

# A new approach to oral dosage forms: carrageenan-based vegan gummies

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**ABSTRACT:** Although the oral route is a common drug administration route, it still causes some patient compliance problems. Gummies are chewable gels that are commonly manufactured as dietary supplement carriers and their pharmaceutical use is still limited. Dexketoprofen trometamol is an anti-inflammatory and antipyretic drug. In the present study, dexketoprofen containing gummies were manufactured using carrageenan (Gelcarin®GP-379) as the gel-forming polymer. Potassium dihydrogen phosphate (KH<sub>2</sub>PO<sub>4</sub>) was used as the gelling agent in the research. The obtained gummies were characterized. For this purpose, gel viscosity measurements, morphological and physical characterizations, thermal analysis, and *in vitro* drug release studies were carried out. The viscosity of the gel mixtures was measured at 50°C, which was the pouring temperature of the gels into molds. The formulation containing the highest carrageenan and KH<sub>2</sub>PO<sub>4</sub> had the highest viscosity. The physical characterization results showed that the gummy formulations could be prepared in a reproducible manner. The DSC thermograms showed that the melting peak of DXT was not observed in the gummy formulation. The *in vitro* dissolution test results of the gummies showed that decreasing the carrageenan and KH<sub>2</sub>PO<sub>4</sub> concentration in gummy formulation accelerated the drug release. The obtained gummies exhibited an extended-release of up to 2 hours.

**KEYWORDS:** Vegan drug gummy; dexketoprofen; carrageenan; oral drug gummy; chewable hydrogel.

## 1. INTRODUCTION

The oral cavity is one of the most significant sites for the administration of drugs. In the oral route, drugs are exposed to several processes from taste perception to swallowing. In the mid-steps, the dosage form is disintegrated and released the drug. These steps might also be followed by the absorption stage [1, 2]. Chewable dosage forms are beneficial for specific patient groups such as pediatrics and geriatrics. These groups accept chewable dosage forms with high compliance. The mouthfeel, taste, and aroma of the dosage forms are important factors for an acceptable oral administration [3]. The development of oral dosage forms special to pediatric patient groups is still a challenge because of its limitations. The shape, texture, or taste of an oral formulation must be acceptable for young children. In addition, dose adjustment is required considering the age of the pediatric patient. To overcome these limitations, orally disintegrating formulations are widely manufactured [4, 5].

Chewing gums are products that are consumed widely for pleasure without swallowing. They have an alternative use for therapy such that the first medicated gum (Aspergum) contained aspirin. As expected, it has analgesic, antipyretic, and anti-inflammatory effects. Researchers have been conducting studies on the use of biodegradable gums in the treatment of specific diseases. Medicated chewing gums might include nutrients or pharmaceutical ingredients. Therefore, they are considered to be promising dosage forms for drug delivery [6].

Gummies are chewable gels that are commonly used for vitamin delivery [7]. Although gummies are mostly prepared to include nutritional supplements, there are also studies where they are used for diagnostic purposes, as an interesting approach [8, 9]. In general, gummies consisted of hydrocolloid-based gelling agents and other excipients such as sweeteners, flavorings, and food colorings. Hydrocolloids are

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gel-forming large molecules that have the capability of the composition of three-dimensional network structures by dispersing in water. [10] The most commonly used hydrocolloid in the preparation of gummies is gelatin or its mixtures with other gelling agents [11]. Gelatin is a natural animal-sourced polymer that is obtained from collagen [12]. While it is possible to produce well-structured gels using gelatin, this polymer is not suitable for use by vegans. Plant-origin foods have recently been an alternative to those of animal origin, especially for vegans. For instance, in the candy and supplement industry, studies on the production of gelatin-free gummy formulations have increased in recent years. This is also important for the field of pharmacy. The development of gelatin-free dosage forms, especially for vegans or children allergic to gelatin, may provide advantages in this area. Hence, a fruit-based gelling agent, pectin or seaweed-based hydrocolloid, carrageenan could be an alternative to gelatin [13]. Carrageenans are natural polysaccharide polymers obtained from marine seaweeds. They have immunomodulatory, antioxidant, and anti-inflammatory effects [14]. It is possible to classify carrageenans into three main groups according to the sulfate groups they contain: kappa- ( $\kappa$ -carrageenan), iota- ( $\iota$ -carrageenan), and lambda- ( $\lambda$ -carrageenan) carrageenans. Carrageenans exhibit a well-known soft-dependent gelation mechanism. The most important parameter of the gelation process of carrageenans is the presence of calcium or potassium salts in the medium. Another significant parameter here is that the gelation process is fully reversible depending on the temperature [15, 16]. Although carrageenan is generally used in the food industry, it also offers promising results in the preparation of pharmaceutical formulations. The different types of carrageenans are excellent candidates for the production of formulations with controlled release properties. There are many studies in the literature in which carrageenan-based hydrogel formulations with controlled release of drugs are prepared. [15, 17, 18].

Patient-specific drug-containing gummies, which are defined as 'drugummies', are dosage forms having the appropriate appearance and organoleptic properties. These dosage forms can improve treatment adherence and reduce adverse psychological symptoms accompanying the diseases, especially in pediatric patients [19]. The difficulty of swallowing oral solid dosage forms is one of the patient compliance problems, especially for specific patient groups such as pediatrics and geriatrics. It can also be a struggle for adolescents due to the shape, size, or taste of the dosage forms. To overcome these problems, scientists have focused on the development of fast-dissolving or chewable dosage forms [20, 21].

Dexketoprofen trometamol (DXT) is a water-soluble salt of an anti-inflammatory, and antipyretic agent, dexketoprofen, a nonsteroidal anti-inflammatory drug (NSAID). DXT is a drug with high efficacy and safety even at low doses. There are oral, intra-articular, and intravenous administrations of DXT in pain management [22-25].

The main objectives of the present work were to produce chewable vegan gummy formulations of DXT and conduct various characterization studies on them. There are few studies in which drug-loaded gummies were developed using three-dimensional (3D) printers. However, the main gelling agent was gelatin in the mentioned studies [19, 26]. To the best of our knowledge, the current study represents an innovation for the preparation of drug-loaded vegan gummies using a plant-based polymer. In this context, dexketoprofen (DXT) containing gummies were manufactured using carrageenan (Gelcarin®GP-379) as the gel-forming polymer. In the study, the characteristics (morphology, physical properties, release profile, thermal behavior and gel viscosity) of the prepared gummies were also evaluated.

## 2. RESULTS

The gummy formulations coded F1-F4 were successfully prepared. The images of the prepared gummies were demonstrated in Figure 1.

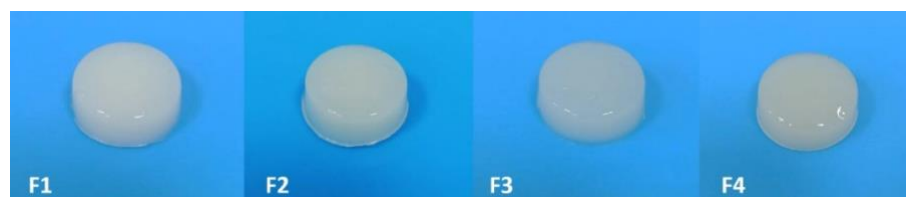


Figure 1. Images of the formulations F1-F4.

## 2.1. Viscosity measurements

The viscosity of the gel mixtures was measured at 50°C, the pouring temperature into molds. Formulation F2 showed the highest viscosity value because of containing carrageenan and  $\text{KH}_2\text{PO}_4$  more than other formulations (Figure 2). The formulations F1 and F2 contained 0.75%  $\text{KH}_2\text{PO}_4$ , while formulations F3 and F4 contained 0.5%  $\text{KH}_2\text{PO}_4$ . In addition, F1-F3 and F2-F4 were prepared at the same carrageenan concentrations. The formulation F2, which consisted of the highest amount of carrageenan and  $\text{KH}_2\text{PO}_4$ , showed the highest viscosity.

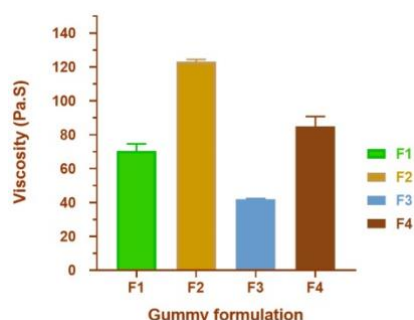


Figure 2. Viscosity results of the formulations F1-F4.

## 2.2. Physical characterizations and drug content of gummies

The thickness, diameter, and weight of the gummy formulations were summarized in Table 1. There was no significant difference between the characterization results of the prepared formulations. A gummy formulation weighing an average of 2.5 g was expected to contain 2.5 mg (1%) of DXT. DXT content of the prepared gummies was calculated as  $91\% \pm 1$ ,  $94\% \pm 2$ ,  $93\% \pm 3$ ,  $94\% \pm 3$  for the formulations F1, F2, F3, and F4, respectively (Table 1).

## 2.3. Scanning electron microscopy (SEM) analyses

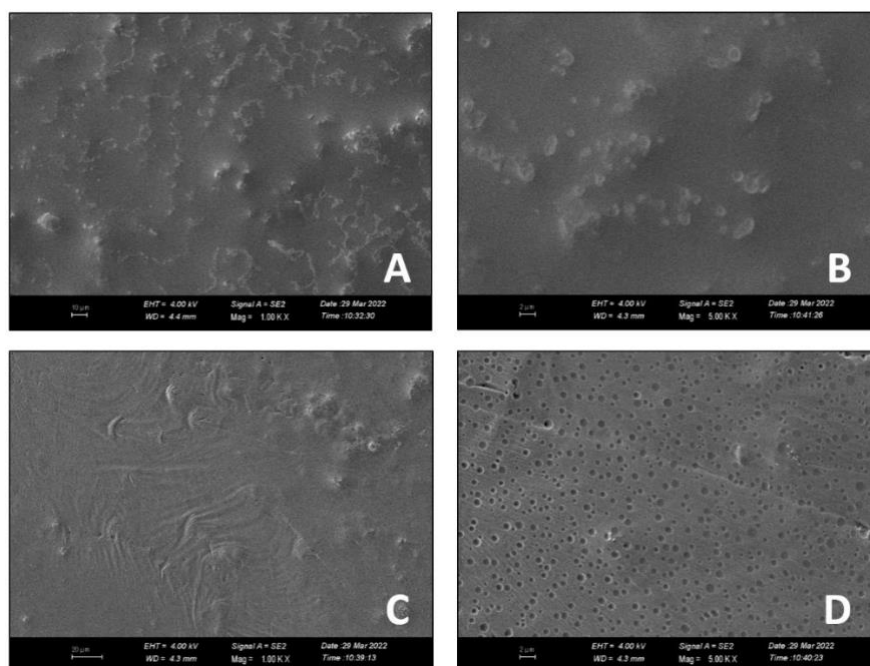
The morphological properties of air-dried gummies were investigated via SEM imaging. While Figures 3A and 3B showed drug loaded F1 gummy, Figures 3C and 3D showed blank F1 gummy. Drug-loaded gummy (drugummy) had a rougher surface than the blank one.

## 2.4. Differential scanning calorimetry (DSC) analyses

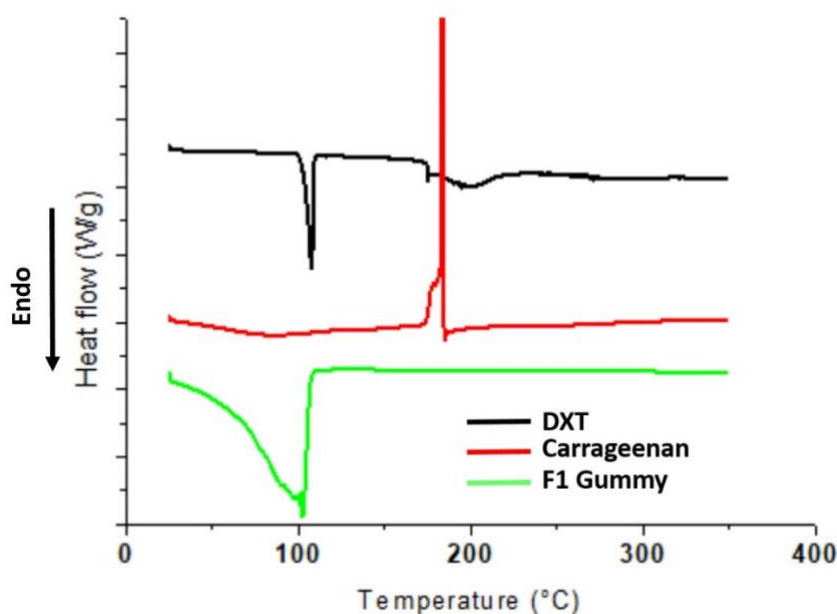
DSC thermograms of DXT, carrageenan, and the formulation F1 were shown in Figure 4. DXT exhibited a sharp endothermic peak at 107°C, which represented the melting point of the drug [27]. Carrageenan revealed an exothermic peak at 178°C, which represented its degradation temperature [28]. The DSC curve of the gummy formulation F1 showed an endothermic peak above 100°C due to the water evaporation event which occurred in the hydrogel structure [26].

Table 1. Physical and drug content analyses results of the formulations F1-F4.

Formulation code	Thickness (mm, n=6 Mean $\pm$ SD)	Diameter (mm, n=6 Mean $\pm$ SD)	Weight (g, n=6 Mean $\pm$ SD)	Drug content (mg, n=3 Mean $\pm$ SD)
F1	6.9 $\pm$ 0.2	18.9 $\pm$ 0.4	2.55 $\pm$ 0.11	22.83 $\pm$ 0.35
F2	7.0 $\pm$ 0.3	18.9 $\pm$ 0.2	2.56 $\pm$ 0.17	23.51 $\pm$ 0.56
F3	6.7 $\pm$ 0.3	18.7 $\pm$ 0.3	2.49 $\pm$ 0.17	23.24 $\pm$ 0.79
F4	7.1 $\pm$ 0.3	18.8 $\pm$ 0.3	2.61 $\pm$ 0.15	23.50 $\pm$ 0.50



**Figure 3.** SEM images of air-dried F1 drug gummy (A,B; 1000x,5000x magnification, respectively), F1 blank gummy (C,D; 1000x,5000x magnification, respectively).



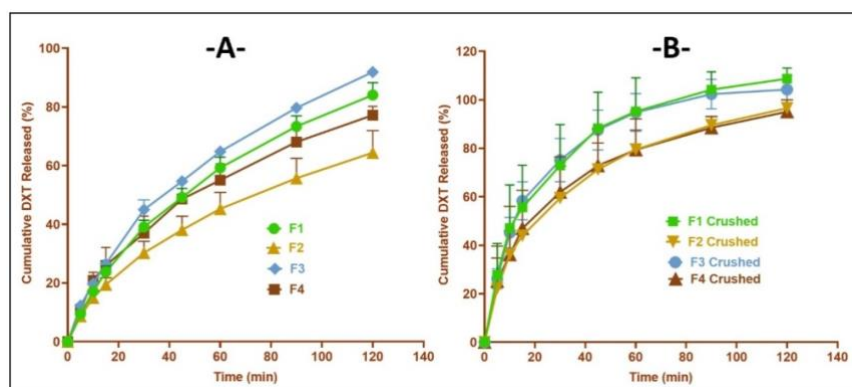
**Figure 4.** DSC thermograms of DXT, carrageenan, and F1 gummy.

## 2.5. Drug release studies

*In vitro* dissolution test is one of the significant quality control tests for oral dosage forms. Dissolution testing is considered among the critical performance tests which provide information on drug absorption and *in vivo* bioavailability of a pharmaceutical formulation after oral administration. These tests are used for defining and predicting the drug release behavior of a dosage form [29, 30]. Investigating the *in vitro* drug release properties of the prepared gummies was one of the main purposes of the present study. In the present study, a 2-hour drug release profile was obtained for all the formulations (Figure 5A).

To investigate the effect of chewing function (in the mouth) on the release profile, the gummy formulations were crushed. The crushed gummies released the drug with a higher dissolution rate,

compared to uncrushed ones. While the crushed forms of F1 and F3 released ~100% of the drug in 120 min, crushed forms of F2 and F4 released ~90% the of drug in 120 min (Figure 5B).



**Figure 5.** *In vitro* drug release profiles of the uncrushed (A) and crushed (B) gummies.

The *in vitro* dissolution data were plotted in different kinetics models to investigate the release mechanism of drug-loaded gummies. Korsmeyer-Peppas kinetics presented the best fit to the experimental data of all formulations according to the highest  $R^2_{adj}$  values. “n” values were found to be between 0.43 and 0.85 (Table 2). In addition, drug release from the formulations F1 and F3 also followed first order kinetics.

**Table 2.** Kinetics models for drug release mechanism of gummies.

Model	Parameter	Equation	Formulation			
			F1	F2	F3	F4
Zero order	$R^2_{adj}$	$F = k_0 \cdot t$	0.8671	0.8397	0.8431	0.7923
	$k_0$		0.824	0.632	0.904	0.771
	AIC		63.2950	59.7707	66.1580	65.2872
First order	$R^2_{adj}$	$F = 100 \cdot [1 - \text{Exp}(-k_1 \cdot t)]$	0.9955	0.9632	0.9940	0.9684
	$k_1$		0.016	0.010	0.019	0.014
	AIC		32.8598	46.5341	36.8396	48.3416
Higuchi	$R^2_{adj}$	$F = k_H t_{1/2}$	0.9798	0.9894	0.9859	0.9941
	$k_H$		7.432	5.728	8.187	7.033
	AIC		46.3492	35.3163	44.4522	33.3008
Korsmeyer-Peppas	$R^2_{adj}$		0.9946	0.9976	0.9951	0.9960
	$k_{KP}$	$F = k_{KP} \cdot t_n$	4.752	4.164	5.804	5.971
	n		0.606	0.576	0.582	0.539
	AIC		35.2520	22.8162	35.8170	30.4748

\*F: the fraction of drug released at time t, and  $k_0$ ,  $k_1$ ,  $k_{KP}$  and  $k_H$  are the rate constants for the mathematical models Zero-order, First-order, Korsmeyer-Peppas, and Higuchi, respectively. “n” is the release exponent of Korsmeyer-Peppas equation. AIC: Akaike information criterion,  $R^2_{adj}$ : Adjusted determination coefficient.

### 3. DISCUSSION

DXT-containing gummy formulations were prepared successfully (Figure 1). Increasing the concentration of carrageenan in gel mixtures increased viscosity as expected [31]. Thus, formulations F2 and F4 exhibited higher viscosity values compared to formulations F1 and F3, respectively. It is known that cations (potassium, calcium, etc.) used as gelling agents affect the rheological and mechanical properties of carrageenan gels [32, 33]. The presence of potassium ions causes rigid and stiff gels of carrageenan [34, 35]. The fact that F2 gel mixture had a higher viscosity than F1 and F4 mixture had a higher viscosity than F2 can be explained by the increase in the amount of potassium in the mixtures (Figure 2) [36].

There was no significant difference between the characterization results of the prepared formulations. It was concluded that the formulations prepared by pouring into the same mold had the



same dimensions. This showed the reproducibility of the manufacturing process (Table 1). When the blank gummy was examined with a higher microscope magnification, pores were observed on its surface. It was thought that the drying process might cause deformation in the gel structure of the carrageenan gummies [37]. Thus, pores were formed on their surfaces (Figure 3D).

According to DSC thermograms, the melting peak of DXT was not observed in the gummy formulation. This can be caused by the low content of the drug. On the other hand, DXT might transform from crystalline to amorphous state resulting in the absence of melting endotherm in the gummy formulation (Figure 4).

The concentration of carrageenan in the formulations F2 and F4 (4.5%) was higher than that in the formulations F1 and F3 (2.5%). Thus F1 and F3 gummy formulations released the drug they contained faster than F2 and F4. In a study by Zhu *et. al*, carrageenan-poloxamer 407 composite gel systems were prepared. As the carrageenan concentration increased in these systems, it was concluded that the drug release was delayed [38]. The gel-forming salt,  $\text{KH}_2\text{PO}_4$ , was thought to affect drug release from the gummies. F1, F3, and F2, F4 contained the same concentration of carrageenan. However, F4 released DXT faster than F2, and F3 released DXT faster than F1. This can be explained by the potassium concentration difference in these formulations (Figure 5A).

The *in vitro* drug release rate difference between the chewed and unchewed gummies showed that chewing function might have an accelerating effect on drug release from carrageenan gummies (Figure 5B). Such a profile comparison is important because patients may swallow the gummy after holding it for a while or chewing it [20]. It is possible to produce oral drug gummies via 3D printing technology. Tagami *et.al*, generated gelatin and hydroxypropyl methylcellulose (HPMC) based gummies using a 3D printer. These formulations exhibited rapid drug release because of the polymers used in the study [26]. In another study, ranitidine HCl gummy formulation was printed by Herrada-Manchón *et. al*. They also used carrageenan for the preparation of gummies. However, the main gelling agent was gelatin there. In this study, one formulation exhibited an immediate-release profile while the other exhibited an extended-release profile [19]. These studies showed that drug gummy formulations might be fabricated to achieve both immediate and controlled release properties. Carrageenan is preferred in the pharmaceutical field due to its sustained-release properties [39]. It has suitable gel-forming properties and promotes sustained drug release [40, 41]. In addition, carrageenanchitosan-based nano-layered coatings were thought to be promising for the controlled release of bioactive compounds [42]. In the study by Sonawane *et.al*, carrageenan was used for the preparation of zaltoprofen extended-release pellets. In our study, carrageenan-based DXT gummies also exhibited an extended-release profile [43]. The *in vitro* dissolution data exhibited a good correlation with the Korsmeyer-Peppas kinetics model considering the highest  $R^2_{\text{adj}}$  values (Table 2). According to the Korsmeyer-Peppas model, drug release from the hydrogels is process and diffusion dependent. The obtained gummies were carrageenan-based hydrogel formulations and thus, performed a diffusion and matrix swelling controlled drug release profile as expected ("*n*" values were found to be between 0.43 and 0.85, that indicated the diffusion and swelling controlled non-Fickian release) [44, 45].

#### 4. CONCLUSION

The oral drug gummy formulations were prepared and characterized successfully, in the current work. One of the most significant points here was that the prepared formulations were gelatin-free and suitable for use by vegans and patients allergic to animal products. This is also important for global sustainability. This has been achieved with an eco-friendly polymer with controlled release properties, carrageenan. The intact form of the resulting gummy formulations exhibited prolonged-release properties, while the crushed ones released the drug faster. Further studies will be conducted to develop gummy formulations with desired and controllable release properties. Gummies, which are considered to be highly acceptable by patients, are thought to be promising in terms of increasing patient compliance with oral administration.

#### 5. MATERIALS AND METHODS

##### 5.1. Materials

Dexketoprofen trometamol (DXT), the active pharmaceutical ingredient (API), was kindly donated by Berko Pharmaceuticals (Turkey). Carrageenan (Gelcarin®GP-379 NF), the gel-forming polymer, was gifted by IFF (Turkey). Potassium dihydrogen phosphate ( $\text{KH}_2\text{PO}_4$ ) and mannitol (sweetener) were

purchased from Isolab (Turkey) and CARLO ERBA Reagents, respectively. Buffering materials, solvents, and other chemicals were of reagent grade.

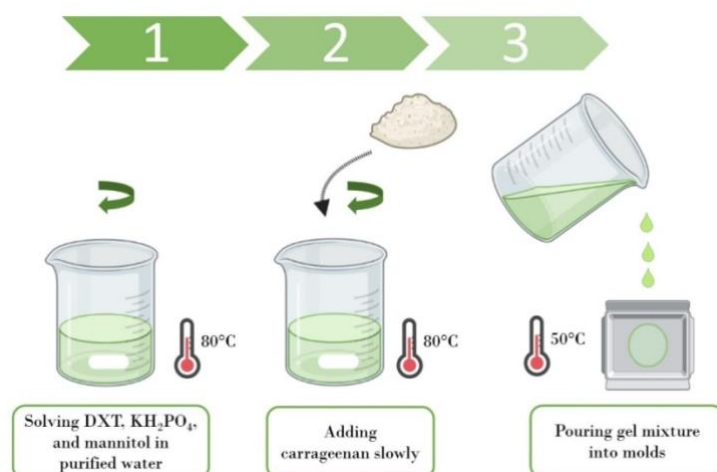
## 5.2. Preparation of drug-loaded gummies

To produce drug gummies, four different mixtures were prepared with DXT, gelling agent (carrageenan), and other excipients. The mixtures were coded from F1 to F4 and the compositions of these mixtures were summarized in Table 3.

**Table 3.** Composition of the mixtures used to prepare gummies.

	F1	F2	F3	F4
Dexketoprofen trometamol (g)	0.4	0.4	0.4	0.4
Gelcarin®GP 379 (g)	1	1.8	1	1.8
KH <sub>2</sub> PO <sub>4</sub> (g)	0.3	0.3	0.2	0.2
Mannitol (g)	1	1	1	1
Purified water (g)	37.3	36.5	37.4	36.6

The gummy preparation process was conducted as follows. Firstly, DXT, KH<sub>2</sub>PO<sub>4</sub>, and mannitol were dissolved in purified water. After setting the temperature of the solution to 80°C, the required amount of carrageenan was added gradually. The gelling process was carried out under magnetic stirring (at 800 rpm) keeping the temperature constant. After gelation was completed, the mixture was cooled to 50°C and poured into molds. The steps of the gummy preparation was shown in Figure 6.



**Figure 6.** The preparation process of the gummies (created with BioRender).

## 5.3. Viscosity measurements

Viscosity measurements of the mixtures which were used for the preparation of gummies were carried out using a rotational viscometer (Brookfield Ametek DV2T Viscometer) equipped with a spindle (LV 65). The rotation speed was set to 50 rpm. The measurements were performed in triplicate. The test was conducted after cooling the gel mixtures to 50°C (the temperature at which gels are poured into molds) and during the test, the temperature was kept constant.

## 5.4. Physical characterization of gummies

To evaluate weight uniformity, 6 gummies were randomly selected and then weighed. The mean and standard deviation (SD) of the measured weight values were calculated. The thickness and diameter of the gummies were also measured with the help of a digital micrometer.

## 5.5. Drug content of gummies

The gummies were dissolved in a 200 mL pH 6.8 buffer solution under magnetic stirring. After the gummies completely dissolved, samples were taken from the gummy solution and filtered through a 0.45

µm membrane filter (Nylon, 25 mm). The concentration of DXT was measured spectrophotometrically at  $\lambda=287.4$  nm using a UV-Vis spectrophotometer (Shimadzu, UV-1280). The used analytical method was fully validated.

### 5.6. Scanning Electron Microscopy (SEM) analyses

The morphological properties of the drug-loaded and blank gummies (only for formulation F1) were examined using a scanning electron microscope (Carl Zeiss 300VP). The drug-loaded (drug gummy) and blank gummies were air-dried and coated by a rotary pump coater (Quorum Q150 Res) before the analysis.

### 5.7. Differential Scanning Calorimetry (DSC) analyses

The thermal behavior of DXT and carrageenan was investigated via a DSC study. In this study, a DSC analysis of the F1 formulation was also performed to check whether the thermal properties of DXT and carrageenan changed during the gummy preparation process. In the analyses, the powder or gummy samples were enclosed in aluminum DSC pans and DSC thermograms were obtained under a nitrogen atmosphere using a DSC (TA Instruments, DSC Q2000) instrument. The study was conducted between the temperatures of 25°C-300°C at a heating rate of 20°C/min.

### 5.8. Drug release studies

The patients may prefer to use the formulation by sucking or chewing. For this reason, *in vitro* drug release studies were carried out both for crushed and uncrushed gummy formulations. The drug release properties of the prepared gummies were examined via a dissolution tester (Pharmatest, PTWS 120D). In the present test, the USP paddle apparatus (Type II) was used at the rotating speed of 75 rpm. The dissolution medium was a simulated saliva fluid (pH 6.8) at  $37 \pm 0.5^\circ\text{C}$ . The test was carried out for 120 min. The time intervals of the aliquots taken were 5th, 10th, 15th, 30th, 45th, 60th, 90th, and 120th min. The amount of DXT in the test samples was spectrophotometrically analyzed at  $\lambda = 287.4$  nm via a UV-Vis spectrophotometer (Shimadzu, UV-1280). To show the effect of chewing, the release properties of crushed gummies were also investigated with the same method. According to the literature, 40-150 N (approximately 500-1000 g force) is applied to the formulation in the mouth with the chewing motion, so in our study, the formulations were thrown into the dissolution medium immediately after applying 1 kg of pressure before the *in vitro* dissolution study [46]. The crushed gummies represented the gummies after being chewed. To predict the drug release behavior of gummies, various kinetic models were applied to the drug release profile. The applied kinetics models were Zero-order, First-order, Higuchi, and, Korsmeyer-Peppas. The mathematical modeling study was conducted via the DDSolver program [47].

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**Conflict of interest statement:** The authors declared no conflict of interest.

## REFERENCES

- [1] Ali J, Zgair A, Hameed GS, Garnett MC, Roberts CJ, Burley JC, Gershkovich P. Application of biorelevant saliva-based dissolution for optimisation of orally disintegrating formulations of felodipine. *Int J Pharm.* 2019; 555: 228-236. <https://doi.org/10.1016/j.ijpharm.2018.11.051>
- [2] Olgac S, Usta DY, Incecayir T. Comparison of tablet splitting techniques for dosing accuracy of nebivolol tablets: Hand splitting versus tablet cutter and knife. *Saudi Pharm J.* 2021; 29(12):1486-1491. <https://doi.org/10.1016/j.jsps.2021.11.005>
- [3] Juvonen H, Antikainen O, Lemmens M, Ehlers H, Juppo A. The effect of relative humidity and formulation variables on chewable xylitol-sorbitol tablets. *Int J Pharm.* 2021; 601: 120573. <https://doi.org/10.1016/j.ijpharm.2021.120573>
- [4] Johannesson J, Hansson P, Bergström CA, Paulsson M. Manipulations and age-appropriateness of oral medications in pediatric oncology patients in Sweden: Need for personalized dosage forms. *Biomed Pharmacother.* 2022; 146: 112576. <https://doi.org/10.1016/j.biopha.2021.112576>



- [5] Gültekin HE, Tort S, Acartürk F. Fabrication of three dimensional printed tablets in flexible doses: A comprehensive study from design to evaluation. *J Drug Deliv Sci Technol.* 2022; 103538. <https://doi.org/10.1016/j.jddst.2022.103538>
- [6] Thivya P, Durgadevi M, Sinija VRN. Biodegradable medicated chewing gum: A modernized system for delivering bioactive compounds. *Future Foods.* 2021; 4: 100054. <https://doi.org/10.1016/j.fufo.2021.100054>
- [7] Yan B, Davachi SM, Ravanfar R, Dadmohammadi Y, Deisenroth TW, Van Pho T, Odorisio PA, Darji RH, Alireza Abbaspourrad A. Improvement of vitamin C stability in vitamin gummies by encapsulation in casein gel. *Food Hydrocoll.* 2021; 113: 106414. <https://doi.org/10.1016/j.foodhyd.2020.106414>
- [8] Lee D, Chua B. Gummy bear-based gnathodynamometer for masticatory diagnostics. *Sens Actuator A Phys.* 2019; 290: 80-89. <https://doi.org/10.1016/j.sna.2019.03.013>
- [9] Li Z, Srigley CT. A novel method for the quantification of long-chain omega-3 polyunsaturated fatty acids (PUFA) in gummy dietary supplements. *J Food Compos Anal.* 2017; 56: 1-10. <https://doi.org/10.1016/j.jfca.2016.11.006>
- [10] Renaldi G, Junsara K, Jannu T, Sirinupong N, Samakradhamrongthai RS. Physicochemical, textural, and sensory qualities of pectin/gelatin gummy jelly incorporated with *Garcinia atroviridis* and its consumer acceptability. *Int J Gastron Food Sci.* 2022; 100505. <https://doi.org/10.1016/j.ijgfs.2022.100505>
- [11] DeMars LL, Ziegler GR. Texture and structure of gelatin/pectin-based gummy confections. *Food Hydrocoll.* 2001; 15(4-6): 643-653. [https://doi.org/10.1016/S0268-005X\(01\)00044-3](https://doi.org/10.1016/S0268-005X(01)00044-3)
- [12] Michelini L, Probo L, Farè S, Negrini NC. Characterization of gelatin hydrogels derived from different animal sources. *Mater Lett.* 2020; 272: 127865. <https://doi.org/10.1016/j.matlet.2020.127865>
- [13] Song X, Chiou BS, Xia Y, Chen M, Liu F, Zhong F. The improvement of texture properties and storage stability for kappa carrageenan in developing vegan gummy candies. *J Sci Food Agric.* 2022;102(9):3693-3702. <https://doi.org/10.1002/jsfa.11716>
- [14] Walayat N, Wang X, Liu J, Nawaz A, Zhang Z, Khalifa I, Cervera MAR, Pateiro M, Lorenzo JM, Nikoo M, Siddiqui SA. Kappa-carrageenan as an effective cryoprotectant on water mobility and functional properties of grass carp myofibrillar protein gel during frozen storage. *LWT.* 2022; 154: 112675. <https://doi.org/10.1016/j.lwt.2021.112675>
- [15] Fenton T, Kanyuck K, Mills T, Pelan E. Formulation and characterisation of kappa-carrageenan gels with non-ionic surfactant for melting-triggered controlled release. *Carbohydr Polym Technol Appl.* 2021; 2: 100060. <https://doi.org/10.1016/j.carpta.2021.100060>
- [16] Baishya H. Carrageenan as Release controlling polymer in insoluble anti-psychotic drug matrix. *World J Pharm Pharm Sci.* 2017; 118-128. <https://doi.org/10.20959/wjpps20175-9093>
- [17] Zhao J, Sun C, Li H, Dong X, Zhang X. Studies on the physicochemical properties, gelling behavior and drug release performance of agar/κ-carrageenan mixed hydrogels. *Int J Biol Macromol.* 2020; 154: 878-887. <https://doi.org/10.1016/j.ijbiomac.2020.03.087>
- [18] Farooq A, Farooq A, Jabeen S, Islam A, Gull N, Khan RU, Shifa ul Haq HM, Mehmood A, Hussain N, Bilal M. Designing Kappa-carrageenan/guar gum/polyvinyl alcohol-based pH-responsive silane-crosslinked hydrogels for controlled release of cephadrine. *J Drug Deliv Sci Technol.* 2022; 67: 102969. <https://doi.org/10.1016/j.jddst.2021.102969>
- [19] Herrada-Manchón H, Rodríguez-González D, Fernández MA, Suñé-Pou M, Pérez-Lozano P, García-Montoya E, Aguilar E. 3D printed gummies: Personalized drug dosage in a safe and appealing way. *Int J Pharm.* 2020; 587: 119687. <https://doi.org/10.1016/j.ijpharm.2020.119687>
- [20] Sabere ASM, Suhaimi NANM, Ahmed QU, Mahat MM, Roslan NC, Azizi J. Soft-chewable paracetamol tablets by melt granulation method: Formulation and characterization. *J Pharm Bioallied Sci.* 2021; 13(3): 312. [https://doi.org/10.4103/jpbs.JPBS\\_783\\_20](https://doi.org/10.4103/jpbs.JPBS_783_20)
- [21] Han X, Yan J, Ren L, Xue M, Yuan Z, Wang T, Yan Z, Yin L, Yang L, Qin C. Preparation and evaluation of orally disintegrating film containing donepezil for Alzheimer disease. *J Drug Deliv Sci Technol.* 2019; 54: 101321. <https://doi.org/10.1016/j.jddst.2019.101321>
- [22] Koçum A, Sener M, İzmirli H, Haydardedeoğlu B, Aribogan A. Efficacy of intravenous dexketoprofen trometamol compared to intravenous paracetamol for postoperative pain management after day-case operative hysteroscopy: randomized, double-blind, placebo-controlled study/Gunubirlik operatif histeroskopi sonrası intravenöz parasetamol ve deksketoprofen trometamol'un analjezik etkinliklerinin karşılaştırılması: Randomize, çift kor, plasebo kontrollü çalışma. *Agri: The Journal of The Turkish Society of Algology.* 2014; 26(1): 15-23. <https://doi.org/10.5505/agri.2014.85047>

- [23] Cámara-Martínez I, Blechar J, Ruiz-Picazo A, García-Arieta A, Calandria C, Merino-Sanjuan V, Langguth P, Gonzalez-Alvarez M, Bermejo M, Al-Gousous J, Gonzalez-Alvarez I. Level A IVIVC for immediate release tablets confirms in vivo predictive dissolution testing for ibuprofen. *Int J Pharm.* 2022; 614: 121415. <https://doi.org/10.1016/j.ijpharm.2021.121415>
- [24] Kuczyńska J, Pawlak A, Nieradko-Iwanicka B. The comparison of dextropropofol and other painkilling medications (review from 2018 to 2021). *Biomed Pharmacother.* 2022; 149: 112819. <https://doi.org/10.1016/j.biopha.2022.112819>
- [25] Demirbolat GM, Altintas L, Yilmaz S, Degim IT. Development of orally applicable, combinatorial drug-loaded nanoparticles for the treatment of fibrosarcoma. *J Pharm Sci.* 2018; 107(5): 1398-1407. <https://doi.org/10.1016/j.xphs.2018.01.006>
- [26] Tagami T, Ito E, Kida R, Hirose K, Noda T, Ozeki T. 3D printing of gummy drug formulations composed of gelatin and an HPMC-based hydrogel for pediatric use. *Int J Pharm.* 2021; 594: 120118. <https://doi.org/10.1016/j.ijpharm.2020.120118>
- [27] Castillo-Henríquez L, Sanabria-Espinoza P, Murillo-Castillo B, Montes de Oca-Vásquez G, Batista-Menezes D, Calvo-Guzmán B, Ramírez-Arguedas N, Vega-Baudrit J. Topical chitosan-based thermo-responsive scaffold provides dextropropofol trometamol controlled release for 24 h use. *Pharmaceutics.* 2021; 13(12): 2100. <https://doi.org/10.3390/pharmaceutics13122100>
- [28] Elnashar MM, Yassin MA. Lactose hydrolysis by  $\beta$ -galactosidase covalently immobilized to thermally stable biopolymers. *Appl Biochem Biotechnol.* 2009; 159(2): 426-437. <https://doi.org/10.1007/s12010-008-8453-3>
- [29] Hellberg E, Westberg A, Appelblad P, Mattsson S. Evaluation of dissolution techniques for orally disintegrating mini-tablets. *J Drug Deliv Sci Technol.* 2021; 61: 102191. <https://doi.org/10.1016/j.jddst.2020.102191>
- [30] Al Ameri MN, Nayuni N, Kumar KA, Perrett D, Tucker A, Johnston A. The differences between the branded and generic medicines using solid dosage forms: In-vitro dissolution testing. *Results Pharma Sci.* 2012; 2: 1-8. <https://doi.org/10.1016/j.rinphs.2011.12.001>
- [31] Bui VT, Nguyen BT, Renou F, Nicolai T. Structure and rheological properties of carrageenans extracted from different red algae species cultivated in Cam Ranh Bay, Vietnam. *J Appl Psychol.* 2019; 31(3): 1947-1953. <https://doi.org/10.1007/s10811-018-1665-1>
- [32] Wang N, Tian J, Janaswamy S, Cao G, Teng W, Song S, Wen C. Role of metal chlorides in the gelation and properties of fucoidan/ $\kappa$ -carrageenan hydrogels. *Int J Biol Macromol.* 2023; 242: 124763. <https://doi.org/10.1016/j.ijbiomac.2023.124763>
- [33] Patel P, Mujmer K, Aswal VK, Gupta S, Thareja P. Structure, rheology, and 3D printing of salt-induced  $\kappa$ -carrageenan gels. *Mater Today Commun.* 2023; 35: 105807. <https://doi.org/10.1016/j.mtcomm.2023.105807>
- [34] Bui VT, Nguyen BT, Nicolai T, Renou F. Mixed iota and kappa carrageenan gels in the presence of both calcium and potassium ions. *Carbohydr Polym.* 2019; 223: 115107. <https://doi.org/10.1016/j.carbpol.2019.115107>
- [35] Vigani B, Rossi S, Gentile M, Sandri G, Bonferoni MC, Cavalloro V, Martino E, Collina S, Ferrari F. Development of a mucoadhesive and an in situ gelling formulation based on  $\kappa$ -carrageenan for application on oral mucosa and esophagus walls. II. Loading of a bioactive hydroalcoholic extract. *Mar Drugs.* 2019; 17(3):153. <https://doi.org/10.3390/md17030153>
- [36] Núñez-Santiago Md, Tecante A, Garnier C, Doublier JL. Rheology and microstructure of  $\kappa$ -carrageenan under different conformations induced by several concentrations of potassium ion. *Food Hydrocoll.* 2011; 25(1): 32-41. <https://doi.org/10.1016/j.foodhyd.2010.05.003>
- [37] Olímpio FM, Mendes AA, Trevisan MG, Garcia JS. Preparation and delayed release study on pancreatin encapsulated into alginate, carrageenan and pectin hydrogels. *J Braz Chem Soc.* 2020; 31: 320-330. <https://doi.org/10.21577/0103-5053.20190184>
- [38] Liu Y, Zhu Y-y, Wei G, Lu W-y. Effect of carrageenan on poloxamer-based in situ gel for vaginal use: Improved in vitro and in vivo sustained-release properties. *Eur J Pharm Sci.* 2009; 37(3-4): 306-312. <https://doi.org/10.1016/j.ejps.2009.02.022>
- [39] Jafari H, Atlasi Z, Mahdavinia GR, Hadifar S, Sabzi M. Magnetic  $\kappa$ -carrageenan/chitosan/montmorillonite nanocomposite hydrogels with controlled sunitinib release. *Mater Sci Eng C.* 2021; 124: 112042. <https://doi.org/10.1016/j.msec.2021.112042>
- [40] Sayed A, Mahmoud AF, Aly AM, Emad K, Mahmoud GA. Design of carrageenan based nanocarrier as a drug nanocarrier for tumor targeting: Radiolabeling and biodistribution. *J Drug Deliv Sci Tech.* 2023; 104573. <https://doi.org/10.1016/j.jddst.2023.104573>

- [41] El-Maadawy MW, Mohamed RR, Hanna DH. Preparation of carrageenan/chitosan-based (N, N, N-trimeth (yl chitosan chloride) silver nanocomposites as pH sensitive carrier for effective controlled curcumin delivery in cancer cells. *OpenNano*. 2022; 7: 100050. <https://doi.org/10.1016/j.onano.2022.100050>
- [42] Pinheiro AC, Bourbon AI, Quintas MA, Coimbra MA, Vicente AA. K-carrageenan/chitosan nanolayered coating for controlled release of a model bioactive compound. *Innov Food Sci Emerg Technol*. 2012; 16: 227-232. <https://doi.org/10.1016/j.ifset.2012.06.004>
- [43] Sonawane RO, Patil SD. Fabrication and statistical optimization of starch- $\kappa$ -carrageenan cross-linked hydrogel composite for extended release pellets of zaltoprofen. *Int J Biol Macromol*. 2018; 120: 2324-2334. <https://doi.org/10.1016/j.ijbiomac.2018.08.177>
- [44] Naiel BH, El-Subruiti GM, Khalifa RE, Eltaweil AS, Omer AM. Construction of gastroretentive aminated chitosan coated (sunflower oil/alginate/i-carrageenan) floatable polymeric beads for prolonged release of Amoxicillin trihydrate. *J Drug Deliv Sci Tech*. 2023; 84: 104534. <https://doi.org/10.1016/j.jddst.2023.104534>
- [45] Vieira WT, da Silva MGC, de Oliveira Nascimento L, Vieira MGA. k-Carrageenan/sericin-based multiparticulate systems: A novel gastro-resistant polymer matrix for indomethacin delivery. *Int J Biol Macromol*. 2023; 232: 123381. <https://doi.org/10.1016/j.ijbiomac.2023.123381>
- [46] Zhou X-y, Yu J-h, Yu H. Effect of gelatin content and oral processing ability on vitamin C release in gummy jelly. *J Food Sci Technol*. 2022; 59(2): 677-685. <https://doi.org/10.1007/s13197-021-05061-0>
- [47] Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C, Xie S. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. *The AAPS J*. 2010; 12: 263-271. <https://doi.org/10.1208/s12248-010-9185-1>