Utilization of Natural Polymer in the Preparation of Oral Jelly of Granisetron

Zahraa Mohammed Kadhim*, Wedad K. Ali*.
Department of Pharmaceutics, College of Pharmacy, Al-Mustansiriyah University/Iraq

DOI: https://doi.org/10.32947/ajps.19.02.00398

Article Info:

Received 27 Jan 2019
Accepted 11 Mar 2019
Published 1 May 2019

Corresponding Author email:
pharm.dr.wedad.ali.@uomustansiriyah.edu.iq
orcid: https://orcid.org/0000-0003-2522-5428

Abstract:

The aim of present study was to formulate and evaluate oral jellies containing granisetron (GSN). This new dosage form was designed for administration of the drug to specific aged patients (i.e. pediatric) in certain condition. GSN is an antiemetic which is usually used for the treatment of nausea and vomiting induced by radiotherapy and chemotherapy. The selection of this dosage form was based on its acceptability by pediatric population, ease of use and no need for water after taking the dose. In this study, two types of natural jellifying agents have been used in different concentrations. The natural jellifying agents which have been used were pectin and sodium alginate. The effect of jellifying agent and their concentrations have been investigated. Oral jell was prepared by heat and congealing method. Then investigations were done by measuring the pH, content uniformity, syneresis, stability, general appearance and production yield. The investigations showed that the formulation F3 with 5% pectin is the best one.

Key words: granisetron, sodium-alginate, pectin, oral jelly.

استخدام بوليمرات طبيعية لتحضير هلام فموي لدواء الغرانيسترون

زهراء محمد كاظم*، وداد كمال علي*
****الجامعة المستنصرية- كلية الصيدلة/ فرع الصيدلانيات***

الخلاصة:

كان الهدف من الدراسة الحالية هو تحضير وتقييم الهلام الفموي المحتوي على مادة غرانيسترون. حيث تم تصميم هذا الشكل الدوائي الجديد كجرع خاصة لاعمار محددة كالأطفال و في حالات معينة. غرانيسترون هو دواء مضاد للقيء والذي يستخدم عادة لعلاج الغثيان والقيء الناجم عن العلاج الإشعاعي والعلاج الكيميائي. كان اختيار هذا الشكل الدوائي (الهلام الفموي) لما له من قبول من قبل الأطفال ، وسهولة الاستخدام وعدم الحاجة إلى الماء بعد تناول الجرعة. في هذه الدراسة ، تم استخدام نوعين مختلفين من البوليمرات الطبيعية في تراكيز مختلفة و منها البكتين والألجينات وقد تم التحقيق في تأثيرنوع وتركيز كل بوليمر. تم تحضير الهلام الفموي بطريقة التسخين و التجميد ثم أجريت عليها دراسات عن طريق قياس درجة الحموضة والتوزيع الموحد للدواء في كل جرعة والاستقرار والمظهر العام والإنتاجية.

الكلمات المفتاحية: غرانيسترون، الجينات الصوديوم، بكتين، الهلام الفموي.

Introduction:

Cytotoxic chemotherapy, radiotherapy and particular types of surgery may cause clinically sever side effect such as nausea and vomiting which represent one of the

major therapeutic challenges that will result in decrease patient desire to continue treatment and consequently threaten the therapy success [1]. Granisetron (GSN) and other drugs belonging to this group have an essential role in controlling nausea and vomiting secondary to chemotherapy, radiotherapy and surgery [2]. GSN has high affinity for both central and peripheral 5HT3 receptors, but the peripheral one is the dominant [3].

GSN is white or almost white powder of an indazole with a chemical formula C18H24N4O and M.Wt of 312.4[3]. According to biopharmaceutical classification system (BSC) GSN is classified as class I drug which is characterized by high solubility and high permeability. (GSN) is highly selective 5 hydroxy tryptamin 3 (5HT3) receptors antagonist so it has no action on adrenergic, dopaminergic, histaminergic and opioid receptors [4].

For pediatric use, GSN is available as injections in the market. Therefore, the idea of designing oral dosage form is to reduce the pain and phobia associated with injections to improve the psychological state of the patients.

Oral dosage forms still the most preferred route for systemic effect for most population including pediatric. About 90% of drug products are designed for oral administration. The oral dosage form ranges from liquid to solids to semisolids dosage form. The preference of oral dosage form is due to many reasons including self-administration, lower cost and ease of production [5].

Jellies or gummies are one of the novel oral dosage forms, which have many advantages. Jelly can be given to patient with dysphagia such as pediatric and geriatric patients. Besides that, it can be used without the need for water, can be given as a uni-dose form, mostly attractive and elegant in shape from the patient point of view. In addition to that jelly as a semi solid dosage form combines the advantages of both solid and liquid dosage form. Therefore, jelly is one of the best oral dosage forms that can be used for pediatric population [6].

Aim

The aim of this study was to formulate GSN in a new dosage form as medicated jelly to increase patient compliance toward drug use in population that suffers from dysphagia regardless of age. Improving compliance will achieve maximum drug efficacy and the administration of antiemetic drug in jelly form before chemotherapy dose to cancer patient will have a positive psychological effect.

Materials and Methods

Materials:

Granisetron hydrochloride was received form Guokang Bio-Technology, China. Sodium alginate was received from Wuhan Senwayer century, China. Citric acid, sucrose, methyl parabene, probyl parabene, amaranth, strawberry taste was received from Himedia, India.

Methods:

Medicated jelly was prepared by heat and congealing method. An accurate amount of the jellifying agent was weighted and added to boiled water gradually with uniform and continuous stirring using magnetic stirrer. When the jellifying agent dissolved completely the required amount of hot syrup, citric acid and glycerin were dissolved in hot water and added to the mixture respectively under continuous stirring [7]. Then a solution of GSN (GSN dissolved in hot water) was added to the mixture with continuous stirring to ensure uniform distribution of the drug and other ingredients. Finally, the coloring and flavoring agents were added at a specified amount. All these steps were carried out at 90 o C using hot plate magnetic stirrer at stirring speed of 1500 rpm.

Six formulas were prepared using two jellifying agents at different concentrations as shown in Table (1).

Table (1): Formulations of GSN oral jellies

Ingredient	F1	F2	F3	F4	F5	F6
GSN (g)	0.02	0.02	0.02	0.02	0.02	0.02
Pectin (g)	3	4	5			
Sodium alginate (g)				1	1.5	2
Citric acid (g)	1	1	1	1	1	1
Glycerin (g)	3	3	3	3	3	3
Syrup (g)	60	60	60	60	60	60
Preservatives (g)	0.2	0.2	0.2	0.2	0.2	0.2
Coloring agent (g)	0.1	0.1	0.1	0.1	0.1	0.1
Flavoring agent (g)	0.1	0.1	0.1	0.1	0.1	0.1
Purified water	q.s	q.s	q.s	q.s	q.s	q.s
Total weight (g)	100	100	100	100	100	100

*Each single jelly wight was 5 g and contain 1mg GSN.

In-Vitro Evaluation of the Prepared Jellies

Physical Appearance

The physical appearance of each jellified formulation was inspected visually for clarity and color [6].

Stickiness and grittiness

The stickiness and grittiness of the medicated jellies were simply evaluated manually by rubbing the jelly between two fingers and any sense for such undesirable properties were recorded [8].

PH

The pH of the medicated jelly must be checked because it does not only influence the stability but also the taste of the final product. The pH was determined using digital pH meter. The jelly was dissolved in a sufficient amount of distilled water to make 1% (w/v) solution, and then the pH was measured for this solution(9). The test was done in triplicate for each sample.

Content Uniformity

This test was done to ensure uniform distribution of GSN in each jellified formula. A medicated jelly was dissolved in a phosphate buffer pH 6.8 to which theoretically calculated to give 0.1 mg/mL solution. The prepared solution was further diluted and the UV absorbance was measured at λ max of 302 nm using UV-visible spectrophotometer[6] .

Syneresis

Syneresis is a matter of de-swelling of a dosage form upon storage. Separation of water and shrinkage of the jelly will result in reduction of quality of the product. This test was performed at 25°C and visually inspected for any change in jelly consistency during 24 hr. Therefore any jelly was undergoing syneresis at room temperature, was excluded from other tests(10). Refrigerator storage condition was also investigated for preparations that may undergo syneresis at room temperature.

Stability Study

The stability test was performed to evaluate samples of jellified formulations prepared with and without preservatives after storage at different environmental conditions for one year. The storage conditions included refrigerator (5°C), room temperature (25°C) and at (40°C) during summer season to observe any changes in color, odor, taste and clarity. Samples of jellified formulations were also prepared without preservative to make comparative study with formulations that contain preservative(11). While the ideal condition for storage of samples is in tightly closed opaque container and cool place.

Determination of Production Yield

The production yield was determined by determining the theoretical weight of each formulas and the practical weight after production and calculating the yield according to the following equation[12]:

$$\text{Percentage of production yield} = \left(\frac{\text{practical weight}}{\text{theoretical weight}}\right) * 100\%$$

***In-vitro* dissolution study**

In-vitro dissolution of the prepared jellies was performed using USP paddle dissolution apparatus in 250 mL phosphate buffer pH 6.8. The temperature of the dissolution media was 37 ^{o}C with continuous stirring (50 rpm) for 15 min.

A sample of 5mL was withdrawn every 5 min and diluted with phosphate buffer pH 6.8 up to 10 ml and the absorbance in UV-visible spectrophotometer was measured and converted to percentage of drug released using previously determined calibration curve equation then plotted versus time for each point[8]. The release study for sample was tested in triplicate.

Results and discussion:

Evaluation of Physical Appearance

GSN jelly formulations were prepared using two different jellifying agents at different concentrations. The visual inspection of the different jelly formulations showed that formulation (F1-F6) have a transparent reddish color with a smooth consistency as shown in Table (2). This homogenous appearance of the final jellies will increase patient compliance and acceptance for the medication. Similar results were obtained using pectin and sodium alginate as jellifying agents[9].

Table (2): Physical Appearance of GSN oral Jelly Formulations.

No.	Formulation code	Clarity	Color	Consistency
1	F1	Transparent	reddish	Smooth
2	F2	Transparent	reddish	Smooth
3	F3	Transparent	reddish	Smooth
4	F4	Transparent	reddish	Smooth
5	F5	Transparent	reddish	Smooth
6	F6	Transparent	reddish	Smooth

Stickiness and grittiness

By crushing formulation between two fingers the grittiness and stickiness results were determined and the results are summarized in Table (3).

Table (3): Stickiness and grittiness evaluation of GSN oral jelly formulations

No.	Formulation code	Grittiness	Stickiness
1	F1	Non-gritty	Non-sticky
2	F2	Non-gritty	Non-sticky
3	F3	Non-gritty	Non-sticky
4	F4	Less gritty	less sticky
5	F5	Less gritty	less sticky
6	F6	Less gritty	less sticky

Measurement of PH

The results of pH measurement of different GSN oral jelly formulations were within the acceptable range for use in oral cavity pH range of (6.2-7.6) (13). The results of this study are shown in Table (4).

Table (4): the pH value of different GSN oral jelly formulations

No.	Formulation code	pH ± SD
1	F1	6.3± 0.02
2	F2	6.2±0.03
3	F3	6.5± 0.02
4	F4	7.2±0.01
5	F5	7.1±0.03
6	F6	7.3±0.07

Content Uniformity

The results showed that the drug content in different formulations is ranging from 98.12% to 101.15% as shown in Table (5). These results comply with the USP acceptable range of ±5% of the average drug content for solid dosage form (tablet) (14)

Table (5): Content uniformity of the different GSN oral jelly formulations

No.	Formulation code	Content uniformity ± SD
1	F1	99.88% ± 0.4
2	F2	99.75% ± o.2
3	F3	101.15% ± 0.15
4	F4	98.12% ± 0.7
5	F5	98.87% ± 0.53
6	F6	99.39% ± 0.55

Syneresis

Syneresis was investigated at room temperature 25±5 ºC. Formulations F1-F3 did not show any syneresis, while F4-F6 showed syneresis as shown in Table (6). Further investigation was done concerning storage condition using formulations F4-F6, it was found that even when these formulations are stored in refrigerator some syneresis was observed. Therefore, according to the results of this study, type of jellifying agent should be considered to obtain jelly with appropriate characteristic. Here pectin as jellifying agent is better than sodium alginate. This variation may be due to the building block of each jellifying agent[15, 16].

Table (6): Results of GSN oral jelly syneresis

No.	Temp. 25 º C	No.	Temp. 25 º C
F1	No	F4	Yes
F2	No	F5	Yes
F3	No	F6	Yes

Stability Study

Throughout the storage period, the clarity, odor and general appearance were observed every week. It was noticed, that formulations which were stored in standard conditions and even without preservative have sufficient stability. While formulations that were stored in open environment even with preservatives have low stability with marked differences between jellifying agents.

Pectin containing formulations are the most stable ones, while formulations containing sodium alginate as jellifying agent were less stable than others if the formulations have not been stored in specified conditions.

Formulations F1-F3, which were prepared using pectin, were stable for more than 5 months without preservative. However, the same formulations which contain a preservative were stable for more than one year in standard conditions.

Alginate containing formulations F4-F6 can withstand 2 months in refrigerator without preservative and the stability increased to 6 months if a preservative was used. In general, the key to increase shelf life of jelly formulations is the storage of products in tight and opaque container in dry and cool place.

Determination of Production Yield

For all prepared jellified formulations, the production yield percent was 80-90%. Only 8 to 9 jellies were obtained instead of 10. This result was expected due to the loss of some of the starting material during production of the jellies.

In-vitro Dissolution Study

The results of dissolution study were shown in Table (7) and Figure 1. According to the results, the percentage of drug released is significantly ($P< 0.05$) affected by the type of polymer used. The formulations F1-F3 that contain pectin polymer showed a satisfactory release profile. The drug was released within accepted time range (15 min), the best result was with F3 that released 99.82% of the drug.

The alginate containing group of jellies (F4-F6) showed a noticeable slow release of the drug within the acceptable time range as shown the best result was 49.17% drug release during 15 min, This is because the polymer has a retardation effect on the release due to the re-swelling property of alginate particles[17].

Table (7): Results of GSN oral jelly release after 15 min

No.	Formulation code	% of release after 15 min
1	F1	85.78
2	F2	85.82
3	F3	99.82
4	F4	49.18
5	F5	37.24
6	F6	34.76

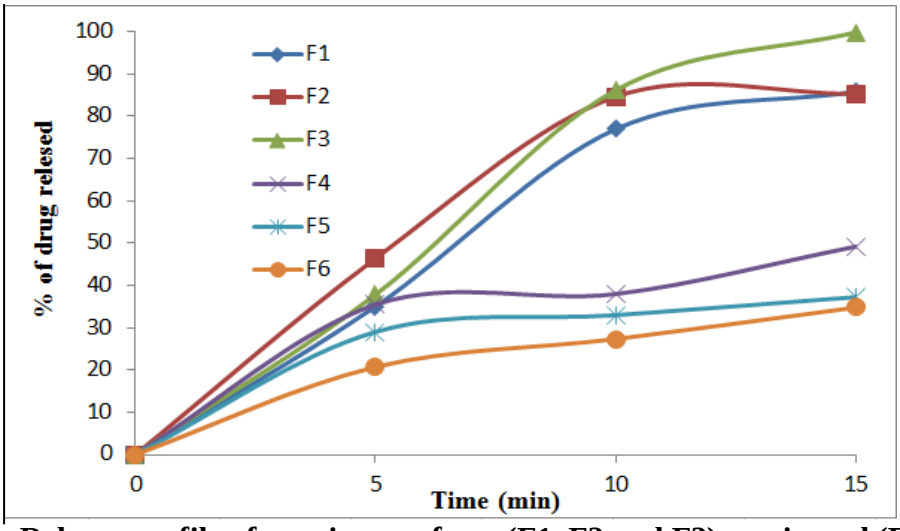

Figure (1): Release profile of granisetron from (F1, F2 and F3) pectin and (F4, F5 and F6) alginate oral jellies.

Conclusions

From all evaluation parameters, it can be concluded that Jelly can be considered as a good alternative dosage form for other oral dosage form specifically liquids, because jelly is combining the advantages of solid and liquid dosage forms. Storage under convenient conditions (tightly closed, opaque containers in cool, dry place) is the key in providing long shelf life to jelly dosage form. The quality of prepared jelly is related to type of jellifying agent and its properties. Alginate as jellifying agent retards the release of the drug from jellies, while pectin provides fastest release that could be helpful for oro-mucosal drug delivery. The formulation (F3) in which pectin was used is selected as the optimum formulation, since it showed acceptable physical characteristic and release profile.

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