RESEARCH ARTICLE

Preparation and Evaluation of Granisetron Chewable Pediatric Oral Jelly

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Received: 08th July, 19; Revised: 12th August, 19, Accepted: 03th September, 19; Available Online: 08th September, 2019

ABSTRACT

This study aimed to formulate granisetron (GSN) in a new dosage form using natural substances and to improve pediatric patient compliance to achieve maximum drug efficacy. The GSN is a 5HT3 receptor antagonist used as prophylaxis for the prevention of nausea and vomiting before radiotherapy and chemotherapy. This dosage form was selected because of sharing both the advantages of liquid and solid dosage forms. In this study, two types of natural jellifying agents have been used in different concentrations. The natural jellifying agents who have been used were gelatin and carrageenan (CRG). The effect of jellifying agent and their concentrations have been investigated. Six formulations of GSN oral jellies were prepared by the heat and congealing method, and the prepared jellies were evaluated by measuring their pH, content uniformity, drug-polymer compatibility, syneresis, physical stability, general appearance, and production yield. Among the prepared formulations, formulation F1 with 4.5% gelatin was considered the best one, since it gave the highest drug release 99.4% in 15 min with acceptance results for all other evaluation tests.

Keywords: Gelatin, CRG, GSN, Oral jelly.

International Journal of Pharmaceutical Quality Assurance (2019); DOI: 10.25258/ijddt.v9i3.4

How to cite this article: Kadhim, Z.M. and Ali, W.K. (2019). Preparation and Evaluation of Granisetron Chewable Pediatric Oral Jelly. International Journal of Drug Delivery Technology, 39(3): 347-351.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Despite the enormous development that occurred in the design of various dosage forms, oral dosage forms are the preferred ones for systemic effect.[1] Perhaps about 90% of all medications that produce a systemic effect is designed for oral route. The oral route is preferred over another route due to self-administration, ease of production, and lower cost.[2] Besides that oral route is the route of choice for health providers and patients. Today patient compliance is gaining more attention in dosage form design, especially those intended to be used for pediatric population.[2]

One of the most critical problems facing pediatric therapy is the off-label and unlicensed use of adult drugs due to the absence of appropriate pediatric dosage form.[3] These methods could be hazardous as they may change the stability, bioavailability and dose accuracy.

Furthermore, a controlled-release tablet cannot be used by the above compounding methods.[4]

The most common pediatric dosage forms are syrups and suspensions. However, disadvantages such as solubility, unpleasant taste, and stability problems may restrict their use and manufacturing. Today the oral solid dosage form is the favored form for infants and children treatment even by world health organization (WHO).[5]

Dysphagia is one of the problems that face pediatric treatment. Dysphagia is a difficulty in swallowing that may occur in childhood due to either behavioral or skill-based disorder.[6]

Jelly is one of the dosage forms that can be appropriate for a patient with dysphagia. It is a viscous thick fluid or semisolid. The term gel is taken from gelatin, and both gel and jelly are adapted from a Latin word gelu for frost and gelar, which means freezing or congealing. Jelly is characterized by sharing the features of the liquid and solid dosage form in a semisolid dosage form.[2]

The most important features of jelly are the avoidance of the first-pass metabolism, be taken without water, accepted by pediatric population, easy to handling and packaging in unite dose or multiple dose container and finally it is suitable for patients with dysphagia, since it is easily chewed and converted to liquid that easily swallowed.[7]

ACTIVE INGREDIENT MANUFACTURER (AIM)

The present study aims to formulate GSN in a new dosage form using natural substances and to improve pediatric patient compliance to achieve maximum drug efficacy.

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MATERIALS AND METHODS

Materials

GSN hydrochloride and carrageenan were received form Guokang Bio-Technology, China. Citric acid, sucrose, methylparaben, propylparaben, amaranth, the strawberry taste was received from Himedia, India.

Methods

Medicated jelly was prepared by the heat and congealing method. An accurate amount of the jellifying agent was weighed and added to boiled water gradually with uniform and continuous stirring using magnetic stirrer. When the jellifying agent dissolved the required amount of hot syrup completely, citric acid and glycerin were dissolved in hot water and added to the mixture respectively under continuous stirring.[8] Then a solution of 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°C using hot plate magnetic stirrer at stirring speed of 1500 rpm.

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

Drug polymer compatibility study by FTIR

Jelly was prepared by mixing the drug with polymers. The probability of chemical interaction that may result in the degradation of GSN is present. Hence FTIR technique was used to determine compatibility between drug and polymer. FTIR was done using KBr disk in the range of 4000-400 cm^{-1}.[9]

In vitro evaluation of prepared jelly

Physical appearance

The physical appearance has been inspected visually to determine the clarity and color of each prepared jelly.[7]

Stickiness and grittiness

Evaluation of grittiness and stickiness have been done manually by rubbing the medicated jelly between two fingers and any sense for such undesirable properties were recorded.[10]

Table 1: Formulations of GSN oral jelly

% W/W	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
GSN	0.001	0.001	0.001	0.001	0.001	0.001
Gelatin	4.5	5	6			
Carrageenan				0.5	1	1.5
Citric acid	1	1	1	1	1	1
Glycerin	3	3	3	3	3	3
Syrup	60	60	60	60	60	60
Preservatives (methyl and propyl parabene)	0.2	0.2	0.2	0.2	0.2	0.2
Coloring (amaranth)	0.1	0.1	0.1	0.1	0.1	0.1
Flavoring (strawberry flavor)	0.1	0.1	0.1	0.1	0.1	0.1
Distilled water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Note: Each single jelly weight was 5 g

Potential of hydrogen (pH)

The pH of each formulation has been evaluated in triplicate using a digital pH meter. Each prepared jelly was dissolved in purified water to form 1% solution, and the pH of the solution was measured.[11]

Content Uniformity

The uniform distribution of GSN, in each formulation, was evaluated by dissolving a medicated jelly in 100 mL phosphate buffer pH 6.8. The UV absorbance was measured at λ max 302 nm using UV-visible spectrophotometer and concentration of drug in the solution was determined.[7]

Syneresis

Syneresis is a matter of de-swelling of dosage form upon storage. Separation of water and shrinkage of the jelly will result in a reduction in the quality of a product. This test was performed at 25°C and visually inspected for any change in jelly consistency during 24 hour. So any jelly was undergoing syneresis at room temperature, must be excluded from other tests.[12] 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 (25oC) and at (40°C) during the summer season to observe any changes in color, odor, taste, and clarity. Samples of jellified formulations were also prepared without preservative to make a comparative study with formulations that contain preservative.[13]

In vitro dissolution study

In vitro dissolution of jelly was performed using the USP paddle dissolution apparatus in 250 mL phosphate buffer pH 6.8. The dissolution media temperature was 37°C with continuous stirring (50 rpm) for 15 min.

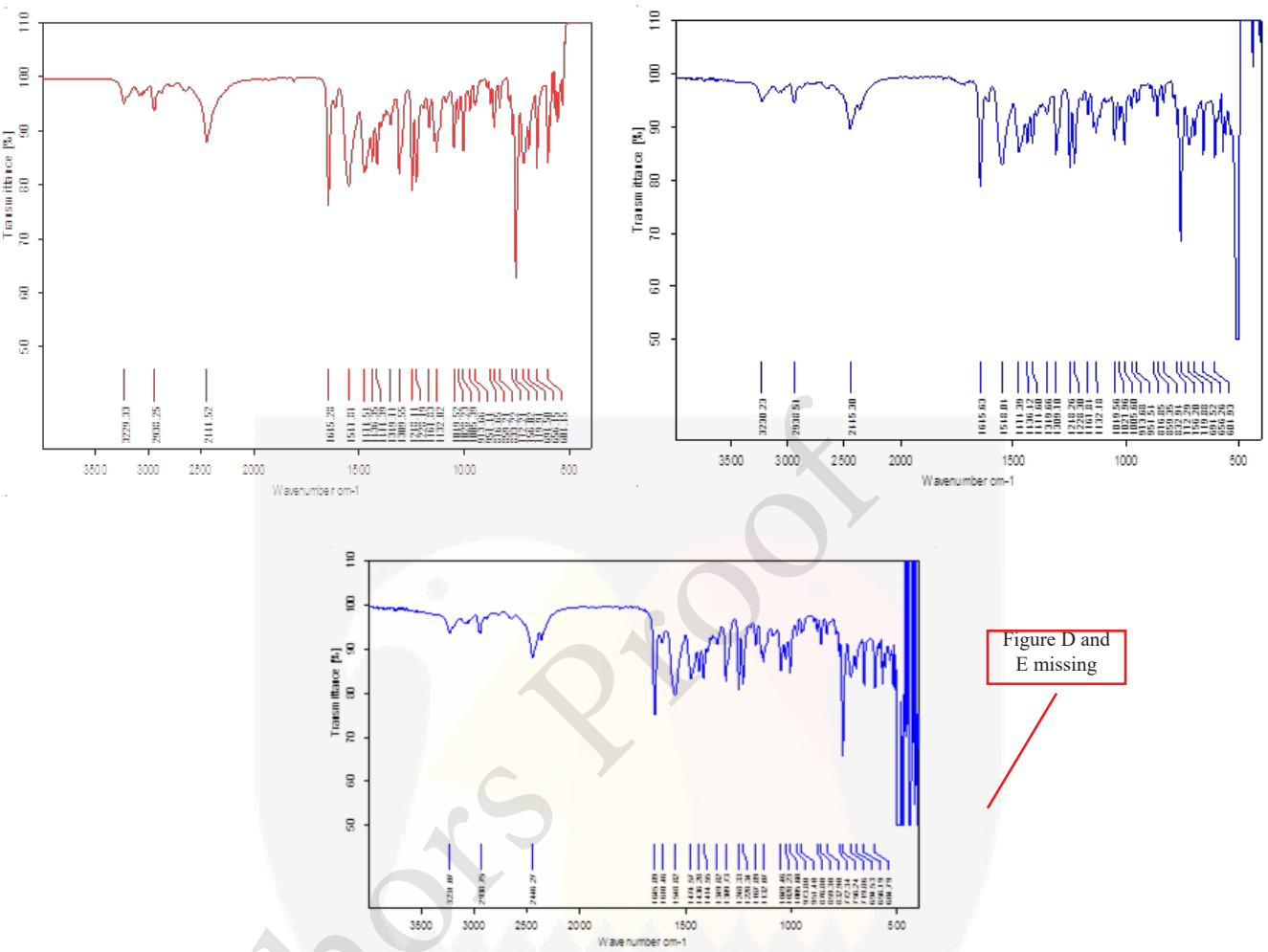
A sample of 5mL was drowned every 5 minutes and diluted with phosphate buffer pH 6.8 up to 10ml to measure the absorbance in UV-visible spectrophotometer and was converted to percent of drug release using previously determined calibration curve equation at pH 6.8 then plotted versus time for each point.[10]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

RESULTS AND DISCUSSION

The GSN oral jellies were successfully prepared using formulations F1-F6 and subjected to further investigations concerning their general appearance, content uniformity, pH, and stability study.

Drug Polymer Compatibility Study by FTIR

The FTIR spectra of the pure GSN powder has shown in Figure 1a. The GSN spectrum showed a characteristic peaks at 3229 cm^{-1} indicating the presence of N-H stretching, at 1645 cm^{-1} indicating the presence of C = O stretching, at



Figs 1A to C: FTIR spectra of pure GSN, combinations of GSN with gelatin alginate and carrageenan in a, b and c respectively

Table 2: Results of GSN oral jelly physical appearance

Sl 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

Table 3: Results of GSN oral jelly stickiness and grittiness evaluation

Sl. No.	*Formulation code*	*Grittiness*	*Stickiness*
1.	F1	Non-gritty	Sticky
2.	F2	Non-gritty	Sticky
3.	F3	Non-gritty	Sticky
4.	F4	Gritty	Non-sticky
5.	F5	Gritty	Non-sticky
6.	F6	Gritty	Non-sticky

1547 cm^{-1} indicating the presence of aromatic ring, at 2938 cm-1 indicating the presence of C-H stretching, at 1228 cm-1 indicating the presence of C-N stretching and the 1474 cm-1 indicating the presence of (C = N).[14]

The FTIR spectra of a mixture of GSN with gelatin and carrageenan are shown in Figure (1b) and (1c) respectively. The comparison between the spectra of pure drug and the spectrum of the drug mixed with polymers showed no specific chemical shift in the spectrum of pure drug. Accordingly, it is demonstrated that there are no chemical interactions between GNS and these polymers during the preparation of jellies and that the polymers used in this study are compatible with the drug.

Evaluation Parameters

Physical Appearance

GSN jelly formulations were prepared using two different jellifying agents at different concentrations. The visual inspections of the different jelly formulations showed that formulation (F1-F6) has 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

Table 4: Results of GSN oral jelly pH

Sl. No.	*Formulation code*	*pH ± SD*
1.	F1	6.8 ± 0.05
2.	F2	6.7 ± 0.04
3.	F3	6.9 ± 0.03
4.	F4	6.5 ± 0.02
5.	F5	6.4 ± 0.06
6.	F6	5.9 ± 0.05

Table 5: Results of GSN oral jelly content uniformity

Sl. No.	*Formulation code*	*Content uniformity ± SD*
1.	F1	102.34% ± 0.2
2.	F2	101.54% ± 0.34
3.	F3	100.69% ± 0.6
4.	F4	99.28% ± 0.71
5.	F5	98.82% ± 0.39
6.	F6	99.4% ± 0.6

Table 6: Results of GSN oral jelly syneresis

Sl. No.	*Temp. 25°C*	*No.*	*Temp. 25°C*
F1	No	F4	Yes
F2	No	F5	Yes
F3	No	F6	Yes

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

Sl. No.	*Formulation code*	*% of release after 15 min*
1.	F1	99.40
2.	F2	97.74
3.	F3	90.27
4.	F4	60.7
5.	F5	55.61
6.	F6	55.30

obtained using pectin and sodium alginate as jellifying agents.[11]

Stickiness and grittiness

The grittiness and stickiness of each formulated jelly were determined by crushing it between two fingers. The degree of grittiness and stickiness were determined by comparing different formulations, and the results of these evaluation tests are summarized in Table 3.

pH

The pH values for all prepared GSN oral jelly solution were within an acceptable range for use in the oral cavity pH of 5-9.[15] The results of this study are shown in Table 4.

Content uniformity

The drug content of the prepared GSN oral jelly has been measured using UV-spectrophotometer. All formulations have been shown to have a uniform distribution of drugs ranging from 98.82%–102.34% as shown in Table 5. These results are within the acceptable range of drug content stated in united state pharmacopeia (USP) ± 5% of total drug dose.[16]

Syneresis

Syneresis was investigated at room temperature 25±5 o C. The formulas F1-F3 did not show any syneresis, while formulas F4-F6 were showing some syneresis even when stored in the refrigerator, as shown in Table 6. These may be due to the low concentration of the jellifying agent.

Stability Study

Throughout the storage period, the clarity, odor, general appearance were observed every week. It was noticed, that formulations which were stored in ideal condition and

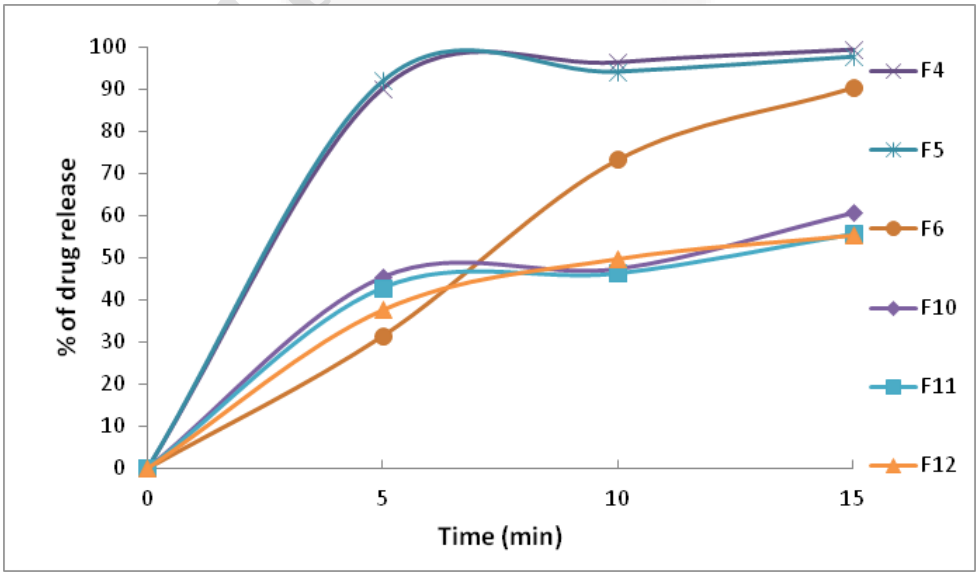


Figure 2: Percent of GSN release from (4.5%, 5% and 6%) gelatin and (0.5%, 1%, and 1.5%) carrageenan oral jellies

even without preservative have sufficient stability. While formulations that were stored in an open environment even with preservatives have low stability with marked differences between jellifying agents.

The F1-F3 formulations containing gelatin can withstand about 3 months without preservative under standard conditions and more than 9 months in the presence of preservative.

On the contrary, the carrageenan containing formulations (F4-F6) can withstand about 2 months in refrigerator without preservative and the resistance increase to more than 6 months if preservative has been used. In general, the key to increase shelf life is the storage of products in a tight and opaque container in a dry and cool place.

In vitro Dissolution Study

The results of the dissolution study were as shown in Table 7. According to this study, it was apparent that the percent of release is significantly ($p< 0.05$) affected by the type of polymer used. The formulations F1-F3 which contain gelatin polymer showed the fastest release compared to other formulations within the acceptable time range that reached up to 99.40% for F1.

The other formulations (F4-F6) which contain the CRG showed a slow release profile within the acceptable time range that reached maximally to 60.7% in F5. The jelly which was made of CRG was taking more than 30 minutes to dissolve completely. According to reference, CRG is classified into three types. The type that has been used in this experiment was the k CRG. This type of CRG is insoluble in water, so it resulted in the retarded release of GSN from jelly.

CONCLUSION

According to the result of the experiment, the following can be concluded:-

The quality of prepared GSN oral jelly is related to the type of jellifying agent and its properties. Fastest drug release could be obtained from jelly using gelatin as a jellifying agent and the optimum formulation is F1since it released 99.40% of GSN in 15 minutes. Therefore, the F1 formulation of oral GSN jelly could be used to prepare GSN jelly to be administered to pediatric and patient suffering from dysphagia.

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