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The conclusion section of the articles (particularly research articles) should include the following topics;

- principles, relationships, and generalizations inferred from the results (but not a repetition of the results),
- any exceptions to or problems with those principles, relationships, and generalizations, as indicated by the results agreements or disagreements with previously published work,
- theoretical implications and possible practical applications of the work,
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Articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used:

Concept, Design, Supervision, Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Search, Writing, Critical Reviews. Initials of the contributing authors (i.e. AA, BB) should be given after these specified titles and all of them must be filled.

Acknowledgments

Acknowledgments should include sources of support, grants, disclaimers, names of those who contributed but are not authors, etc. The names of funding organizations should be written in full. If no funding or help has been provided for the research, please include the "None" statement.

Conflict of Interest Declaration

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work. If no conflict exists, the authors should include the "The authors declare no conflict of interest." statement under this section.

Ethics Committee Approval

When reporting experiments conducted with humans indicate that the procedures were in accordance with ethical standards set forth by the committee that oversees human experimentation. Approval of research protocols by the relevant ethics committee, in accordance with international agreements.

Helsinki Declaration of 1964, revised 2013 available at

https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

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is required for all experimental, clinical, and drug studies. Patient names, initials, and hospital identification numbers should not be used. Manuscripts reporting the results of experimental investigations conducted with humans must state that the study protocol received institutional review board approval and that the participants provided informed consent.

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References

Citation in text must be numbered as [1] or [1-5]. Please ensure that every reference cited in the text is also present in the reference list. References should be accurate and numbered sequentially [in square brackets] in the text and listed in the same numerical order in the reference section with the DOI link. All authors must be cited and there should be no use of the phrase et al. The abbreviations of the journal names should be used. No references sould be given for the abstract section. Date of access should be provided for online citations. Furthermore, the references can easily be edited with the **JPharmTech** EndNote Style.

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Journal

[1] Ates M, Kaynak MS, Sahin S. Effect of permeability enhancers on paracellular permeability of acyclovir. *J Pharm Pharmacol*. (2016); 68(6): 781-790. https://doi.org//10.1111/jphp.12551

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Book

[4] Fotaki N, Klein S. *In vitro* drug release testing of special dosage forms. New Jersey: John Wiley & Sons; (2019). ISBN:1118341473

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Conference Paper

[8] Yurtdaş Kırımlığlu G, Özer S. "Formulation and *in vitro* characterization studies of levofloxacin hemihydrate incorporated PLGA based nanoparticles." Poster. 2nd International Gazi Pharma Symposium Series, Ankara, October 11-13, 2017. p. 93.

Patent

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Website

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RESEARCH ARTICLE

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Preparation, characterization, and radiation absorption study of bentonite clay included soft chewable lozenge formulations

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ABSTRACT

Lozenges are renewed popularity as a means of administering many different drugs and may be considered as alternatives to current dosage forms. Lozenges are solid/semi-solid dosage forms that can contain one or more active ingredients, generally prepared as aromatized and sweetened, dissolve or dispersed in the mouth, chewable, absorbable. They can be used in local treatment of mouth and throat infections or irritation to slowly release a fixed amount of drug into the oral cavity or cover the throat tissues with the drug solution, and sometimes to achieve systemic effects when the drug is well absorbed through the buccal membranes or chewed and swallowed. Recently, soft lozenges and chewable lozenges have been re-introduced into the pharmacy and their popularity is increased. At present, we are all exposed to a certain level of radiation. Scientific evidence from past events has demonstrated that any major uncontrolled release of radiation could be harmful and warrants immediate response to assess and minimize public health risks. Bentonite is a natural highly colloidal clay and is used for protection from radiation. This study aims to prepare soft chewable lozenge formulations containing different bentonite doses by using 2 different preparation techniques (hand-rolling and molding techniques), to make quality control tests of the lozenges and to determine the degree of radiation absorption.

1. INTRODUCTION

Oral dosage forms are very diverse and have many advantages over other dosage forms. Oral medication is the easiest way to administer therapeutic agents to achieve a systemic effect since it can be used without any help. In the use of oral dosage forms, it is always the most preferred form of medicine due to its high patient compliance, availability of various formulations, and easy transportation. They are economical and safe for the patient. However, it still has some disadvantages. They are not suitable dosage forms for children and infants, especially for patients with chronic vomiting problems and gastrointestinal disorders such as diarrhea, constipation, ulcer, hyperacidity. Their use is not preferred in cases requiring urgent intervention and in patients with loss of consciousness [1].

Lozenges are renewed popularity as a means of administering many different drugs and may be considered as alternatives to current dosage forms. Lozenges are solid/semi -solid dosage forms that can contain one or more active ingredients, generally prepared as aromatized and sweetened, dissolve or dispersed in the mouth, chewable, absorbable. They are also called troches or pastilles [2]. They can be used in local treatment of mouth and throat infections or irritation to slowly release a fixed amount of drug into the oral cavity or cover the throat tissues with the drug solution, and sometimes to achieve systemic effects when the drug is well absorbed through the buccal membranes or chewed and swallowed [1,3,4]. In general, the absorption time of the oral lozenge is considered to be about 30 minutes in solid absorbable lozenges, but the dissolution and absorption of the lozenge may vary depending on the patient's absorption state. Also, suction and subsequent continuous production of saliva can cause the drug to be diluted and accidentally swallowed [1,4,5]. As a result, high variations can occur in the amount of medication given with each application of the lozenge. Absorption and subsequent saliva production may also cause the drug to be diluted and accidentally swallowed [1]. Lozenge formulations have many advantages: It is convenient and easy to use for pediatric and geriatric patients with difficulty swallowing. It has a pleasant taste and is enough to stay in the oral cavity for a while to bring out a certain effect. It does not require water requirement for patients to use. It can be prepared by a pharmacist in a pharmacy for a small amount of substance and for a short time [4,6,7]. Besides, there are disadvantages such as the tendency to accidentally use as candy by children, risk of swallowing hard lozenges for children under 6 years of age,

and the uncommon distribution of the drug in saliva for local treatment [4,6]. Nowadays, there are many types of lozenges such as chewable lozenges, compressed lozenges, hard candy lozenges, center filled hard lozenges, soft lozenges. Recently, soft lozenges and chewable lozenges have been re-introduced into the pharmacy and their popularity is increased. The soft lozenges generally have a polyethylene glycol base and the chewable lozenges have a glycerinated gelatin base. These usually are chewable and this chewability is a means of delivering the product to the gastrointestinal tract for systemic absorption. Commercial lozenges are made by a tableting machine using high compression pressures and by moulding. Also, the hand-rolling technique is used for soft lozenges or in small scale formulations [1,4,6].

At present, we are all exposed to a certain level of radiation. Radiation exposure of humans can be studied in many branches for research and control. The National Council on Radiation Protection and Measurements of the United States (NGRP, 1971) describes radiation as natural radiation, radiation applied in research on human subjects, radiation from medical procedures, occupational irradiation, and man-made environmental radiation. Also, radiation exposures are usually categorized as internal or external in reference to the location of the source relative to the irradiated individual [8,9].

Natural radiation sources are broadly categorized into cosmic, terrestrial (e.g., earth's crust, soil, and construction material, radon from rocks), and internal radiation. Unfortunately, human exposure to natural radiation is not controllable. Also, people are routinely exposed to man-made radiation from nuclear medical diagnostics (e.g., X-ray and Computerized Tomography scans) and treatment procedures, nuclear power plants, commercial flying, and even smoking. However, scientific evidence from past events has demonstrated that any major uncontrolled release of radiation could be harmful and warrants immediate response to assess and minimize public health risks. However, exposure to man-made radiation can be controlled by taking precautions [8,10]. The rapid development in science technology causes radiation widely used in many research areas, which have increased people's exposure to different kinds of radiation. Three main methods are usually utilized for protection from radiation: time, distance, and shielding. Among the three methods, shielding is the most important protection method. Thus, shielding materials become very important. Different radiation protection materials (lead, copper, bismuth, steel, concretes and organic compounds such as oils, paraffins, plastics and rubber) have been developed to reduce the damage caused by radiation to the human body. But, natural materials like bentonite clay can be used as shelters from nuclear waste because of its availability and low cost [11]. Clays are common ingredients used in pharmaceutical products as excipients and active substances [12]. The ability of clay minerals to adsorb and desorb organic molecules is well known and makes them very attractive for pharmaceuticals [13]. All bentonites are from the montmorillonite group of clay minerals and are an aluminum hydrosilicate with soft colloidal property. Montmorillonite minerals show a three-layered structure and this is their characteristic feature. Water and organic molecules enter between these layers and cause the structure to expand/swell, so it is frequently used as a viscosity enhancer with its large surface area [14]. Bentonite is a natural highly colloidal clay mainly composed of montmorillonite that is abundant and non-expensive. The reliability of bentonite in humans and animals has been proven by studies. Bentonite does not influence serum concentrations of vitamins and nutrients in humans [15]. Bentonite clay has been shown to act as a detoxifying agent. This property is referred to its cationic nature, which leads to the absorption of negative charge toxins. Also, it is generally used in the form of blocks as an ideal backfill material for a high-level radioactive waste tank in deep rocks [15,16]. Bentonite is known to inhibit diffusive transport of most radionuclides due to its good absorption properties. There are many studies on the absorption of radioactive materials such as uranium, cesium, nickel and lead by bentonite [16,17]. Bentonite is frequently used for protection from gamma radiation. Bentonite has been proven to be highly effective against gamma radiation in the studies of Hager et al. [11] and Ishii et al.[18].

In the literature evaluation, there is no dosage form of bentonite prepared for protection from radiation. This work we have done is the first. But, in many countries, the drinkable form of food-grade bentonite is sold for the protection from toxins and radiation [19]. Based on the information given above, it was decided to study the bentonite lozenge formulation, which is a dosage form that can be easily used by humans. So, this study aims to prepare soft chewable lozenge formulations containing different bentonite doses by using 2 different preparation techniques (hand-rolling and molding techniques), to make quality control tests (determination of organoleptic properties, weight variation, diameter-thickness, friability test, dispersion time) of the lozenges with optimum properties and to determine the degree of radiation absorption. Technetium (^{99m}Tc) was used in the radiation absorption study. ^{99m}Tc emits gamma radiation and bentonite absorbs gamma radiation [20]. Gamma radiation is one of the main types of nuclear radiation, which have to be considered. In this study, the absorption ability of bentonite in lozenge form is evaluated.

2. MATERIALS AND METHODS

2.1. Materials

Pharmaceutical grade bentonite was obtained as a gift from Galenik Ecza (İzmir, Turkey). Gelatin and carboxymethylcellulose sodium (NaCMC) were kindly supplied by Gelita (Germany) and Doğa İlaç (Turkey), respectively. All other chemicals were in analytical or pharmaceutical grade.

2.2. Preparation of Bentonite Included Soft Chewable Lozenges

Lozenges were prepared by molding and hand-rolling techniques [1]. Bentonite and all excipients were mixed in certain proportions using a magnetic stirrer in accordance with the technique. Bentonite was added last during the preparation. Prepared lozenges were wrapped with wax paper and put in well-closed containers.

In the hand-rolling technique, the prepared mixture was placed on a glass table and the mixture was made homogeneous with the help of a spatula by adding bentonite last. The mixture was then rolled by hand to form a long strip, and it was measured with a ruler and cut with a knife to contain the desired dose. The lozenge formulations prepared with this technique were designed to contain 1.5 g and 2 g bentonite doses.

In the molding technique, the prepared mixture was poured in certain amounts into the molds, the inner walls of which were covered with starch, to prevent sticking to the mold, and cooled to room temperature and formed. The lozenge formulations prepared by this technique were designed to contain bentonite at a dose of 0.25 g and 0.5 g. Ingredients of all formulations prepared with both molding and hand-rolling technique are given in **Table 1**.

Table 1. *Ingredients of all formulations*

Ingredients weights (g)	Molding Technique		Hand-rolling Technique	
	M0.25	M0.5	H1.5	H2
Bentonite	0.25	0.50	1.50	2.00
Citric acid	0.10	0.10	0.10	0.10
Menthol	0.10	0.10	0.10	0.10
Peppermint oil	0.05	0.05	0.05	0.05
Glycerin	0.25	0.25	0.25	0.25
Methyl paraben	0.01	0.01	0.01	0.01
Sodium saccharin	0.10	0.10	0.10	0.10
NaCMC	0.20	0.20	0.25	0.25
Gelatin	0.80	0.80	-	-
PEG 4000	0.20	0.20	-	-
Distilled water	4.00	5.50	2.00	2.25
Carmine	q.s.	-	-	-
Toluidin blue	-	q.s.	-	-
Fast green FCF	-	-	q.s.	-
Eosine	-	-	-	q.s.

The same procedures were applied for lozenges that do not contain bentonite (blank lozenges), and the only bentonite was not added into the mixture. “Fast Green FCF” dye and “carmine” were used as a dye in the lozenges prepared by hand-rolling and molding technique, respectively. Prepared lozenges were wrapped with wax paper and put in boxes.

2.3. Characterization of Soft Chewable Lozenges

2.3.1. Organoleptic properties

The prepared lozenges were evaluated for its organoleptic properties like taste, odour, colour, softness, chewability, and shape [21].

2.3.2. Weight variation

For weight variation, 20 lozenges were taken and weighed each individually on a precision balance. After the average weight of the lozenges was found, the deviation values of each lozenge from the average weight were found in %. The weight variation of any lozenge should not exceed 10% according to the USP limit [22].

2.3.3. Diameter and thickness

20 lozenges were taken and each one was measured with a vernier caliper for their diameter and thickness. The average diameter-thickness values in mm and standard deviation of lozenges were found [22].

2.3.4. Friability

10 lozenges were taken and all were weighed together on precision balances. The weighed lozenges were rotated for 4 minutes in the friabilitor at 25 rpm per minute and the friability values were calculated in %. The friability value should not exceed 1% [23].

2.3.5. Disintegration time

6 lozenges were taken and put into a disintegrator. The disintegration time was determined in pH 6.8 artificial saliva fluid at 37ºC and 100 rpm [23]. Artificial saliva (at pH 6.75) was prepared according to the following formulation [24]:

Rx

Disodium Hydrogen Phosphate	2.382 g
Potassium Dihydrogen Phosphate	0.190 g
Sodium Chloride	8.000 g
Ultrapure water q.s.	1 L

2.4. Determination of Radiation Absorption

This study was carried out in Atatürk University Faculty of Medicine, Department of Nuclear Medicine. 4 pieces of lozenges containing bentonite, which have optimum properties, were exposed to ^{99m}Tc radiation (starting intensity is 497 mCi) for the specified time in a closed steel case. The ^{99m}Tc half-life is 6 hours. Then, the radiation in the lozenges was measured with an appropriate measuring device (well counter) at the 6th hour, and the radiation absorption efficiency of the lozenges containing bentonite was evaluated by calculating the average of radiation (mCi) per lozenge.

All results were given with standard deviation value. Statistical analysis was made by using One way ANOVA test through the SPSS Statistics 20.0 (SPSS Inc., Chicago, Illinois, USA) program. In the evaluation of the results obtained, data with a P-value of less than 0.05 ($p<0.05$) were considered as significant.

Table 2. *Organoleptic properties of bentonite included soft chewable lozenges*

Organoleptic properties	Molding Technique		Hand-rolling Technique	
	M0.25	M0.5	H1.5	H2
Taste	Sweet	Sweet	Sweet	Sweet
Odour	Menthol-Mint	Menthol-Mint	Menthol-Mint	Menthol-Mint
Colour	Pink	Purple	Green	Light Orange
Softness	Soft	Soft	Medium Hard	Medium Hard
Chewability	Good	Good	Good	Good
Shape	Round	Square	Cylinder	Cylinder

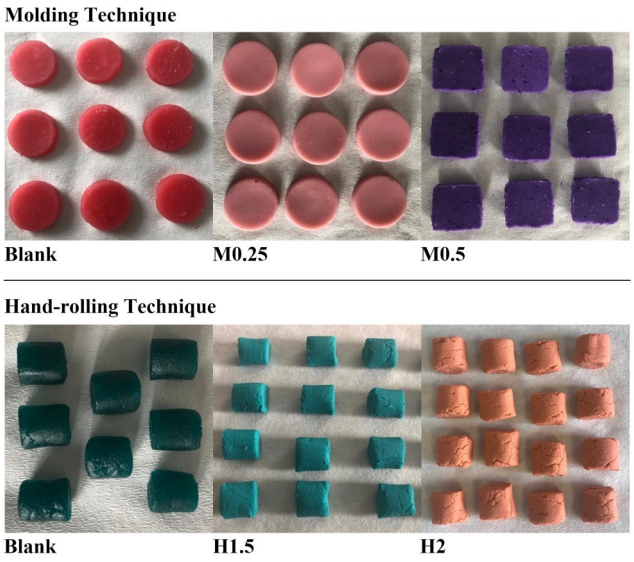

Figure 1. *Images of soft chewable lozenges*

3. RESULTS AND DISCUSSION

3.1. Preparation of Bentonite Included Soft Chewable Lozenges

Bentonite included lozenges in 4 different doses and were successfully prepared with the blank ones by using molding and hand-rolling techniques. All the formulations showed good physical appearance. The gelatin used in the molding method as binder enabled the lozenges containing low-dose bentonite to keep their shape due to its gelling feature [25]. Images of bentonite included and blank lozenges are given in **Figure 1**.

3.2. Characterization of Soft Chewable Lozenges

3.2.1. Organoleptic properties

Organoleptic properties are optimized so that a patient can adapt to chewing. The prepared lozenges are formulated in accordance with their purpose in terms of taste, odour, colour, softness, chewability, and shape properties. Organoleptic properties are at a level acceptable to the patient. Organoleptic properties of bentonite included lozenges are given in **Table 2**.

3.2.2. Weight variation, diameter, thickness, friability, and disintegration time

The weight variation, diameter, thickness, friability, and disintegration time of bentonite included lozenges were evaluated and the results are given in **Table 3**. The weight variation, diameter, and thickness values were given as average±standard deviation. All the formulations were found to show acceptable weight, diameter, and thickness. The percentage of weight variation was within the USP limits and the values varied between -4.83% and 3.89% for M0.25, -5.07% and 4.37% for M0.5, -1.28% and 0.41% for H1.5, and -1.74% and 2.41% for H2. Diameter and thickness values are within acceptable limits in terms of easy chewing. Only one formulation (M0.5) exceeded the 1% limit in the friability test. When all formulations are compared, it is seen that formulation M0.5 has the most water. This excess water made the lozenges more fragile and sticky, so this formulation was stick more to the friabilator. But, it can be said that the other formulations (M0.25, H1.5 and H2) are suitable for packaging.

Disintegration time was found to be in the range of 35 min and 120 min. Since the lozenges are soft and chewable, their disintegration time is very long. Therefore typical disintegration times may not be achieved with these lozenges. In the United States Pharmacopeia (USP 35), the disintegration time of nystatin lozenges is 90 minutes [26]. Nystatin lozenges can be given as an example to this case. H1.5 and H2 formulations contain high amounts of bentonite. Since bentonite is a swelling material [17], it is primarily swollen in the lozenge, and in this case, it has made it difficult to disperse in artificial saliva.

Table 3. *The evaluation parameters and results of bentonite included soft chewable lozenges*

Evaluation Parameters	Molding Technique		Hand-rolling Technique	
	M0.25	M0.5	H1.5	H2
Weight variation (g)	5.85±0.19	7.21±0.25	4.02±0.02	4.82±0.06
Diameter (mm)	33.80±0.00	26.53±0.28	14.94±0.78	15.84±1.37
Thickness (mm)	5.65±1.41	9.67±0.67	17.61±0.96	15.39±1.04
Friability (%)	0.47	1.72	0.69	0.53
Disintegration time (min)	35	60	120	120

Table 4. *The radiation absorption of bentonite included soft chewable lozenges*

Radiation Absorption	Molding Technique		Hand-rolling Technique	
	M0.25	M0.5	H1.5	H2
At the end of the 6th hour (mCi)	0.98±0.08	1.01±0.16	1.08±0.11	1.65±0.40

Table 5. *Statistical analysis of bentonite included soft chewable lozenges*

		Mean Difference (I-J)	Std. Error	Sig.	Interval	
					Lower Bound	Upper Bound
H2-At the end of the 6th hour	H1.5-At the end of the 6th hour	0.57000	0.15871	0.004	0.2242	0.9158
	M0.5-At the end of the 6th hour	0.63500	0.15871	0.002	0.2892	0.9808
	M0.25-At the end of the 6th hour	0.66500	0.15871	0.001	0.3192	1.0108

3.3. Determination of Radiation Absorption

The average radiation absorption efficiency of the lozenges containing bentonite was given at **Table 4**. When the average amount of radiation per lozenge was examined, the highest dose of lozenges (H2) containing 2 g of bentonite showed the highest absorption and the results were significant ($p<0.05$, **Table 5**). As the amount of bentonite increased, the amount of radiation absorbed increased. In a study, bentonite was applied to patients with irritable bowel syndrome at a dose of 3 g 3 times a day for 8 weeks and was found to be effective. There were no side effects from this dose. In our study, the highest dose was chosen as 2 g and it is thought to be a safe dose [15,27].

It is written in the literature that bentonite is used for protection from radiation and studies on this subject are still ongoing. In Tanaka's study (2012), it clearly stated that the wastewater tanks were covered with bentonite to prevent the spread of radiation in the wastewaters of Fukushima Dai-ichi Nuclear Power Stations. It has also been stated that bentonite is used to fix/inhibit radioactive cesium (Cs) and the mobility of Cs in bentonite clay is about 3 mm for 300 years [28]. In Ishii's study, detailed information was given about the fact that the radioactive Cs in the vegetables produced in the Fukushima region is not found due to the dense clay content in the soil and this clay absorbs the radioactive Cs and that these vegetables are safely consumed [18]. Also, Martínez-Costaa et al. concluded that, it was found that bentonite acts as a photocatalyst by absorbing UV and solar radiation and that radiation does not disrupt the crystal structure of clay [29]. Clays with high montmorillonite content protect RNA and RNA-like molecules from UV radiation was found in another study by Biondi et al [30]. Russian and Japanese scientists have regularly used bentonite to protect against radiation. Even after the Chernobyl disaster, bentonite chocolate and biscuits were distributed to the people of the region. After the Chernobyl disaster, the plant and its vicinity were covered with bentonite to minimize the negative effects of radiation. In Japan, hundreds of thousands of tons of clay was poured into the ocean in the Fukushima nuclear disaster caused by the earthquake [31]. So, the bentonite-containing lozenges we have prepared can help to remove radiation from the body.

4. CONCLUSION

In this study, lozenges containing bentonite were successfully prepared and characterization studies were carried out. In addition, the radiation absorption study was conducted and the effectiveness of bentonite in this formulation was evaluated. Radiation absorption increased significantly with the increase of the bentonite dose. This result has given us hope. The effectiveness of these lozenges in terms of absorbing radiation should be clarified with more detailed studies in the future. Nowadays, lozenges are preferred in chewable form and are easily used by many people due to their tolerable taste. Because of the ease of using the lozenges, it is thought that it may be useful and effective in radiation protection or removal of the exposed radiation from the body, especially for hospital workers who are frequently exposed to radiation and patients undergoing radiation therapy. It is foreseen that these workers or patients can chew these soft lozenges without any additional procedure such as drinking with water or injection.

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CONFLICT OF INTEREST DECLARATION

The authors report no conflict of interest. The authors alone are responsible for the content and the writing of the paper.

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Is electrosurgery a revolution? Mechanism, benefits, complications, precautions

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ABSTRACT

Approximately one and a half-century ago, it was revealed that high-frequency alternating current flows through the tissue without causing a painful electrical shock and produces heat instead of muscle stimulation. The application of electrical current to the tissue produces effects such as fulguration, desiccation/coagulation, or vaporization/ablation. Devices that use high-frequency electric current are called energy devices. The development of these devices that facilitated dissection and bleeding control pioneered a new era in surgery. After the Bovie units, which have monopolar and bipolar modes, advanced energy devices were also developed. Advanced bipolar devices use pulsed bipolar energy and feedback control of the energy output during tissue coagulation. There is an electrosurgical unit in each operating theater now. However, these devices are not exempted from complications. Complications related to energy devices occur in 2 to 5 per 1000 procedures. The leading causes of these complications are the thermal diffusion effect, smoke plumes, and stray current. As the surgical experience increases, complications decrease and reach a plateau. Surgeons should understand the mechanism of action; they should have knowledge about the prevention and treatment of potential complications.

1. INTRODUCTION

The concept of electrosurgery was born with the use of the high-frequency electrical current in cutting and hemostasis. Devices that use high-frequency electric current are also called energy devices. The development of these devices that facilitated dissection and bleeding control pioneered a new era in surgery [1]. Devices developed using electrical current have enabled the performance of operations that were previously considered inoperable, shortened the operation times, and reduced postoperative complications such as hematoma and seroma. Nevertheless, it was not easy to reach this level. Many surgeons have made severe criticisms of new devices and users. However, increasing number of surgeons used these devices and proved their benefits. Thus, energy devices became widespread and are extensively used today [2].

The development of energy devices follows a parallel course to the development of the electrical current. Firstly becquerel tried using direct current for coagulation rather than pouring hot oil. It passed direct current through a wire and cauterized the tissue after the wire was warmed up. D'arsonval revealed that high-frequency alternating current flows through the tissue without causing a painful electrical shock and produces heat instead of muscle stimulation [3]. In the early 1900s, French physician Joseph Rivere observed that the electrical current coagulated the skin in a limited area while treating a patient with insomnia using electrical current [4]. Whereupon he used this current to treat a carcinomatous ulcer on the hand of a patient. This application was the first correct use of electricity in surgery [2]. Later, its use in tissues with intense blood supply such as skin, oral cavity, and hemorrhoids became commonplace. Doyen placed the grounding pad under the patient for the first time [5]. In 1926, the first electrosurgery unit, based on high-frequency electrical current, was constructed in Boston by William Bovie. Dr. Harvey Cushing used this unit for the first time to remove vascular myeloma from the head of a 64-year-old patient [6]. Cushing had tried to resect this tumor with traditional methods several days earlier but failed due to the vascularity of the mass [7]. After this experience, surgeons were heartened more about electrosurgery [8].

2. BIOPHYSICS

Low-frequency electrical current below 10000 Hz. can cause muscle and nerve stimulation. Therefore, high-frequency electrical current is used in energy devices (200000-3000000 Hz) [4,9]. The application of electrical

current to the tissue produces effects such as fulguration, desiccation/coagulation, or vaporization/ablation [10].

Electrosurgery is performed with monopolar or bipolar instruments. The difference between them is the pathway traveled by the current. In a monopolar instrument, electrical current is obtained from the electrosurgical unit. The current continues from the tip of the monopolar device through the tissue and leaves the patient's body from the lowest resistance zone. A ground pad is attached to the patient for easy and safe passage of the current [2,4]. In bipolar instruments, the electrical current proceeds to the tissue from the positive tip of the device and completes the circuit by leaving the tissue from the negative tip (return electrode) [11,12]. In bipolar instruments, electrodes have a structure that resembles forceps [2,4,13].

3. CUT AND COAGULATION

The surgeon could adjust the electrosurgical unit and use the device in cutting or coagulation modes. In cutting mode, high-frequency current is applied continuously and at low voltage. In this way, high energy is given to a small area in a short time. The temperature rises to 400 degrees, vaporization develops, and cutting occurs [14,15]. To cut tissue, the tip of the electrode should be kept very close but and should not direct contact with the tissue. In the coagulation mode, a high voltage current is given intermittently (94% off, 6% on). Hence a lower density current occurs in a wider area. The tissue temperature increases moderately. Dehydration and protein denaturation takes place in the tissue. Vascular structures below a specific diameter are sealed by tissue dehydration and protein denaturation. Coagulation mode is an effective mode to control leaks on large surfaces [14].

Several "blend" options are also available, combining various proportions of the two main modalities. As electrical current is applied to the tissue, heat is generated due to the tissue's resistance. Desiccation, vaporization, or fulguration occurs depending on the contact time of the surgical instrument with the tissue and the nature of the voltage from the electrosurgery unit [3,16].

Desiccation: It occurs by direct contact of the tip of the device and the tissue. It is a result of protein denaturation and dehydration. Desiccation could be created with cut or coagulation modes [17].

Vaporization: It occurs with the cut mode without the tip of the instrument contacting the tissue. The high heat generated suddenly by the current vaporizes the tissue immediately adjacent to the tip of the electrode. The cells explode, and cutting occurs.

Fulguration: The tip of the electrode in coagulation mode affects the large area without touching the tissue. Fulguration is useful for hemostasis in wide areas and it causes charring of the tissue [3].

4. THERMAL SPREAD

Energy devices have varying degrees of thermal diffusion effect [18]. The thermal spread could cause tissue necrosis in undesirable areas. Tissue necrosis in the surgical area might lead to prolonged postoperative recovery and wound nfection [19]. Due to thermal spread, adjacent organs such as the ureter, bladder, and bowel might also be damaged. Therefore, surgeons need to be aware of the potential thermal spread from specific electrosurgical devices and perform with caution [20].

Table 1. *Thermal spread of some devices* [21]

Device	Thermal Spread (mm)
Traditional bipolar device	2 to 22
Ultrasonic cutting and coagulation device (Harmonic Scalpel)	0 to 3
Vessel sealing devices	
EnSeal Tissue Sealing and Hemostasis System	1.1
10 mm Ligasure	1.8
5 mm Ligasure	4.4

Energy devices might generate smoke plumes during the process. The smoke plume contains potentially toxic and biohazardous substances [22]. In high concentrations, these plums could irritate the eyes and respiratory tracts of operation room staff [23]. In addition, as using energy devices during laparoscopy, there could be aerosolized blood -borne viral content in the smoke plume [24]. The probability of viral transmission is higher in ultrasonic devices that do not generate high temperatures [25-28]. 2020 is a year that the world struggles with the Covid-19 pandemic. According to recent studies, sars-cov-2 has been detected in some abdominal organs and peritoneal fluid [29,30]. However, it has not been proven to become aerosol during laparoscopy or using energy devices [31,32]. Nevertheless, it is reasonable to take precautions such as smoke evacuation systems and personal protective masks to minimize the risk. Many smoke evacuation systems available on the market could filter sars-cov-2 with approximately 0.06-0.14 microns. [32]. Thus, it is an important precaution to use appropriate smoke evacuation devices containing Ultra-Low Particulate Air (ULPA) or HEPA (High-Efficiency Particulate Air) filters [33].

5. SAFETY

In grounding systems used before the 1970s, the risk of current discharge from the patient through alternative pathways was higher. These alternative pathways could be the metals on the operation table, electrocardiogram leads, or tips of intravenous fluid sets. However, dispersion pads that are currently used are placed close to the surgical area. Thus they provide a safe outlet for the current, minimizing the risk of complications [34]. If the dispersion pad is not fully attached or partially peeled off, the risk of skin burn may increase. New modern electrosurgical devices have sensors that measure pad-to-skin contact and current density; these devices sound an alarm and automatically turn off the current if contact is poor [4].

To avoid complications caused by stray current, instruments used as monopolar should be inspected for insulation failure prior to surgery. Metals on the skin, such as piercings, should be removed if they are located close to the surgical area [35].

Cardiac implantable devices that use electric current may be affected by the use of energy devices. These are cardiac

implantable electronic devices (CIED) (e.g., cardiac pacemaker, implantable cardioverter-defibrillator [ICD], cardiac resynchronization device, ventricular assist device), neurologic or spinal cord stimulators, and gastric neurostimulators. In such cases, the technical assistance of the devices should be necessary or alternative devices should be used (bipolar devices, ultrasonic scalpels, or topical hemostatic agents). In monopolar electrosurgery, current flows from the active electrode (hand-held electrode) to the dispersion pad. In bipolar electrosurgery, current flows between the two electrodes of the device, and the stray current is minimal [36,37]. If the monopolar device is necessary, the dispersion pad should be placed in the appropriate place closest to the surgical site, with the other magnetic devices outside the pathway [38].

6. ADVANCED ENERGY DEVICES

6.1. Advanced Bipolar Devices

Advanced bipolar devices use pulsed bipolar energy and feedback control of the energy output during tissue coagulation. Therefore, heat production is low compared to basic and other advanced electrical surgical devices. They minimize tissue sticking, smoke, and lateral thermal spread. Ensell (Ethicon, USA) and ligasure (Medtronic, USA), introduced in 1998, are the first and most commonly used devices. The energy flow to the tissue progressively increases up to approximately 100 degrees, and at this temperature, energy flow is stopped, and the tissue is cut with a blade. In advanced bipolar devices, electrodes are located inside the jaw, and lateral thermal damage is minimal compared to other devices[18]. It seals vessels up to 7 mm and produces smoke plumes less than other advanced energy devices [20,39].

6.2. Ultrasonic Scalpels

Ultrasonic scalpels have been used since the first half of the 1990s, and the most frequently used device is the harmonic (Ethicon, USA) scalpel. Ultrasonic devices which contain piezoelectric transducers convert electricity into mechanical energy and produce a high vibration frequency in the 55 kHz ultrasonic range. They increase the temperature up to 200 degrees in the tissue and cause protein denaturation. It safely closes vessels whose diameters are 5 mm or less [40]. Ultrasonic Devices are faster and smokeless than other devices but are more likely to cause lateral thermal damage [39,41].

6.3. Integrated Bipolar and Ultrasonic Devices

Integrated bipolar and ultrasonic devices combine the safety of advanced bipolar devices with the speed of ultrasonic devices [42]. Thunderbeat system (Olympus, Japan) is the most frequently used integrated system. In the Thunderbeat device, bipolar heat energy is applied laterally, while additional sealing and cutting are achieved by ultrasonic energy in the central part of the device. Integrated devices reach high burst pressures and seal even in large vessels and give superiority to other energy devices in terms of speed [43]. Integrated energy devices reach high-temperature degrees in the tissue like other ultrasonic devices [44]. Therefore, the probability of lateral thermal damage is higher than advanced bipolar devices [45].

6.4. Complications

Complications related to energy devices occur in 2 to 5 per 1000 procedures. As the surgical experience increases, complications decrease and reach a plateau. The most severe and fatal complications related to energy devices are small bowel or colon perforations. Symptoms of bowel perforation usually appear 4 to 10 days postoperatively. It could be fatal if not detected early [46]. Adjacent organs could be injured due to lateral thermal spread [47]. During dissection close to ureters and intestines, the possibility of injury to these organs should be kept in mind, and the voltage should be kept at the lowest level possible [4]. Some electrosurgical complications are more common during laparoscopic surgery [48].

Direct coupling: Inadvertent contacting or taking place very close of two non-insulated instruments (i.e., metal trocar and metal grasper) causes direct coupling in electrosurgery. Electrical current could flow to the secondary instrument. If the secondary instrument is in contact with the bowel, skin, or other sensitive organs, injury of these organs is highly probable. With direct coupling, bile duct injuries may occur in laparoscopic cholecystectomy; delayed bile leaks can be seen [49,50].

Capacitive coupling: If two conductors are separated by an insulator, a capacitor might appear in the electrical circuit. An example of this in surgery would be an insulative coated surgical instrument placed in a hybrid trocar [4]. Capacitor occurs with the alternating current given to the surgical instrument. Thus, tissues such as skin and intestines that contact or soo close with the second conductor may be injured [34,51]. The magnitude

Table 2. *Features of energy devices* [39]

	Monopolar	Bipolar	Ultrasonic	Advanced Bipolar	Integrated Bipolar + Ultrasonic
Sealing	Yes	Yes	Yes	Yes	Yes
Transection	Yes	Yes	Yes	Yes	Yes
Hemostasis	Yes	Yes	Yes	Yes	Yes
Burst pressure (5-7 mm vessel)	-	-	450 mmHg	615-720 mmHg	730 mmHg
Lateral thermal spread	++++	++	+++	+	+++
Maximum vessel size	2-3 mm	2-3 mm	5 mm	7 mm	7 mm
Important points	Cost-effective	Cost-effective optionally can add water irrigation tool	Fast High propensity of collateral tissue damage	Low lateral thermal spread	Fast, highest burs pressure, high propensity of collateral tissue damage

of the current induced from the capacitor depends on the proximity of the two conductors, the conductor, the amount and duration of the voltage.

During laparoscopic surgery, the electrosurgical unit is connected to laparoscopic instruments. Instruments such as graspers and scissors can be used as monopolar devices. The current flows from the shaft of the laparoscopic instruments to the tip. There might be insulation failures in the shaft of these instruments [52]. In this instance, the current could pass from the shaft to the intraabdominal organs. If reusable or disposable instruments are used by sterilizing repeatedly, the probability of injury to the abdominal organs increases. Reusable instruments should be checked before use, and disposable instruments should not be reused [52,53].

Technological improvements and developments of new devices are likely to continue. There is not enough contemporary information about new technologies in the current medical and residency education curriculum [54]. To address this gap, the Fundamental Use of Surgical Energy (FUSE) program was designed by a multidisciplinary team of doctors, engineers, nurses, and educators. The FUSE program aims to reduce the frequency of complications by filling the education gap [55].

7. CONCLUSION

Energy devices have revolutionized surgical practice since the first unit of BOVIE. They reduced complications and shortened operation time. Surgical procedures, which were previously considered impossible, have been performed. There is an electrosurgical unit in each operating theater now. However, these devices are not exempted from complications. Surgeons should understand the mechanism of action; they have knowledge about the prevention and treatment of potential complications. Therefore, it is beneficial to expand education programs.

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CONFLICT OF INTEREST DECLARATION

The authors report no conflict of interest. The authors alone are responsible for the content and the writing of the paper.

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